

Randomised Trials in Child and Adolescent Health in Developing Countries

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Please send suggestions about this booklet to:

Prof Trevor Duke
University of Melbourne, Department of Paediatrics
The Royal Children's Hospital
Parkville, 3052, Victoria, Australia
Email: trevor.duke@rch.org.au

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Introduction

This booklet has been compiled annually to summarize the evidence on child and adolescent health derived from randomized or controlled trials in developing countries over the previous year. The aim is to make this information widely available to paediatricians, nurses, other health workers and administrators in lower resource settings where up-to-date information is hard to find. I hope that this information will be helpful in reviewing treatment policies, clinical practice, teaching, and public health strategies.

The method of searching for studies uses PubMed, a search engine that is freely available and widely used in countries throughout the world. The search strategy has been chosen to capture as many relevant studies as possible, although it is possible that I have missed some. If you know of a relevant RCT or meta-analysis that has not been included in this year's review, please let me know. The search strategy is reproducible by anyone with access to the Internet, through <http://www.ncbi.nlm.nih.gov/sites/entrez>

Randomized controlled trials (RCTs) are not the only valuable scientific evidence, and some RCTs, because of problems with design or implementation, have limited value. However, the method of the Randomized Trial is the Gold Standard for determining attributable benefit or harm from clinical and public health interventions. When done properly they eliminate bias and confounding. Their results should not be accepted uncritically but they should be evaluated for quality and validity. Before the result of an RCT can be generalized to another setting there must be consideration of wider applicability or reproducibility, feasibility and potential for sustainability.

This year 600 trial publications were identified. These were conducted in countries from all regions of the world, and the topics are as diverse as the problems are for children and adolescents in the world of 2025. Several of these trials will lead to changes in child health recommendations, and some are low quality evidence.

Where there were no trials this year under a certain sub-heading I have left the heading in the book, to indicate the lack of trials this year. Many trials could be listed under several sub-headings, and there is overlap in the sub-headings, so there may be fewer gaps than is first apparent.

Some of the most complex and consequential problems facing children in today's world do not lend themselves to controlled trials of course. Rather they are problems of political will, inequity, violence in all its forms, and environments that are not conducive to health, development, and well-being. But it is impressive that even in the harshest environments, health research, including that outlined in this booklet, is being done that can lead to positive changes for children and adolescents.

Most of the papers this year have free on-line access, which you can link to through the hyperlink in the title. Through HINARI (<http://www.who.int/hinari/en/>) a program set up by WHO in collaboration with publishers, the full-text versions of over 14,000 journal titles and 30,000 e-books are available to health institutions in over 100 countries. If your health

institution (medical school, teaching hospital, nursing school, government office) has not registered with HINARI, you can check your eligibility and register online.

Please feel free to distribute this booklet to your colleagues. The previous editions (2002-2024) are available at: <https://pngpaediatricsociety.org/research-2/>

Trevor Duke
August 2025

Summary

A summary of some of the important results from July 2024 to June 2025:

In a large cluster RCT involving nearly 280,000 mothers and babies in Tanzania, implementation of the Safer Births Bundle of Care program: interventions to improve the quality of care for mother and baby, perinatal death decreased from 15.3 to 12.5 deaths per 1000 births (adjusted relative risk, 0.82; 95% confidence interval [CI], 0.73 to 0.92; $P = 0.001$). The beneficial effect being in reduction of neonatal deaths, with no effect on stillbirths.¹

Insecticide treated bed nets have made a huge impact on malaria reduction for over 20 years, however resistance to insecticides, and adherence have limited their effectiveness in the last decade. In a cluster-randomised trial comparing two newer-generation LLINs (pyrethroid-piperonyl butoxide and pyrethroid-pyriproxyfen), there was a modest reduction in malaria incidence (23%) following the distribution of these newer-generation bed-nets, but the reduction was sustained for only 12 months, highlighting the need for improved strategies to maintain net effectiveness.²

In studies of intermittent mass drug administration of Ivermectin for the prevention of malaria, head lice were much decreased in Mozambique,³ but there was no change in malaria incidence in Burkina Faso and Guinea Bissau.^{4 5}

RCTs in childhood vaccines this year confirmed the necessity of the birth dose of hepatitis B vaccine for the prevention of mother to child transmission of hepatitis B,^{6,7} preliminary testing of a hookworm vaccine showing it generates good humeral immunity,⁸ maternal immunization with the RSV vaccine produced strong immune responses in over 7000 pregnant women and transfer of maternal antibodies to their newborns, with 82% protective efficacy against RSV disease.⁹ A study in Bangladesh showed high seroconversion rates for measles vaccine (MMR) at 6 months (94%) and rose to 99% with a second-dose at 9 months, suggesting the value of a 6-month dose to protect young infants during measles outbreaks or in regions of high transmission.¹⁰

Heat stress has adverse effects on foetal and child growth, as demonstrated in the secondary analysis of an RCT in a rural area in The Gambia. Among infants exposed to a mean daily temperature of 30°C in the preceding 90-day period there were significant reductions in mean weight for height and weight for age z-scores, compared to infants exposed to a mean daily temperature of 25°C.¹¹

There were several trials of community-based mobilisation and incentivisation, proactive home visits to reduce child mortality and improve other health outcomes. In a complex cluster RCT in Pakistan involving over 21,000 children, formation of village committees which conducted awareness activities, and more particularly conditional incentives lead to more fully immunised children, increased sanitation, and increased oral rehydration solution use.¹² In 137 villages in rural Mali, the preparation for a trial of proactive home visits, which involved system-strengthening measures: including removal of primary care user fees, and improved resourcing of community health centres in both arms, was associated with dramatic reductions in child mortality, independent of home visits.¹³

In children living with HIV, in the ODDESEY trial in 7 countries, dolutegravir led to faster virological suppression and lower risk of virological failure than non-nucleoside reverse transcriptase inhibitors and boosted protease inhibitor-based therapy, and protected against resistance if commenced as primary treatment.¹⁴

In a systemic review of 15 RCTs of children with pneumonia, short course antibiotic treatment (<6 days) was as effective as longer course antibiotic treatment (>7 days).¹⁵ In a small placebo-controlled RCT of children with pneumonia, selenium reduced the requirement for ventilation; non-conclusive and hypothesis generating.¹⁶

There were many studies involving adolescents, including: trials of decentralising health and social care for adolescents with HIV, and other trials of school health initiatives to improve girls' self-esteem, improve access to sexual and reproductive health, and reduce pregnancies. In Sierra Leone, among pregnant adolescent girls, community-based mentoring intervention from pregnancy up to 1 year after birth reduced perinatal and neonatal mortality.¹⁷ Peer-facilitated support for improving mental health in Cameroon reduced anxiety and depression.¹⁸ Sport played a part in some trials. Among displaced youth in a humanitarian refugee setting in Uganda, engagement in a 16-week sport-for-protection program significantly improved objective markers of anxiety and depression.¹⁹ In Kenya, among urban youth, anxiety and depression was significantly reduced by therapy delivered by lay providers, in this case young barbers who were given literacy about mental health problems.²⁰

Several studies investigated point-of-care (POC) testing to inform antibiotic prescribing, in Burkina Faso and Uganda. In a large stepped wedge cluster randomized trial in 15 villages in rural Uganda, POC c-reactive protein used by 65 community health workers reduced antibiotic prescribing for 1280 children with respiratory infection, with overall low rates of clinical failure.²¹

Trials continued to explore the role of azithromycin mass drug administration in high mortality regions in Africa. In a complex cluster RCT involving 380,000 children in rural Niger, twice-yearly distribution of azithromycin to infants and in other clusters to children up to 5, there was a lower mortality in children 20-59 months, but not in those 1-11 months.²² Other analyses of the Niger study suggested that part of the effect may be on reducing colonisation with *B. pertussis* and *Haemophilus influenzae* type b, although colonisation with *Streptococcus pneumoniae* was not significantly affected.²³ A trial in Burkina Faso confirmed no effect of azithromycin routine prophylaxis on 32,000 infants 1-11 months.²⁴ Other studies evaluated the effect of azithromycin exposure on antimicrobial resistance and changes in the

microbiome, which seems inconclusive at this stage. A systematic review of 5 RCTs concluded that among children 12-59 months, MDA-azithromycin significantly reduced mortality (RR: 0.85 [0.79, 0.91]; $P < 0.00001$), but this is highly context specific.²⁵ WHO's recommendation remains that azithromycin MDA may have a role only in very high mortality regions in Africa, but that the opportunity costs for addressing other gaps in health care need to be considered.

In children and adolescents in Mali where the control of type 1 diabetes was improved (HbA1C markedly lower and fewer episodes of ketoacidosis) by the use of once-daily long-acting insulin analogue glargine using pre-filled syringe, plus bolus of rapid acting insulin with meals.²⁶ In a small study of Indian children with newly diagnosed type 1 diabetes, high strength probiotics in the first 6 months was associated with lower HbA1C, and markers of immune regulation.²⁷

In a systematic review of RCTs of resuscitation in septic shock, balanced salt solution was associated with decreased risk of acute kidney injury, need for renal replacement therapy and lower rates of hyperchloremia, but no effect on mortality, when compared to 0.9% saline.²⁸ In a paediatric intensive care unit in North India, 50 mechanically ventilated children randomised to receive intravenous fluids restricted to 40% standard maintenance had more ventilator free days than 50 children managed with fluids at 70-80% of maintenance fluids.²⁹

In sickle cell disease, studies this year established the efficacy of hydroxyurea in preventing vaso-occlusive crises, but at a cost of greater dose limiting toxicities from the drug.³⁰ Another study showed IV ketorolac to be a good alternative to IV morphine in painful vaso-occlusive crises, and that IV arginine (a nitric oxide precursor and vasodilator) also has an opioid sparing effect.^{31,32} In Malawi and Uganda children with sickle cell disease had much fewer episodes of malaria when they received prophylaxis with weekly dihydroartemisinin-piperaquine than with monthly sulfadoxine-pyrimethamine.³³

In a trial of treatment for hookworm in Tanzania involving adolescents, a new antihelminth emodepside compared with albendazole was more effective (cure rate 96% vs 81%) however emodepside was associated with more side effects, including transient blurred vision, headache and dizziness.³⁴

In a cluster RCT of a cluster-randomized controlled trial of an integrated mental health strategy among 360 families (children aged 10-15 and their female caregivers) in Burkina Faso, maternal depression fully mediated the intervention effect on children's depression and child's self-esteem, and violent parenting partly mediated the intervention effect on children's depression.

In a blinded placebo controlled RCT, probiotics in Indian children with autism spectrum disorder (ASD) aged 2-9 years, significantly reduced severe symptoms, including social withdrawal or lethargy, stereotypic behaviour, hyperactivity and inappropriate speech, constipation and diarrhoea.³⁵ Similar results were reported in another trial in India using oral folinic acid supplementation.³⁶

In a multi-country RCT in Asia, women deemed to be at high risk for preterm pre-eclampsia who took aspirin from before 16 weeks until 36 weeks' gestation had a 42% reduction in the risk of early preterm birth, with the effect being greatest the earlier the gestation (at 24 weeks, aspirin delayed delivery by 3.63 weeks, while at 37 weeks, the delay was only 0.25 weeks).³⁷

More studies of kangaroo mother care in low birth weight infants were published this year, including a meta-analysis of RCTs which showed KMC reduced all cause neonatal mortality, sepsis, hypothermia and apnoea.³⁸ Individual RCTs showed KMC increased human milk intake, and regional cerebral oxygen saturation.^{39,40}

In a cross-over RCT in preterm infants in Nigeria, the use of automated titration of oxygen therapy in a low-cost continuous positive airway pressure (CPAP) device resulted in far greater time spent in the safe SpO₂ range compared with manual oxygen titration, with potential for protection against retinopathy or dangerous episodes of hypoxaemia.⁴¹

In preterm infants in India, rapid feed advancement and early fortification (enteral feed advanced at 25-30 ml/kg/day, fortification at 50 ml/kg/day) resulted in shorter time to full enteral feeding, lower rates of sepsis, and higher weight and head circumference at 12 months of age, compared to slow feed advancement and late fortification (feed advanced at 15-20 ml/kg/day, fortification at 100 ml/kg/day).⁴²

Studies clearly showed that environmental enteric dysfunction (EED) is linked to poor growth and development.⁴³ However trials of interventions to address this (provision of an oral amino acid formulation, low aflatoxin flour)^{44,45} alone did not address the effects of EED. A trial of improved home water and sanitation had a greater effect on weight and linear growth among children with evidence of EED, compared to those children who did not have EED,⁴⁶ suggesting that the underlying environmental causes are fundamental and need to be addressed.

In an RCT among Kenyan pre-school children, the best source of absorbable zinc was not zinc-enriched maize, but maize enriched by household crickets or the chitin skeleton from crickets.⁴⁷

In a non-randomised controlled trial of 8 schools in Pakistan, using a the socio-ecological model to increase physical activity, there were numerous benefits reported in the 4 intervention schools: reduction in fast food consumption, an increase in physical activity frequency, decreased screen time, increased normal sleep duration, and greater reduction in BMI.⁴⁸

In 144 children with septic shock in India, a study comparing two blood pressure targets (5th centile and 50th centile) showed no difference in 28 day mortality, but in the 50th centile group there was use of higher doses and longer durations of noradrenaline, and greater probability of acute respiratory distress syndrome developing.⁴⁹

In a large study of 1204 children in South Africa with non-severe tuberculosis, trialing 4 versus 6 months of TB treatment, there were no differences in TB outcomes between those who were living with HIV and those who were not; 4 months was non-inferior to 6 months in

treating non-severe TB. However, children with HIV had higher rates of anaemia, malnutrition and mortality.⁵⁰ Non-severe pulmonary TB is opacification confined to a single lobe, with no cavities, miliary disease pattern, complex pleural effusions, or significant airway compression. In another trial in South Africa which involved people with TB of all ages, the use of treatment monitors (sequential electronic, telephone and home visit reminders if doses missed) lead to much greater treatment adherence (80% adhered to 80% of doses, compared to 51% adhered to 80% of doses in the standard care group).⁵¹

In a cluster RCT in Cameroon and Uganda, 3-month rifampicin-isoniazid (3RH) regimen administered by community health workers to child TB contacts was safe. Shorter courses of TB preventative therapy and decentralised delivery models may improve effectiveness.⁵²

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Search strategy

("Developing Countries"[Mesh] OR (austere OR limited resource* OR "resource limited" OR low resource* OR transitioning econom* OR lami countr* OR transitional countr* OR "low gdp" OR "low gnp" OR "low gross domestic" OR "low gross national" OR ((emerging OR developing OR "low income" OR "middle income" OR (low AND middle) OR underdeveloped OR "under developed" OR under-developed OR underserved OR "under served" OR under-served OR (less-developed) OR deprived OR poor) AND (countr* OR nation* OR econom* OR population OR world)) OR "third world" OR LMIC OR LMICs) OR "Africa"[Mesh] OR "caribbean region"[Mesh] OR "central america"[Mesh] OR "latin america"[Mesh] OR "mexico"[Mesh] OR "south america"[Mesh] OR "europe, eastern"[Mesh] OR "indian ocean islands"[Mesh] OR "pacific islands"[Mesh] OR "New Guinea"[Mesh] OR India OR Africa OR Asia OR South-America OR Papua-New-Guinea OR Pacific) AND (newborn* OR new-born* OR baby OR babies OR neonat* OR neo-nat* OR infan* OR boy OR boys OR girl OR girls OR child OR children OR childhood OR pediatric* OR paediatric* OR adolescen* OR youth OR youths OR teen OR teens OR teenage*) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized-controlled-trial*[tiab] OR randomised-controlled-trial*[tiab] OR randomized-trial*[tiab] OR randomised-trial*[tiab] NOT (animals[mh] NOT humans[mh]))

The yield from this search from July 1, 2024 to June 30, 2025, was 5855 publications (some duplicates). Of these 607 (10.4%) separate papers are included in this edition.

Acute respiratory infection

(See also: Zinc; Vaccines - Pneumococcal vaccine; Hygiene and environmental health)

Treatment of pneumonia

Pediatrics. 2024 Aug 1;154(Suppl 1):e2024066588G.

doi: 10.1542/peds.2024-066588G.

[Efficacy of Antibiotic Regimens for Pneumonia in Young Infants Aged 0-59 Days: A Systematic Review](#)

[Krysten North](#)^{1,2}, [Alejandro Frade Garcia](#)³, [Mark Crouch](#)⁴, [Spencer Kimsen](#)⁴, [Amber Hoey](#)⁵, [Carrie Wade](#)², [Yumin Kim](#)⁶, [Roger Chou](#)⁷, [Karen M Edmond](#)⁸, [Anne C C Lee](#)^{1,2}, [Chris A Rees](#)⁹

Abstract

Context: Pneumonia is a leading cause of death in young infants.

Objectives: To evaluate the efficacy of different antibiotic regimens to treat young infant pneumonia on critical clinical outcomes.

Data sources: MEDLINE, Embase, CINAHL, World Health Organization (WHO) Global Index Medicus, Cochrane Central Registry of Trials.

Study selection: We included randomized controlled trials of young infants aged 0 to 59 days with pneumonia (population) comparing the efficacy of antibiotic regimens (intervention) with alternate regimens or management (control) on clinical outcomes.

Data extraction: We extracted data and assessed risk of bias in duplicate. We used Grading of Recommendations, Assessment, Development, and Evaluation to assess certainty of evidence.

Limitations: Trials were heterogeneous, which precluded data pooling.

Results: Of 2601 publications screened, 10 randomized controlled trials were included. Seven trials were hospital-based (n = 869) and 3 were nonhospital-based (n = 4329). No hospital-based trials evaluated WHO-recommended first-choice regimens. One trial found the WHO-recommended second-choice antibiotic, cefotaxime, to have similar rates of treatment success as non-WHO-recommended regimens of either amoxicillin-clavulanate (RR 0.99, 95% confidence interval 0.82-1.10) or amoxicillin-clavulanate/cefotaxime (RR 1.02, 95% confidence interval 0.86-1.12). Among 3 nonhospital-based trials comparing oral amoxicillin to alternate regimens to treat isolated tachypnea among infants aged 7-59 days, there were no differences in treatment failure between amoxicillin and alternate regimens. Certainty of evidence was low or very low for all primary outcomes.

Conclusions: We found limited evidence to support the superiority of any single antibiotic regimen over alternate regimens to treat young infant pneumonia.

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[Evaluating Short-Course Antibiotic Therapy for Pediatric Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis](#)

[Erdenetuya Bolormaa](#)¹, [Cho Ryok Kang](#)², [Young June Choe](#)^{3,2}, [Young Yoo](#)^{3,2}, [Jue Seong Lee](#)^{3,2}, [Ji Young Park](#)³, [Seung Ah Choe](#)¹, [Giannoula S Tansarli](#)⁴, [Eleftherios Mylonakis](#)⁵

Abstract

Background: The optimal duration of antibiotic therapy for community-acquired pneumonia (CAP) in children remains uncertain. In this study, we aimed to evaluate whether short-course antibiotic therapy (≤ 6 days) is associated with poor clinical outcomes compared with long-course antibiotic therapy (> 7 days) in children with CAP.

Methods: A comprehensive search was conducted across databases, including PubMed, Embase, Cochrane Library, and KoreaMed. Studies comparing the efficacy and safety of short-course with long-course antibiotic regimens in children with CAP were eligible. We assessed the risk of bias using the RoB 2 and ROBINS-I tools. Study characteristics such as publication year, country, setting, study design and antibiotic regimens were recorded. Pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for clinical outcomes, including clinical cure, treatment failure, total adverse events, serious adverse events, relapse and hospitalization. The primary outcomes were clinical cure and treatment failure. Secondary outcomes included total and serious adverse events, relapse and hospitalization rates.

Results: Seventeen studies comprising 155,944 children met the inclusion criteria, with 15 of these studies being randomized controlled trials. There were no significant differences between short-course and long-course treatments in clinical cure [21,156 patients; RR, 1.01 (95% CI, 0.97-1.05); $P = 0.73$; $I^2 = 81\%$], treatment failure [28,942 patients; RR, 0.88 (95% CI, 0.51-1.51); $P = 0.64$; $I^2 = 94\%$] or total adverse events [24,446 children; RR, 0.94 (95% CI, 0.61-1.44); $P = 0.77$; $I^2 = 90\%$]. However, short-course treatment was associated with fewer serious adverse events [4194 patients; RR, 0.89 (95% CI, 0.79-0.99); $P = 0.04$; $I^2 = 11\%$]. Relapse rates were nominally lower with short-course treatment compared with long-course treatments (5.5% vs. 6.2%; $P = 0.04$). This difference was primarily observed in the subgroup analysis comparing 5-day treatments to ≥ 10 -day treatments. Hospitalization rates were similar between the two groups [122,607 patients; RR, 1.20 (95% CI, 0.85-1.68); $P = 0.29$; $I^2 = 0\%$].

Conclusions: Short-course antibiotic treatment is as effective as long-course treatment for pediatric CAP in terms of clinical cure and treatment failure while resulting in fewer serious adverse events.

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doi: 10.1371/journal.pone.0323353. eCollection 2025.

Societal cost of day-care approach (DCA): A low-cost approach in urban and rural settings for management of childhood severe pneumonia in Bangladesh

[Marufa Sultana^{1,2}](#), [Jennifer Watts¹](#), [Nur H Alam²](#), [Nausad Ali²](#), [Abu S G Faruque²](#), [Sabiha Nasrin²](#), [Mohammad Jobayer Chisti²](#), [George J Fuchs³](#), [Niklaus Gyr⁴](#), [Tahmeed Ahmed²](#), [Julie Abimanyi-Ochom¹](#), [Lisa Gold¹](#)

Abstract

Objective: Childhood severe pneumonia is the leading cause of under-five deaths in Bangladesh. A new day-care management approach (DCA) was implemented in primary-level healthcare facilities in urban and rural areas of Bangladesh. Reliable cost estimates are important to determine the economic viability of the new management approach. The objective of this study were to estimate the mean societal cost per patient for a new Day-care approach (DCA) in managing childhood severe pneumonia, to assess cost variation in urban and rural healthcare settings, and to determine important cost predictors.

Study design: This study was conducted alongside a cluster randomized trial conducted in Bangladesh Children diagnosed with severe pneumonia were enrolled between November 2015 and March 2019. Employing a bottom-up micro-costing approach from a societal perspective, detailed household and provider cost data were collected from sixteen intervention facilities (n = 16). Data collection involved structured questionnaires administered face-to-face with facility staff, interviews with parents/caregivers, and patient record reviews. Analysis measured mean cost and cost variation across socio-economic groups, facility location, clinical variables, and determined cost-sensitive parameters. A p-value of < 0.05 was considered as statistically significant level.

Results: 1,745 children were enrolled, 63% were male, and 57% were less than a year old. The mean societal cost per patient was US\$94.2 (95% CI: US\$92.2, US\$96.3) with a mean length-of-stay (LoS) of 4.1 days (SD $\pm$ 3.0). Costs of medical personnel (US\$32.6), caregiver's productivity loss (US\$26) and medicines (US\$22) were the major cost contributors. Mean cost was significantly higher for urban-located facilities compared to rural (difference US\$17, 95% CI: US\$12.6, US\$20.8). No cost variation was found by age, sex, and clinical variables.

Conclusion: Findings suggest that this novel DCA management approach is a low-cost management option, and particularly beneficial for rural residences and therefore has the potential to reduce the overall cost burden for childhood severe pneumonia management. These findings have implications for policy-making decisions in resource-poor settings for childhood pneumonia management.

J Trop Pediatr. 2025 Feb 5;71(2):fmaf010.

doi: 10.1093/tropej/fmaf010.

Effect of nutritional supplementation with lipid-based therapeutic food on body composition of non-severely malnourished African children aged 6-59 months hospitalized with severe pneumonia

[Damalie Nalwanga^{1,2}](#), [Victor Musiime^{1,3}](#), [Sarah Kiguli¹](#), [Peter Olupot-Olupot^{4,5}](#), [Florence Alaroker⁶](#), [Robert Opoka^{1,7}](#), [Abner Tagoola⁸](#), [Hellen Mnjala⁹](#), [Christabel Mogaka⁹](#), [Eva Nabawanuka¹](#), [Elisa Giallongo¹⁰](#), [Charles Karamagi^{1,11}](#), [André Briend^{12,13,14}](#), [Kathryn Maitland^{9,15}](#)

Abstract

Pneumonia remains an important cause of morbidity and mortality among children in low- and middle-income countries. Poor outcomes are associated with undernutrition. Nutritional supplementation may be beneficial. We examined the effect of supplementation with lipid-based ready-to-use therapeutic food (RUTF) on the body composition of children with severe pneumonia. Non-severely malnourished children (6-59 months) with severe pneumonia enrolled into the Children's Oxygen Administration Strategies and Nutrition trial in Uganda and Kenya, and randomized to receive a diet supplemented with RUTF (500 Kcal/day) for 56 days versus usual diet alone (control) were included. We assessed arm anthropometry and bioimpedance analysis at admission and days 28, 90, and 180 of follow-up. We used mixed effects linear regression to compare body composition between groups. We included 737 participants (369 in intervention; 368 in control group). The median age was 16 months (IQR; 9, 26), and 58.1% were male. Overall, baseline mean arm fat area (AFA), arm muscle area, and arm muscle circumference were 5.8 ± 1.8 cm², 11.6 ± 2.3 cm², and 12.3 ± 1.2

cm², respectively. The mean fat mass and fat-free mass calculated in 116 participants were 5.5 ± 1.5 kg and 5.5 ± 1.5 kg, respectively. There were modest increases in most body composition parameters. RUTF significantly increased AFA at days 28 and 90 but not at day 180 (P-value = .03, .02, and .99, respectively). RUTF did not change other body composition parameters. Despite initial increases in AFA, RUTF did not change the body composition of children with severe pneumonia.

Indian Pediatr. 2025 May;62(5):351-355.

doi: 10.1007/s13312-025-00028-2. Epub 2025 Apr 9.

Oral Selenium as an Adjunct in the Treatment of Acute Lower Respiratory Tract Infections in Children: A Double-Blind Randomized Controlled Trial

[Rubeena Jamir Shaikh¹](#), [Trupti Amol Joshi²](#), [Smita Madhusudan Mundada¹](#), [Shilpa Yashwant Pawar¹](#), [Prabha Bhaskar Khaire More¹](#)

Abstract

Objective: To evaluate the role of oral selenium in clinical recovery of acute lower respiratory tract infections (ALRTI) in under-five children.

Methods: This double-blind, randomized controlled trial included children aged 6 months to 5 years hospitalised with ALRTI at a tertiary care hospital. Participants were randomized in 1:1 ratio to receive oral selenium (20-30 mcg/day) or placebo, once daily until discharge, along with standard treatment. The primary outcome was the time for clinical recovery. The secondary outcomes were the duration of hospital stay, modes of oxygen support required and side effects of selenium.

Results: A total of 60 children were randomized to either groups. The median (IQR) time required for clinical recovery was 72 (54, 144) h in the selenium group and 96 (54, 120) h in the placebo group (P = 0.346). The median (IQR) duration of hospital stay was 6 (5, 7) days and 6 (6, 8) days in the selenium and placebo groups, respectively (P = 0.680). Mechanical ventilation was required in 10 (16.6%) and 21 (35%) children in the selenium and placebo groups, respectively (P = 0.020). No side effects were reported with the intervention.

Conclusions: Oral selenium administered as an adjunct in a daily dose of 20-30 mcg orally for 5-7 days, does not reduce the time needed for clinical recovery or the duration of hospitalization but reduces the need for mechanical ventilation in under-five children with ALRTI.

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doi: 10.7189/jogh.15.04169.

Management of chest indrawing pneumonia in children aged 2-59 months by community-level workers compared to standard care on clinical outcomes: systematic review and meta-analysis

[Barsha Gadapani Pathak^{1,2}](#), [Yasir Bin Nisar³](#), [Uma Chandra Mouli Natchu¹](#), [Rukman Manapurath^{1,2}](#), [Archana Thakur¹](#), [Sarmila Mazumder¹](#), [Temsunaro Rongsen Chandola¹](#), [Bireswar Sinha^{1,4}](#)

Abstract

Background: World Health Organization recommends that children aged 2-59 months, with chest indrawing pneumonia, are treated with a five-day course of oral amoxicillin initiated at a health facility. We synthesised the evidence on the effectiveness and safety of community-

level health care workers (CLHW)-led management compared to standard care at a hospital or health facility among children aged 2-59 months with chest indrawing pneumonia in terms of clinical outcomes.

Methods: We conducted a comprehensive search in PubMed, EMBASE, and Cochrane Central for studies published from January 2000 to August 2024, with no language restriction. The search included quasi and/or randomised controlled trials. We conducted data extraction using the Cochrane checklist, and we used GRADE to assess the quality of the evidence. Given that the included studies were from different settings and used different methods, we applied a random-effects model for data synthesis. The primary outcome was treatment failure by six days of treatment initiation. Secondary outcomes included mortality and other serious adverse events (SAEs) (excluding mortality) by 14 days.

Results: Of the 6883 eligible articles, we included three randomised controlled trials involving 11 779 children aged 2-59 months with chest indrawing pneumonia without danger signs. The CLHW-led management significantly reduced the risk of treatment failure by 34% (relative risk (RR) = 0.66, 95% confidence interval (CI) = 0.44, 0.98; low quality evidence). The RR of mortality for CLHW-led management compared to standard care was RR = 0.85 (95% CI = 0.31, 2.30; low quality evidence). The RR for other SAEs was RR = 1.20 (95% CI = 0.34, 4.26; low quality evidence).

Conclusions: The findings suggest that CLHW-led management may reduce treatment failure rates by day six without any significant differences in mortality or other SAEs compared to standard care. However, given the low certainty of the evidence, these results should be interpreted with caution and more research is required.

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doi: 10.1002/ppul.27465. Online ahead of print.

Six Versus Three Doses of Intrapleural Streptokinase in Childhood Empyema: A Randomized Controlled Trial

[Chirag Thakur¹](#), [Joseph L Mathew¹](#), [Akshay K Saxena²](#), [Archana Angrup³](#), [Ram Samujh⁴](#)

Abstract

Objective: To compare the efficacy and safety of administering six doses of intrapleural streptokinase (SK) versus the conventional three doses, in children with empyema.

Study design: In this open label, placebo-controlled, randomized trial, we enrolled 53 children with empyema, who received three doses of intrapleural SK. Thereafter, those without clinical improvement (n = 34) and those showing clinical improvement but having persistent pleural fluid width > 10 mm on chest ultrasonography (n = 13), were randomized to receive three additional doses of SK, or three doses of placebo (normal saline). The remaining 6 children improved clinically and radiologically, hence were not randomized. The outcomes recorded were cumulative volume of pleural fluid drained, total duration of intercostal drainage, time taken for clinical improvement, duration of hospitalization, proportion of children with treatment failure requiring surgery, and adverse events. Spirometry, 6-min walk test, chest X-ray and ultrasonography were done 3 months following discharge. We analyzed by intention-to-treat.

Results: The baseline characteristics of children who received six versus three doses SK were comparable. There was no statistically significant difference in the cumulative volume of

fluid drained; median (IQR): 810.0 (330.0, 1630.0) [95% CI: 505, 1463] mL versus 530.0 (255.2, 1325.0) [95% CI: 325, 1131] mL, p 0.46. There were no significant inter-group differences in the total duration of intercostal drainage, time taken for clinical improvement, duration of hospitalization, treatment failure, surgical decortication and adverse events.

Conclusion: In children with empyema, intrapleural therapy with six doses of SK is not superior to three doses, although it is safe.

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doi: 10.1016/S2352-4642(25)00067-7.

Efficacy and safety of ziresovir in hospitalised infants aged 6 months or younger with respiratory syncytial virus infection in China: findings from a phase 3 randomised trial with 24-month follow-up

[Han Zhang¹](#), [Wei Zhao²](#), [Xiaoyan Zhang³](#), [Lei Zhang⁴](#), [Run Guo⁵](#), [Han Huang⁶](#), [Li Lin⁷](#), [Feng Liu⁸](#), [Haidan Chen⁹](#), [Fangfang Shen⁵](#), [Jinzhun Wu¹⁰](#), [Xiaowen Huang¹¹](#), [Xiaoping Zhu¹²](#), [Feng Li¹²](#), [Gang Zou¹²](#), [Jason Chien¹³](#), [Michael Humphries¹²](#), [Quan Lu¹⁴](#), [Jim Z Wu¹⁵](#), [Shunying Zhao³](#), [Hanmin Liu¹⁶](#), [Xin Ni³](#); [AIRFLO Study Group](#)

Abstract

Background: Respiratory syncytial virus (RSV) is a particularly dangerous infection in some populations, including very young infants. This study examined the efficacy and safety of ziresovir in hospitalised infants aged 6 months or younger with RSV infection.

Methods: In this double-blind, randomised, placebo-controlled trial conducted across 28 hospitals in China, patients aged 1-24 months hospitalised for virologically confirmed RSV infection were randomly allocated (2:1) to receive ziresovir (10-40 mg by weight twice daily) or placebo orally for 5 days, with 2 years of follow-up. Patients were included if they had a Wang bronchiolitis clinical score (WBCS) of at least 5 at first dosing and were administered their first dose of study drug within 7 days of the onset of symptoms of RSV infection. In this prespecified subanalysis of patients aged 6 months and younger at randomisation, we analysed the primary endpoint (change from baseline in WBCS on day 3 [48 h post-baseline]) in the intention-to-treat infected (ITT-i) population (comprising patients who received at least one dose of study drug and who had PCR-confirmed RSV infection). Safety endpoints were assessed in all patients who received at least one dose. This study is registered with ClinicalTrials.gov ([NCT04231968](#)) and is completed.

Findings: Participants were recruited from Sept 22, 2020, to Jan 19, 2022, and followed up to Feb 4, 2024. Among patients aged 6 months or younger, 188 participants (125 in the ziresovir group and 63 in the placebo group) received at least one dose of study drug and were included in the safety analysis, while the ITT-i population included 150 patients (100 in the ziresovir group and 50 in the placebo group). In the ziresovir group, 33 (26%) of 125 patients were female, 92 (74%) were male, mean age was 3.4 months (SD 1.4), and mean baseline WBCS was 6.8 (SD 1.7). In the placebo group, 15 (24%) of 63 patients were female, 48 (76%) were male, mean age was 3.3 months (1.5), and mean baseline WBCS was 6.9 (1.8). The least-squares mean change in WBCS from baseline to day 3 was -3.5 points (95% CI -3.9 to -3.1) with ziresovir versus -2.2 points (-2.8 to -1.7) with placebo (difference -1.2 [95% CI -1.9 to -0.6], $p=0.0004$). Drug-related treatment-emergent adverse events occurred in 22 (18%) of 125 patients who received ziresovir and seven (11%) of 63 patients who received placebo. No drug-related serious adverse events were observed and no deaths occurred.

Interpretation: Ziresovir had a favourable safety profile and was associated with a significant clinical benefit during the treatment period compared with placebo in patients aged 6 months or younger.

Prevention of pneumonia

Oxygen therapy

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doi: 10.1097/PCC.0000000000003521. Epub 2024 Apr 19.

High-Flow Nasal Cannula Versus Nasal Prong Bubble Continuous Positive Airway Pressure in Children With Moderate to Severe Acute Bronchiolitis: A Randomized Controlled Trial

[Malini Maya¹](#), [Ramachandran Rameshkumar^{1,2}](#), [Tamil Selvan¹](#), [Chinnaiah Govindhareddy Delhikumar¹](#)

Abstract

Objectives: To compare high-flow nasal cannula (HFNC) versus nasal prong bubble continuous positive airway pressure (b-CPAP) in children with moderate to severe acute bronchiolitis.

Design: A randomized controlled trial was carried out from August 2019 to February 2022. (Clinical Trials Registry of India number CTRI/2019/07/020402).

Setting: Pediatric emergency ward and ICU within a tertiary care center in India.

Patients: Children 1-23 months old with moderate to severe acute bronchiolitis.

Intervention: Comparison of HFNC with b-CPAP, using a primary outcome of treatment failure within 24 hours of randomization, as defined by any of: 1) a 1-point increase in modified Wood's clinical asthma score (m-WCAS) above baseline, 2) a rise in respiratory rate (RR) greater than 10 per minute from baseline, and 3) escalation in respiratory support. The secondary outcomes were success rate after crossover, if any, need for mechanical ventilation (invasive/noninvasive), local skin lesions, length of hospital stay, and complications.

Results: In 118 children analyzed by intention-to-treat, HFNC (n = 59) versus b-CPAP (n = 59) was associated with a lower failure rate (23.7% vs. 42.4%; relative risk [95% CI], RR 0.56 [95% CI, 0.32-0.97], p = 0.031). The Cox proportion model confirmed a lower hazard of treatment failure in the HFNC group (adjusted hazard ratio 0.48 [95% CI, 0.25-0.94], p = 0.032). No crossover was noted. A lower proportion escalated to noninvasive ventilation in the HFNC group (15.3%) versus the b-CPAP group (15.3% vs. 39% [RR 0.39 (95% CI, 0.20-0.77)], p = 0.004). The HFNC group had a longer median (interquartile range) duration of oxygen therapy (4 [3-6] vs. 3 [3-5] d; p = 0.012) and hospital stay (6 [5-8.5] vs. 5 [4-7] d, p = 0.021). No significant difference was noted in other secondary outcomes.

Conclusion: In children aged one to 23 months with moderate to severe acute bronchiolitis, the use of HFNC therapy as opposed to b-CPAP for early respiratory support is associated with a lower failure rate and, secondarily, a lower risk of escalation to mechanical ventilation.

BMC Pediatr. 2024 Sep 19;24(1):595.

doi: 10.1186/s12887-024-05058-6.

"Comparison between high-flow nasal cannula (HFNC) therapy and noninvasive ventilation (NIV) in children with acute respiratory failure by bronchiolitis: a randomized controlled trial"

[Ana Carolina Etrusco Zaroni Santos¹](#), [Carolina Marques Caiado²](#), [Alessandra Geisler Daud Lopes²](#), [Gabriela Cunha de França²](#), [Ana Karolina Antunes Eisen³](#), [Danielle Bruna Leal Oliveira^{3,4}](#), [Orlei Ribeiro de Araujo⁵](#), [Werther Brunow de Carvalho⁶](#)

Abstract

Background: The objective of this study was to compare HFNC therapy to noninvasive ventilation (NIV/BiPAP) in children with bronchiolitis who developed respiratory failure. We hypothesized that HFNC therapy would not be inferior to NIV.

Methods: This was a noninferiority open-label randomized single-center clinical trial conducted at a tertiary Brazilian hospital. Children under 2 years of age with no chronic conditions admitted for bronchiolitis that progressed to mild to moderate respiratory distress (Wood-Downes-Férres score < 8) were randomized to either the HFNC group or NIV (BiPAP) group through sealed envelopes. Vital signs, FiO₂, Wood-Downes-Férres score and HFNC/NIV parameters were recorded up to 96 h after therapy initiation. Children who developed respiratory failure despite receiving initial therapy were intubated. Crossover was not allowed. The primary outcome analyzed was invasive mechanical ventilation requirement. The secondary outcomes were sedation usage, invasive mechanical ventilation duration, the PICU LOS, the hospital LOS, and mortality rate.

Results: A total of 126 patients were allocated to the NIV group (132 randomized and 6 excluded), and 126 were allocated to the HFNC group (136 randomized and 10 excluded). The median age was 2.5 (1-6) months in the NIV group and 3 (2-7) months in the HFNC group ($p = 0.07$). RSV was the most common virus isolated in both groups (72% vs. 71.4%, NIV and HFNC, respectively). Thirty-seven patients were intubated in the NIV group and 29 were intubated in the HFNC group (29% vs. 23%, $p = 0.25$). According to the Farrington-Manning test, with a noninferiority margin of 15%, the difference was 6.3% in favor of HFNC therapy (95% confidence interval: -4.5 to 17.1%, $p < 0.0001$). There was no significant difference in the PICU LOS or sedation duration. Sedation requirement, hospital LOS and invasive mechanical ventilation duration were lower in the HFNC group.

Conclusion: HFNC therapy is noninferior to NIV in infants admitted with mild to moderate respiratory distress caused by bronchiolitis that progresses to respiratory failure.

Indian Pediatr. 2025 Jun;62(6):440-450.

doi: 10.1007/s13312-025-00081-x. Epub 2025 Apr 29.

Effectiveness of Bubble Continuous Positive Airway Pressure for Treatment of Children Aged 1-59 Months with Severe Pneumonia and Hypoxemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

[Mohammad Tanashat¹](#), [AlMothana Manasrah²](#), [Omar Abdullah Bataineh³](#), [Ahmad Abdelrazek⁴](#), [Mohamed Abouzid^{5,6}](#)

Abstract

Objective: Continuous positive airway pressure (CPAP) is a standard treatment for children with moderate to severe respiratory distress; however, ventilators are often unavailable in

developing countries. Bubble CPAP (bCPAP) is considered a simple, cost effective and less invasive alternative to CPAP, however, its efficacy has not been assessed for children with pneumonia until recently. This meta-analysis aims to compare the effectiveness of bCPAP with low-flow oxygen for treating severe pneumonia and hypoxemia in children.

Methods: PubMed, EMBASE, Cochrane Library, Web of Science, and CENTRAL were searched to identify eligible randomized controlled trials reported up to March 23, 2024. Outcomes were reported as risk ratios (RRs) or mean difference (MD) and confidence intervals (CIs) using Review Manager software. P value < 0.05 was considered statistically significant.

Results: Three studies with 2030 patients were included and revealed no significant difference between bCPAP and control in overall mortality [RR (95% CI) 0.46 (0.09, 2.32); P = 0.348], death during hospital stay [0.48 (0.02, 9.09), P = 0.619], composite primary outcome [0.48 (0.12, 1.97), P = 0.301], pneumothorax [1.94 (0.16, 23.11), P = 0.601], leaving hospital against medical advice [0.63 (0.16, 2.39), P = 0.489], and length of hospital stay [MD (95%CI) 0.15 days (- 0.66, 0.96), P = 0.706]. Children on bCPAP had significantly fewer events of severe hypoxemia [RR (95% CI) 0.22 (0.10, 0.49), P < 0.001], and less requirement for mechanical ventilation [RR (95% CI) 0.38 (0.15, 0.99), P = 0.048].

Conclusion: bCPAP is not superior to low-flow oxygen for improving survival and reducing hospital stay in children with pneumonia, albeit the need for mechanical ventilation decreases.

Asthma

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Online ahead of print.

[Mobile Direct Observed Therapy \(MDOT\) for Inhaler Therapy in Children With Newly Diagnosed Asthma: A Pilot Study](#)

[Amit Pathania¹](#), [Kana Ram Jat²](#), [Meenakshi Pathania³](#), [Rakesh Lodha⁴](#), [Sushil K Kabra⁴](#)

Abstract

Objective: We aimed to assess the acceptability of Mobile Direct Observed Therapy (MDOT) amongst the parents/caregivers of children with asthma.

Methods: This open-label pilot randomized controlled trial enrolled newly diagnosed children aged 5-15 years with asthma, who were followed up telephonically for six weeks. Parents of children in the intervention arm were requested to record share a video of the metered dose inhaler with spacer (MDI-S) technique of their child on a mobile phone and share it through WhatsApp with investigator who then provided corrective measures as required by text/video message. The children in the control arm continued follow-up telephonically without exchange of any videos for six weeks. The primary outcome measures were the acceptability of MDOT and the effect of such interaction on the correctness of the MDI technique. Secondary outcome measures were the level of asthma control as per GINA guidelines and the caregivers' perception and feedback about MDOT.

Results: A total of 30 children were enrolled, 15 in each arm. Thirteen (86%) parents uploaded good-quality videos. The average number of incorrect steps decreased from 2.64 in the first video to 0.18 after the fourth video and nil after the fifth video in the MDOT group. At six weeks of follow-up, the average number of incorrect steps was significantly lower in the

MDOT group compared to the control group (0 vs 2.9; $P < 0.0001$). The proportion of children having controlled asthma was better in the MDOT group compared to controls (85% vs 70%) ($P = 0.39$). All parents liked MDOT.

Int J Nurs Stud. 2024 Sep 7;160:104905.

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Effectiveness of psychosocial interventions for improving asthma symptoms and parental stress in families of school-age children with asthma: A systematic review and meta-analysis

[Xu Wang¹](#), [Wai Tong Chien²](#), [Yuen Yu Chong³](#)

Abstract

Background: Asthma is a prevalent chronic disease affecting school-age children, with substantial psychosocial implications for children and their parents.

Objectives: This review aimed to synthesise current evidence on the effects of psychosocial interventions for families of school-age children with asthma and investigate the optimal features of effective interventions.

Methods: Embase, MEDLINE, PsycINFO, CINAHL, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, Google Scholar, CNKI, and Wanfang Data were searched from inception to November 2023. Randomised controlled trials (RCTs) examining psychosocial interventions in children aged six to twelve with asthma on asthma symptoms and parental stress were included. Emergency department visits, hospitalisations, lung function, psychological symptoms and health-related quality of life in both children and parents were secondary outcomes. Data were pooled for short-term ($\leq$ three months), medium-term ($>$ three months and $\leq$ six months), and long-term ($>$ six months) follow-ups. Risk of bias was appraised using version 2 of the Cochrane risk of bias tool for randomised trials. Meta-analysis was performed using RevMan 5.4.1.

Results: Seven RCTs with 884 parent-child dyads from two countries were included. Meta-analyses found that psychosocial interventions improved asthma control ($k = 2$, $n = 301$, standardised mean difference [SMD] 0.35, 95 % confidence interval [CI] 0.12 to 0.58, $P = 0.003$), sleep problem ($k = 2$, $n = 149$, SMD -0.47, 95 % CI -0.79 to -0.14, $P = 0.005$), cough ($k = 2$, $n = 149$, SMD -0.97, 95 % CI -1.59 to -0.35, $P = 0.002$), wheezing ($k = 2$, $n = 149$, SMD -0.76, 95 % CI -1.09 to -0.42, $P < 0.0001$), and parental stress ($k = 6$, $n = 813$, SMD -0.32, 95 % CI -0.61 to -0.02, $P = 0.03$), compared to controls in the short term. Subgroup analysis revealed significant effects of psychoeducation, family empowerment interventions, and acceptance and commitment therapy-based interventions on reducing parental stress. No significant intervention effects were observed on parental symptoms of depression at any follow-up. Narrative synthesis indicated that psychosocial interventions may provide benefits in children's health-related quality of life in the short term, parental symptoms of anxiety in the medium term, and activity limitation, cough, and wheezing in the long term. The intervention effects for other reviewed outcomes were inconsistent.

Conclusions: Psychosocial interventions demonstrate possible benefits for families of school-aged children with asthma in asthma symptoms, parental stress, and children's health-related quality of life within three months post-intervention and parental symptoms of anxiety at six months post-intervention. Future research with rigorous design should

investigate the optimal duration, frequency, and intervention approaches of psychosocial interventions.

Matern Child Health J. 2024 Dec;28(12):2115-2125.

doi: 10.1007/s10995-024-03987-3. Epub 2024 Sep 21.

Educational Intervention to Promote Parent/Caregiver Self-Efficacy in the Management and Control of Childhood Asthma: A Randomized Clinical Trial

[Elizamar Regina da Rocha Mendes¹](#), [Kamila Ferreira Lima¹](#), [Ana Lúcia Araújo Gomes²](#), [Emanuella Silva Joventino Melo³](#), [Paulo César de Almeida⁴](#), [Francisca Elisângela Teixeira Lima¹](#), [Leidiane Minervina Moraes de Sabino³](#), [Jardeliny Corrêa da Penha⁵](#), [Lorena Pinheiro Barbosa¹](#)

Abstract

Background: Asthma is a leading cause of pediatric hospitalization and morbidity, necessitating the development of educational interventions for its management and control.

Objective: To evaluate the effectiveness of an educational intervention in promoting parent/caregiver self-efficacy in the management and control of their children's asthma.

Methods: A clinical trial was conducted in Fortaleza, Ceará, Brazil, involving two randomized groups of parents/caregivers of children: the comparison group (CG) (n = 42) and the intervention group (IG) (n = 42). Data collection took place in two phases: the first included face-to-face sessions followed by the educational intervention in the IG, and the second included telephone follow-up. The educational intervention included the use of an educational booklet and a brief motivational interview.

Results: The groups were homogeneous at baseline. After the intervention, the mean self-efficacy scores of the IG were significantly higher than those of the CG ($p < 0.05$), and children whose parents/caregivers were in the CG were 1.43 times more likely to experience an asthma crisis than those in the IG.

Conclusions: The educational intervention proved effective in increasing parent/caregiver self-efficacy in asthma management and control. Furthermore, children whose parents/caregivers did not receive the educational intervention were more likely to experience an asthma crisis.

Arch Dis Child. 2025 Jun 25;archdischild-2024-327452.

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Use of intravenous short-acting beta-2 agonist in addition to standard first-line treatment versus placebo in children and adolescents with acute severe asthma exacerbation: a systematic review and meta-analysis

[Ibtihal Siddiq Abdelgadir¹](#), [Ali Hamud²](#), [Khalid Mudawi³](#), [Adham Alhaji⁴](#), [Aiman Zou Zou⁴](#), [Amjad Tonbari⁴](#), [Naim Alnasif⁴](#), [Ramadan Salem⁴](#), [Salah Alsaleh⁴](#), [Abdul Kareem Pullattayil^{5,6}](#), [Colin Powell⁷](#)

Abstract

Importance: The role of intravenous short-acting beta-2 agonist (SABA) in acute asthma in childhood is unclear.

Objectives: To assess the safety and efficacy of intravenous SABA versus placebo for acute asthma.

Data selection and extraction: We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Web of Science and the Cumulative Index to Nursing and Allied Health Literature up to May 2024. We included only randomised controlled trials (RCTs) and followed the international guidelines for conducting systematic reviews. Outcomes measured were morbidity, escalation of care, length of hospital stay, adverse events, mortality and changes in lung functions.

Results: Four RCTs were included (total participants=183). Intravenous SABA group had better asthma severity scores (risk ratio (RR)=0.38, 95% CI 0.19 to 0.78, $p=0.009$), similar need for mechanical ventilation (RR=0.13, 95% CI 0.01 to 2.42, $p=0.17$), similar escalation of intravenous treatment (RR=1.51, 95% CI 0.60 to 3.82, $p=0.38$), shorter duration of hospital stay (hours) (mean difference (MD)=-18.68, 95% CI -36.76 to -0.61) and less duration of oxygen supplementation (days) (MD=-1.73, 95% CI -3.01 to -0.45, $p=0.008$). Adverse events were tachycardia, hypotension and hypokalaemia. One study reported a single participant with arrhythmia and a non-significant increase in troponin I among the intravenous SABA group.

Conclusion: This review found low-to-moderate certainty evidence that intravenous SABA would improve acute asthma severity with infrequent adverse events reported. However, this evidence is limited due to the limited number of included studies.

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Second-line treatment option for children aged 18 years and under with an acute severe asthma exacerbation: a systematic review and meta-analysis of randomised controlled trials

[Ibtihal Siddiq Abdelgadir¹](#), [Khalid Mudawi²](#), [Ali Hamud³](#), [Amjad Tonbari⁴](#), [Adham Alhaji⁵](#), [Ramadan Salem⁵](#), [Naim Alnasif⁶](#), [Salah Alsaleh⁷](#), [Aiman Zou Zou⁶](#), [Abdul Kareem Pullattayil^{8,9}](#), [Colin Powell¹⁰](#)

Abstract

Importance: Evidence regarding second-line treatment for severe asthma is limited.

Objectives: To evaluate the safety and efficacy of intravenous aminophylline, intravenous short-acting beta agonist (SABA), intravenous magnesium sulphate, intravenous ketamine or subcutaneous adrenaline as a second-line treatment for severe asthma.

Methods: We included only randomised controlled trials (RCTs) and followed the international guidelines for conducting systematic reviews. We performed a comprehensive literature search up to May 2024. Outcomes included morbidity, escalation of care, length of hospital stay, adverse events, mortality and changes in lung functions.

Results: Nine RCTs were included (total participants=546). Compared with other treatments, intravenous aminophylline showed no significant difference in the duration of hospital stay in hours, except for critically ill ventilated patients who had a shorter stay (mean difference (MD)=-12.99, 95% CI -33.13 to 7.15). The need for additional intravenous medications (RR=2.17, 95% CI 0.48 to 9.71) and asthma severity scores postinterventions (MD=0.97, 95% CI -0.91 to 2.85) was similar. More nausea and emesis were observed in the intravenous aminophylline group. The intravenous SABA group showed no difference in hospital stay (MD=-10.12, 95% CI -45.74 to 25.49) or need for ventilation (RR=0.25, 95% CI 0.03 to 2.21). There were no frequent serious adverse events. The intravenous magnesium sulphate group had a lower hospitalisation rate (RR=1.52, 95% CI 1.26 to 1.84), reduced need for additional

intravenous medication (RR=6.30, 95% CI 2.62 to 15.17) and a rapid improvement in asthma severity scores ($p<0.05$).

Conclusion: There is low-to-very-low certainty evidence demonstrating the superiority of any intravenous second-line treatment options for acute asthma.

Arch Dis Child. 2025 Jun 25:archdischild-2024-327492.

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Use of intravenous aminophylline in addition to the standard first-line treatment in children and adolescents with an acute asthma exacerbation: a systematic review and meta-analysis of randomised controlled trials

[Khalid Mudawi¹](#), [Ali Hamud¹](#), [Colin Powell²](#), [Naim Alnasif³](#), [Amjad Tonbari¹](#), [Aiman Zou Zou³](#), [Adham Alhaji⁴](#), [Ramadan Salem⁴](#), [Salah Alsaleh⁴](#), [Abdul Kareem Pullattayil^{5,6}](#), [Ibtihal Siddiq Abdelgadir⁷](#)

Abstract

Importance: The role of intravenous aminophylline in acute asthma in childhood is unclear.

Objectives: To assess the safety and efficacy of intravenous aminophylline for asthma in children.

Methods: From 1966 to May 2024, we searched MEDLINE, Embase, CINAHL, Web of Science and the Cochrane Central Register of Controlled Trials. We included only randomised controlled trials testing standard treatment in combination with aminophylline and followed the international guidelines for conducting systematic reviews. The outcomes measured were morbidity, escalation of care, length of hospital stay, adverse events, mortality and lung functions. We used the random-effects model for data analysis and the fixed-effects model to evaluate heterogeneity.

Results: Nine studies (466 participants) fulfilled our a priori eligibility criteria. No significant difference was found in post-treatment asthma severity score (mean difference (MD)=0.13, 95% CI -0.79 to 1.06, $I^2=0\%$), hospitalisation rate (risk ratio (RR)=0.66, 95% CI 0.27 to 1.59, $I^2=0\%$), paediatric intensive care unit admission (RR=0.73, 95% CI 0.51 to 1.05, $I^2=0\%$), intubation rate (RR=0.09, 95% CI 0.01 to 1.64, $p=0.1$) or length of hospital stay (MD=-3.62, 95% CI -13.05 to 5.82, $I^2=31\%$). Emesis (RR=3.52, 95% CI 2.04 to 6.06, $I^2=0\%$) and nausea (RR=4.92, 95% CI 2.41 to 10.06, $I^2=0\%$) occurred more in the aminophylline group. One study showed improved lung function in the aminophylline group, while others showed no difference.

Conclusion: This review showed limited evidence of the benefit of intravenous aminophylline in managing asthma in most prevention severity parameters. However, lowering the intubation rate and improving lung function deserve more attention.

Arch Dis Child. 2025 Jun 25:archdischild-2024-327486.

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Use of intravenous magnesium sulfate in addition to standard first-line treatment with inhaled/nebulised short-acting beta 2 agonist and systemic steroids in the management of acute asthma exacerbations in children: a systematic review and meta-analyses of randomised controlled trials

[Ali Abdalla Hamud¹](#), [Khalid Mudawi²](#), [Colin Powell³](#), [Salah Alsaleh¹](#), [Ramadan Salem¹](#), [Naim Alnasif¹](#), [Amjad Tonbari¹](#), [Aiman Zou Zou¹](#), [Adham Alhaji¹](#), [Abdul Kareem Pullattayil^{4,5}](#), [Ibtihal Siddiq Abdelgadir⁶](#)

Abstract

Background: The role of intravenous magnesium sulfate in asthma exacerbation is unclear.

Aims: To determine the efficacy and safety of intravenous magnesium sulfate in managing asthma exacerbation in children.

Methods: We searched MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials and the Web of Science up to May 2024. We included randomised controlled trials and followed the international guidelines for conducting systematic reviews. Outcomes included morbidity, escalation of care, length of hospital stay, lung functions, adverse events, and mortality.

Results: Nine studies (total participants=473) were included. Hospitalisation rate and the need for non-invasive ventilation were less among the intravenous magnesium sulfate group (mean difference (MD)=0.70, 95% CI 0.54 to 0.90, I^2 7%, n =115) and (risk ratio (RR)=0.17, 95% CI 0.15 to 0.54, p =0.003, n =143), respectively. Asthma severity scores (MD=-0.18, 95% CI -1.35 to 0.98, I^2 2%, n =115), length of hospital stay (MD=-78.86, 95% CI -200.37 to 42.66, I^2 99%, n =284) and the need for invasive ventilation (RR=0.35, 95% CI 0.11 to 1.17, I^2 0%, n =237) were similar. There was no difference in the Paediatric Intensive Care Unit (PICU) admission rate (p =0.43 n =61). Peak expiratory flow improved in the intravenous magnesium group (p <0.001, n =20). No serious adverse events were reported.

Conclusion: We found low-certainty evidence that intravenous magnesium sulfate results in a lower hospitalisation rate and less need for non-invasive ventilation. Asthma scores, PICU admission, invasive ventilation and length of hospital stay were similar. While the evidence base is weak, the favourable safety profile suggests that intravenous magnesium sulfate can be considered a treatment for asthma exacerbations.

Adolescent health

Overall health and well-being

Public Health. 2024 Dec;237:316-321.

doi: 10.1016/j.puhe.2024.10.040. Epub 2024 Nov 7.

[Effectiveness of health literacy-based motivational interviewing and health education on adolescents' nutrition and exercise behaviors in Türkiye: A randomized controlled trial](#)

[Ayşegül Akca¹](#), [Sultan Ayaz-Alkaya²](#)

Abstract

Objective: To measure the effectiveness of health literacy-based motivational interviewing and health education to improve adolescents' nutrition and exercise behaviors.

Study design: A randomized controlled trial.

Methods: The study was completed with 63 adolescents (aged 14-15 years) of which 21 were in the motivational interviewing group, 21 were in the health education group, and 21 were in the control group. Data collection tools were applied to all groups before the intervention, after the completion of the intervention (post-test), at the third and sixth month. The data were analyzed using Chi-square test and two-way mixed design ANOVA with Bonferroni test.

Results: The mean scores of nutrition and exercise at the post-test, third month, and sixth month of the motivational interviewing and health education groups were significantly higher than the control group. The intervention had a large effect size.

Conclusion: Health literacy-based motivational interviewing and health education were effective in improving nutrition and exercise behaviors among adolescents.

J Med Internet Res. 2025 Mar 10:27:e60102.

doi: 10.2196/60102.

Optimizing Engagement With a Smartphone App to Prevent Violence Against Adolescents: Results From a Cluster Randomized Factorial Trial in Tanzania

[Roselinde Janowski¹](#), [Lucie D Cluver^{1,2}](#), [Yulia Shenderovich^{3,4}](#), [Joyce Wamoyi⁵](#), [Mwita Wambura⁵](#), [David Stern⁶](#), [Lily Clements⁶](#), [G J Melendez-Torres⁷](#), [Lauren Baerecke⁸](#), [Abigail Ornellas⁸](#), [Angelique Nicole Chetty⁸](#), [Jonathan Klapwijk¹](#), [Laetitia Christine⁹](#), [Ateamate Mukabana⁹](#), [Esmee Te Winkel⁶](#), [Anna Booij¹⁰](#), [Gervas Mbosoli⁵](#), [Jamie M Lachman^{1,8,11}](#)

Free article

Abstract

Background: Violence and abuse exert extensive health, social, and economic burdens on adolescents in low- and middle-income countries. Digital parenting interventions are promising for mitigating risks at scale. However, their potential for public health impact hinges on meaningful engagement with the digital platform.

Objective: The objective of this study was to evaluate the impact of 3 intervention design and implementation factors aimed at increasing engagement with a noncommercialized, offline-first smartphone app for caregivers of adolescents in Tanzania, in partnership with the United Nations Children's Fund, the World Health Organization, and the Tanzanian national government.

Methods: Following Multiphase Optimization Strategy (MOST) principles, we conducted a 2×2×2 cluster randomized factorial trial involving caregivers of adolescents aged 10 to 17 years. Caregivers were recruited by community representatives from 16 urban and periurban communities (ie, clusters) in the Mwanza region of Tanzania. Each cluster was randomized to 1 of 2 levels of each factor: guidance (self-guided or guided via facilitator-moderated WhatsApp groups), app design (structured or unstructured), and preprogram digital support (basic or enhanced). Primary outcomes were automatically tracked measures of engagement (app launches, modules completed, and home practice activities reviewed), with secondary outcomes including modules started, time spent in the app, and positive behaviors logged. Generalized linear mixed-effects models assessed the impact of experimental factors on engagement.

Results: Automatically tracked engagement data from 614 caregivers were analyzed, of which 205 (33.4%) were men. Compared to self-guided participants, receiving guidance alongside the app led to significantly more app launches (mean ratio [MR] 2.93, 95% CI 1.84-4.68; P<.001), modules completed (MR 1.29, 95% CI 1.05-1.58; P=.02), modules started (MR 1.20, 95% CI 1.02-1.42; P=.03), time spent in the app (MR 1.45, 95% CI 1.39-1.51; P<.001), and

positive behavior logs (MR 2.73, 95% CI 2.07-3.60; $P < .001$). Compared to the structured design, unstructured design use resulted in significantly more modules completed (MR 1.49, 95% CI 1.26-1.76; $P < .001$), home practice activity reviews (MR 7.49, 95% CI 5.19-10.82; $P < .001$), modules started (MR 1.27, 95% CI 1.06-1.52; $P = .01$), time spent in the app (MR 1.84, 95% CI 1.70-1.99; $P < .001$), and positive behavior logs (MR 55.68, 95% CI 16.48-188.14; $P < .001$). While analyses did not detect an effect of enhanced digital support on directly observed engagement, the combination of enhanced digital support and guidance positively influenced engagement across a range of outcomes.

Conclusions: This study is the first to systematically optimize engagement with a digital parenting intervention in a low- and middle-income country. Our findings offer important learnings for developing evidence-based, scalable digital interventions in resource-constrained settings.

Adolescent mental health

Glob Health Action. 2025 Dec;18(1):2455236.

doi: 10.1080/16549716.2025.2455236. Epub 2025 Feb 3.

[Effectiveness of a resilience, gender equity and mental health group intervention for young people living in informal urban communities in North India: a cluster randomized controlled trial](#)

[Varadharajan Srinivasan^{1,2}](#), [Miguel San Sebastián³](#), [Samson Rana¹](#), [Pooja Bhatt¹](#), [Greg Armstrong⁴](#), [Smita Deshpande⁵](#), [Kaaren Mathias^{1,6}](#)

Abstract

Background: Mental health problems are the leading cause of disease burden among young people in India. While evidence shows that youth mental health and resilience can be improved with group interventions in school settings, such an intervention has not been robustly evaluated in informal urban settings.

Objective: This study aimed to evaluate whether the Nae Disha 3 group intervention could improve youth resilience, mental health and gender equal attitudes among disadvantaged young people from low-income urban communities in India.

Methods: This cluster randomised controlled trial used an analytic sample of 476 adolescents and young adults aged 11-25 years from randomised clusters in urban Dehradun, India. The 251 intervention group participants were 112 boys and 139 girls, and the 225 young people in the wait-control group were 101 boys and 124 girls. Five validated tools measuring resilience gender equity and mental health were filled by participants at three different points in time.

Results: Difference in difference (DiD) analysis at T2 showed that scores improved among girls in intervention group, for adjusted model, resilience (DiD = 4.12; 95% CI: 2.14, 6.09) and among boys, for resilience (DiD = 5.82; 95% CI: 1.57, 9.74).

Conclusions: The Nae Disha 3 intervention among disadvantaged urban youth moderately improved resilience for both young men and women, though it did not significantly impact mental health, self-efficacy, or gender-equal attitudes. We establish potential merit for this

approach to youth mental health but recommend further research to examine active ingredients and the ideal duration of such group interventions.

J Affect Disord. 2025 Aug 1:382:399-406.

doi: 10.1016/j.jad.2025.04.128. Epub 2025 Apr 23.

[A culturally sensitive act-belong-commit-based school intervention reduces the burden of anxiety and depression in adolescents: A pilot cluster-randomized trial from Uganda](#)

[Davy Vancampfort](#)¹, [Philip B Ward](#)², [Japheth Nkiriyehe Kwiringira](#)³, [Tine Van Damme](#)⁴, [Simon Rosenbaum](#)⁵, [James Mugisha](#)⁶

Abstract

Introduction: Schools can be pivotal in addressing mental health challenges, especially in low-income settings like Uganda. However, randomized controlled trials tailored to cultural and contextual factors are scarce. This pilot cluster-randomized trial examines the impact of a culturally sensitive Act-Belong-Commit (ACT) intervention, combined with physical activity, sleep hygiene and stress management measures on anxiety and depression among Ugandan adolescents attending secondary school.

Methods: A total of 2598 adolescents (1295 intervention; 1303 control; 1199 boys [46.1 %]; mean age 16.3 ± 1.0 years) from four secondary schools were randomized by school to either a 12-week, weekly two-hour teacher- and peer-led ACT intervention or a care-as-usual control. Anxiety (GAD-7) and depression (PHQ-9-A) were measured at baseline and immediately post-intervention. Childhood trauma (CTQ-SF), self-reported health, wealth, and food security were assessed at baseline. Linear mixed modeling was used to evaluate intervention effects.

Results: At baseline, the mean GAD-7 score was 6.4 ± 4.4 and PHQ-9-A was 7.4 ± 5.1. The intervention group showed greater improvements in mental health, with moderate effects on anxiety (Cohen's d = 0.50, 95 % CI = 0.42-0.57) and small effects on depression (Cohen's d = 0.44, 95 % CI = 0.36-0.52). Moderation analyses were based on pre-specified baseline variables.

Conclusion: This pilot trial provides preliminary evidence that a culturally adapted ACT intervention combined physical activity, sleep hygiene and stress management measures may be a promising whole-school approach to reduce anxiety and depression in adolescents. Further trials with more clusters are needed.

J Affect Disord. 2025 May 1:376:84-91.

doi: 10.1016/j.jad.2025.02.001. Epub 2025 Feb 3.

[A sport-for-protection program reduces anxiety and depression in youth affected by displacement: A randomized controlled trial of the Game Connect program in Uganda](#)

[Kathleen Latimer](#)¹, [Rita Larok](#)², [John Paul Nyeko](#)³, [Lydia Murungi](#)³, [Ronald Luwangula](#)⁴, [Bashir Lukungu](#)⁵, [Jeroen Carrin](#)¹, [Robinah Nannungi](#)³, [Daniel Ojara Comboni](#)³, [Esther Nanfuka Kalule](#)⁵, [Simon Rosenbaum](#)⁶, [Davy Vancampfort](#)⁷

Abstract

Introduction: Youth affected by displacement are at risk for anxiety and depression. Supervised sport programs are a potentially effective strategy, however trials from displacement contexts are lacking.

Methods: Displaced youth and youth from host communities in five humanitarian settings across Uganda aged 15 to 24 years, and with at least mild anxiety and/or depression, were randomized to a 16-week sport-for-protection program or a wait-list control condition. The Generalized Anxiety Disorder-7 (GAD-7) and Patient Health Questionnaire-9, adolescent version (PHQ-9-A) were assessed pre- and post-intervention. Linear mixed modelling was conducted.

Results: 834 young people were randomized (421 in the experimental and 413 in the control condition; median age = 19.0 years; 46.9 % boys; 14.7 % with self-reported or observed disability; 29.5 % from host community and 70.5 % displaced youth). Large effect sizes were found for the anxiolytic (Cohen $d = 1.21$, 95%CI = 1.06-1.36) and antidepressant (Cohen $d = 1.32$, 95%CI = 1.17-1.47) effects of sport-for-protection in comparison with a wait-list control condition. In subgroup analyses, large effect sizes were observed in displaced youth (Cohen d GAD-7 = 1.15, 95%CI = 1.0-1.32; Cohen d PHQ-9-A = 1.33, 95%CI = 1.16-1.51) and youth from host communities (Cohen d GAD-7 = 1.34, 95%CI = 1.06-1.61; Cohen d PHQ-9-A = 1.30, 95%CI = 1.03-1.58); in boys (Cohen d GAD-7 = 1.23, 95%CI = 1.03-1.43; Cohen d PHQ-9-A = 1.36, 95%CI = 1.14-1.58) and girls (Cohen d GAD-7 = 1.11, 95%CI = 0.89-1.33; Cohen d PHQ-9-A = 1.26, 95%CI = 1.05-1.47); and in those with (Cohen d GAD-7 = 0.99, 95%CI = 0.61-1.37.; Cohen d PHQ-9-A = 1.53, 95%CI = 1.12-1.94) and without disability (Cohen d GAD-7 = 1.24, 95%CI = 1.08-1.49; Cohen d PHQ-9-A = 1.28, 95%CI = 1.12-1.44).

Conclusion: Sport-for-protection is an effective stand-alone or adjunctive intervention to reduce symptoms of anxiety and depression among young people affected by displacement within humanitarian settings.

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Effectiveness of a group psychological intervention to reduce psychosocial distress in adolescents in Pakistan: a single-blind, cluster randomised controlled trial

[Syed Usman Hamdani¹](#), [Zill-E Huma²](#), [Aiysha Malik³](#), [Asad Tamizuddin-Nizami⁴](#), [Hashim Javed²](#), [Fareed Aslam Minhas²](#), [Mark J D Jordans⁵](#), [Marit Sijbrandij⁶](#), [Nadia Suleman²](#), [Um-Ul Baneen²](#), [Richard Allan Bryant⁷](#), [Mark van Ommeren³](#), [Atif Rahman⁸](#), [Duolao Wang⁹](#)

Abstract

Background: Emotional problems in adolescents living in low-income and middle-income countries (LMICs) remain largely unaddressed; key reasons include a scarcity of trained mental health professionals and unavailability of evidence-based, scalable psychological interventions. We aimed to evaluate the effectiveness of a non-specialist-delivered, group psychological intervention to reduce psychosocial distress in school-going adolescents in Pakistan.

Methods: In a two-arm, single-blind, cluster randomised controlled trial, eligible public school clusters from a rural subdistrict of Gujar Khan, Rawalpindi, Pakistan, were randomised (1:1, stratified by sex) using permuted block randomisation into intervention (n=20) and wait-list control (n=20) groups. Adolescents aged 13-15 years who provided informed assent and caregivers' consent were screened for psychosocial distress using the youth-reported Pediatric Symptoms Checklist (PSC; total psychosocial distress scores from 0 to 70), and those scoring 28 or more and their caregivers were enrolled into the trial. Adolescents in the intervention group received seven weekly group sessions and their

caregivers received three biweekly group sessions in school settings from trained non-specialists. The primary outcome was change from baseline in the total PSC scores at 3 months post-intervention. The trial was registered prospectively with the International Standard Randomised Controlled Trial Number registry, ISRCTN17755448.

Findings: From the 40 school clusters that were included, 282 adolescents in the intervention group and 284 adolescents in the wait-list control group were enrolled between Nov 2 and Nov 30, 2021. At 3 months, adolescents in the intervention group had significantly lower mean total score on the PSC compared with adolescents in the control group (mean difference in change from baseline 3.48 [95% CI 1.66-5.29], $p=0.0002$, effect size 0.38 [95% CI 0.18-0.57]; adjusted mean difference 3.26 (95% CI 1.46-5.06), $p=0.0004$, effect size 0.35 (0.16-0.55). No adverse events were reported in either group.

Interpretation: The group psychological intervention most likely represents a feasible and effective option for adolescents with psychosocial distress in school settings.

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Effect of three group interventions on psychosocial functioning in adolescents exposed to interpersonal violence in Chile: A pilot clinical trial

[Cristóbal Guerra¹](#), [Emily P Taylor²](#), [Valeria Arredondo³](#)

Abstract

Background: In Chile demand for specialist care following exposure to interpersonal violence (IPV) in youth far exceeds capacity. Group interventions may improve access to care for youth.

Objective: To evaluate the effectiveness and acceptability of two low-intensity group interventions: Trama Focused Cognitive Behavioral Therapy (TF-CBT); Interpersonal Psychotherapy (IPT); and treatment as usual, Art therapy-based support (ATBS). Outcomes measured were post-traumatic stress symptoms, depression, interpersonal functioning and affect regulation.

Participants and setting: Participants were 67 Chilean youth aged 13-17 years, victims of IPV on a waiting list to receive specialist individual intervention.

Methods: Using a randomised controlled trial design, participants were randomly assigned to one of the interventions. Self-report measures were completed at 5 timepoints between baseline and follow up eight weeks after intervention ended. Dropout rates and attendance were also analysed.

Results: TF-CBT showed significant decreases for PTSD ($d = 0.91$) and depression ($d = 0.77$) symptoms, sustained at follow-up with affect regulation problems also showing significant decrease from baseline ($d = 0.43$). IPT showed significant decreases in PTSD symptoms ($d = 0.64$) and affect regulation problems ($d = 0.66$), both sustained at follow-up. ATBS showed statistically significant decrease for PTSD ($d = 0.79$) and interpersonal problems ($d = 0.65$) but only change in PTSD was sustained at follow-up. There were no significant differences in dropout or attendance between the interventions.

Conclusion: Group interventions provide a viable and effective first-phase option for reducing psychological distress in IPV-exposed youth in high-demand contexts. Effectiveness may be further improved through the more active involvement of parents and carers.

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Effectiveness of barber-facilitated "Doing What Matters in Times of Stress" intervention among urban literate youths in Western Kenya: A cluster randomised trial

Protus Musotsi Yabunga^{1,2,3}, Phiona Naserian Koyiet⁴, Harriet Musimbi¹, Ken Simiyu¹, Elijah Chemorei¹, Peter Koskei⁵, Stella Evangelidou², Mary Nangukhula¹

Abstract

Youth with mental health disorders are a growing concern in Kenya, yet services are inaccessible. "Doing What Matters in Times of Stress (DWM)" is a scalable self-help intervention that can be delivered by lay providers. However, its effectiveness in low-resource, non-humanitarian settings is unknown. We evaluated the effectiveness of barber-facilitated DWM intervention in reducing psychological distress, while improving functioning and resilience among literate urban youths in Western Kenya. This cluster randomised trial involved 15 barbers in intervention group and 15 in the waiting-list control. Barbers were from 30 barbershops in Bungoma and Kitale towns, aged 18-30 years and literate in English. Using mental health-themed music as an entry point, barbers recruited youth aged 18-29 years, fluent in English, and had mild or moderate psychological distress and functioning difficulties. Intervention participants received DWM guide and/or audios, supported by barbers through three individual sessions. Waiting-list control participants received the intervention after five weeks. Outcome measures included Patient Health Questionnaire (PHQ-9), Generalised Anxiety Disorder-7 (GAD-7), Perceived Stress Scale (PSS-10) and psychological outcome profiles (PSYCHLOPS). We analysed data using cumulative ordinal multilevel models. Between 31st July 2023-27th January 2024, 330 eligible youths were enrolled (n = 158, from 11 intervention arm barbers and n = 172 from 10 control barbers). Post-intervention, intervention group youth had 95%, 82% and 71% lower odds of higher depression (AOR = 0.05, 95% CI 0.02-0.10, p < 0.001), anxiety (AOR = 0.18, 95% CI 0.09-0.34, p < 0.001) and stress (AOR = 0.29, 95% CI 0.12-0.71, p = 0.007), respectively. They also had 86% lower odds of higher self-identified problem severity scores (AOR = 0.14, 95% CI = 0.08 -0.27, p < 0.001) and 4.3 times higher odds of higher resilience levels (AOR = 4.33, 95% CI 2.00-9.36, p < 0.001). DWM effectively reduced psychological distress and improved resilience among youths. Barbershops are promising community places for mental health promotion. Long-term, multi-site studies are required to assess outcome sustainability and scalability.

Asian J Psychiatr. 2024 Sep 21;102:104248.

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Effectiveness of mental health literacy intervention and contact-based education on knowledge, attitude, and stigma towards mental health among secondary school students in Chennai, South India: A cluster randomized controlled trial

M Suresh Kumar¹, Hanisha Arulvendan², G Sanjana², B Priyadarshni², Chiranjeevi Arumugam², Jothilakshmi Durairaj², Fredric Azariah³, Moitreyee Sinha³, Vijaya Raghavan⁴, R Thara²

Abstract

Background: Global trends indicate a rise in mental health disorders among youth, prompting need for effective interventions. Mental health literacy interventions have demonstrated benefits such as improved knowledge, treatment understanding, help-seeking behaviors, and stigma reduction. This study aimed to assess the impact of a comprehensive mental health literacy program on knowledge, attitudes, and stigma related to mental health among secondary school students in Chennai.

Methods: Cluster-randomized controlled trial was conducted among students from four secondary schools. Randomization was at cluster level to minimize contamination. Participating schools provided consent, and all ninth-grade students were invited to participate. Written informed consent was obtained from parents/guardians, and assent was obtained from students. There were no specific exclusion criteria, except for students who declined to participate. Analyses were performed using intention-to-treat principles, with multiple imputation for missing outcome data.

Results: After adjusting for cluster effects, the intervention group showed a significant improvement in attitude scores compared to the control group (mean difference 0.85, 95 % CI: 0.32-1.39, $p = 0.002$). However, no significant differences were observed between the two groups in terms of knowledge and stigma.

Conclusion: The findings suggest that delivering a mental health literacy curriculum alongside contact-based education involving individuals with lived experiences of mental disorders positively influences students' attitudes toward mental health. Although no significant changes were observed in knowledge and stigma levels, the integration of mental health literacy programs with personal narratives from those with lived experiences holds promise for addressing mental health stigma and promoting positive attitudes among school students.

Sci Rep. 2024 Sep 28;14(1):22412.

doi: 10.1038/s41598-024-68709-9.

Exploring the efficacy of memory specificity training on depression among Iranian adolescents: a comparative analysis of online vs. in-person delivery

Mohsen Salamat¹, Alireza Moradi², Jafar Hasani¹, Sharareh Farahimanesh³, Fateme Ayatmehr¹, Hanieh Yavarzadeh¹, Laura Jobson⁴

Abstract

Depression in adolescence is common worldwide, with the burden being highest in low- and middle-income countries. This study assessed the efficacy of in-person Memory Specificity Training (MeST) and computerized MeST (c-MeST) as cognitive training programs aimed at addressing depression among Iranian adolescents. A secondary aim was to evaluate the efficacy of MeST and c-MeST on autobiographical memory specificity, emotion regulation and cognitive control. Ninety Iranian male adolescents (aged 13-18 years) with depression were randomly assigned to three groups; MeST group ($n = 30$), c-MeST group ($n = 30$) and the non-active control group ($n = 30$). Participants completed the Beck Depression Inventory-II, Autobiographical Memory Test, Cognitive Emotion Regulation Questionnaire, Wisconsin Card Sorting Test and Stroop Color and Word Test. The groups underwent either MeST and c-MeST. All the assessments were re-conducted after the intervention (post-intervention) and at 1-month post-intervention (follow-up). The in-person MeST group exhibited significantly higher autobiographical memory specificity at post-intervention and follow-up compared to the c-MeST group. Both groups demonstrated significantly lower levels of depression at

post-intervention and follow-up. Both groups showed improvements in emotion regulation and cognitive control, which were found to mediate improvements in depression symptomatology. c-MeST and MeST appear promising brief interventions for the treatment of depression among adolescents in Iran.

J Pediatr (Rio J). 2024 Jul-Aug;100(4):367-376.

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Substance use and adolescent mental health during the COVID-19 pandemic in Brazil: a longitudinal approach

[Rodrigo Garcia-Cerde¹](#), [Gabriela A Wagner¹](#), [Juliana Y Valente¹](#), [Zila M Sanchez²](#)

Abstract

Objective: To describe the changes in alcohol and drug use by Brazilian adolescents during the COVID-19 pandemic (April-August 2021), and to analyze the relationship between alcohol use changes and psychiatric symptomatology.

Methods: A secondary analysis with a longitudinal approach was performed with data from a cluster-randomized controlled trial, conducted in 73 public middle schools in three Brazilian cities, to evaluate the effectiveness of a drug use prevention program. The sample included 535 students (61% girls; $M_{age} = 15.2$ years). Data were collected pre-intervention (February-March 2019), after 9 months (November-December 2019), and after 26 months (April-August 2021), when the students were in their first year of high school. The authors analyzed drug use prevalence (alcohol, binge drinking, tobacco, inhalants, marijuana, cocaine, and crack) in a lifetime, past year, and past month periods, and the association between alcohol use change subsamples with psychiatric symptoms. Logistic regressions were adjusted by sex, age, socioeconomic status, city, and group (control and intervention).

Results: The present findings suggest that the COVID-19 pandemic led to a decrease in past-year substance use and in past-month substance use frequency, despite the gradually increased (but decelerating) prevalence of lifetime use. However, some adolescents initiated, maintained, or increased the frequency of their alcohol use. Mainly, they were more likely to present behavioral problems, as well as symptoms of inattentive hyperactivity, and peer and emotional problems.

Conclusions: Despite the extensive decline in substance use during the pandemic period, these results suggest an association between previous mental health conditions and behavioral risk factors, leading to increased alcohol consumption and behavioral disorders manifestations.

J Am Acad Child Adolesc Psychiatry. 2024 Jul;63(7):708-719.

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Integrating Youth Readiness Intervention and Entrepreneurship in Sierra Leone: A Hybrid Type II Cluster Randomized Trial

[Jordan A Freeman¹](#), [Jordan C Farrar²](#), [Matias Placencio-Castro²](#), [Alethea Desrosiers³](#), [Robert T Brennan⁴](#), [Nathan B Hansen⁵](#), [Adeyinka M Akinsulure-Smith⁶](#), [Shaobing Su²](#), [Joseph Bangura⁷](#), [Theresa S Betancourt⁸](#)

Abstract

Objective: Conflict-affected youth are at risk for poor psychological and social outcomes, yet few receive mental health services. Strategies to expand access and sustain evidence-based interventions (EBIs) across novel delivery platforms must be tested. The present study was a hybrid type II implementation-effectiveness trial using a cluster randomized design. The primary goal was to evaluate feasibility and impact of using the collaborative team approach to deliver the Youth Readiness Intervention (YRI), an EBI, integrated into a youth entrepreneurship program (ENTR) with quality control in post-conflict Sierra Leone.

Method: Youth were screened and randomly assigned to control, ENTR, or combined YRI and ENTR (YRI+ENTR). Implementation outcomes were dissemination and implementation indicators, competence, and fidelity. Effectiveness outcomes were emotion regulation, psychological distress, and interpersonal functioning. Secondary outcomes were third-party reporter assessments of youth functioning and behavior.

Results: Data were collected and analyzed from 1,151 youth participants and 528 third-party reporters. Scores on implementation constructs, competence, and fidelity demonstrated acceptable intervention response and quality. YRI+ENTR participants showed overall improvements in depression ($\beta = -.081$, 95% CI -0.124 to -0.038, $d = -0.154$) and anxiety ($\beta = -.043$, 95% CI -0.091 to -0.005, $d = 0.082$) symptoms compared with control participants. Community leaders indicated that YRI+ENTR participants demonstrated improvements in overall work or training performance compared with control participants ($\beta = -.114$, 95% CI 0.004 to 0.232, $d = 0.374$).

Conclusion: Integration of EBIs such as the YRI into youth employment programs has the potential to address limited reach of EBIs in conflict and post-conflict settings. A collaborative team implementation approach can facilitate integration and fidelity.

Adolescent sexual and reproductive health

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doi: 10.1016/j.eclim.2024.102934. eCollection 2024 Dec.

[Effectiveness of economic support, comprehensive sexuality education and community dialogue on early childbearing and sitting for grade nine exams among adolescent girls in rural Zambia: a cluster randomised trial](#)

[Ingvild Fossgard Sandøy^{1,2}](#), [Mweetwa Mudenda^{1,2,3}](#), [Hanne Keyser Hegdahl^{1,2}](#), [Joseph Mumba Zulu^{1,4}](#), [Taran Grønvik^{1,2}](#), [Ecloss Munsaka^{1,5}](#), [Choolwe Jacobs^{1,4}](#), [Joar Svanemyr^{1,2,6}](#), [Bertil Tungodden^{1,6,7}](#), [Astrid Blystad^{1,2}](#), [Linda Kampata Olowski^{1,2,4}](#), [Mpundu Chikoya Makasa^{1,4}](#), [Karen Marie Moland^{1,2}](#), [Ottar Mæstad^{1,6}](#), [Amani Thomas Mori^{1,2,6}](#), [Knut Martin Fylkesnes^{1,2}](#), [Patrick Musonda^{1,2,4}](#)

Abstract

Background: Adolescent pregnancies pose a risk to young mothers and their babies. In Zambia, one third of 18-year-old girls have given birth. Poverty, low secondary school enrolment, misinformation, and community norms contribute to early childbearing. We assessed the effectiveness of economic support alone and combined with comprehensive sexuality education (CSE) and community dialogue on childbearing and sitting for grade nine exams among girls.

Methods: This cluster randomised trial had one control and two intervention arms. In 2016, 157 rural schools (units of randomisation) were included, and girls in grade seven were eligible. After recruitment, schools were stratified by district and randomised (ratio 31:63:63). In one arm, girls and their guardians were offered economic support. Another arm combined CSE and community dialogues with the economic support. The interventions were implemented for 27 months, and the participants were followed for another 2 years. The primary outcomes were *birth within 8 months of the end of the intervention period*, *birth before the 18th birthday*, and *sitting for grade nine exams*. The trial is registered with ISRCTN (ISRCTN12727868).

Findings: Between 3rd March and 15th July 2016, 4922 girls were recruited, with 999 randomised to the control, 2004 to the economic and 1919 to the combined arm. The combined support gave a moderate reduction in the incidence of birth within eight months of the intervention period's end (risk difference (RD) -0.042 (95% CI -0.084, -0.0003), possibly a minimal reduction in birth before the 18th birthday (RD -0.010 (95% CI -0.053, 0.032), and a substantial increase in sitting for grade nine exams (RD 0.17 (95% CI 0.11, 0.22). The economic support alone tended to give slightly smaller effects.

Interpretation: Our findings suggest that a combination of economic support, CSE and community dialogue may give small reductions in adolescent childbearing. The same interventions can increase completion of basic education.

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Effect of a digital school-based intervention on adolescent family planning and reproductive health in Rwanda: a cluster-randomized trial

[Rebecca Hémono^{#1}](#), [Emmyson Gatara^{#2}](#), [Laetitia Kayitesi²](#), [Lauren A Hunter³](#), [Laura Packel³](#), [Nicole Ippoliti⁴](#), [Diego Cerecero-García⁵](#), [David Contreras-Loya^{6,7}](#), [Paola Gadsden⁸](#), [Sergio Bautista-Arredondo⁹](#), [Felix Sayinzoga²](#), [Michael Mugisha¹⁰](#), [Stefano M Bertozzi^{3,9,11}](#), [Rebecca Hope⁴](#), [Sandra I McCoy³](#)

Abstract

We conducted a cluster-randomized hybrid effectiveness-implementation study of CyberRwanda, a digital family planning and reproductive health intervention for Rwandan adolescents. Sixty schools were randomized 1:1:1 to control or to one of two implementation models-self-service (self-guided access on tablets) or facilitated (peer-led clubs plus tablet access) with no masking. Eligible participants were aged 12-19 years, in secondary school levels 1 or 2, and willing to provide consent or assent/parental consent and contact information for follow-up. In 2021, 6,078 randomly selected adolescents were enrolled. At 24 months, 91.3% of participants were retained and included in the primary intention-to-treat analyses (control, n = 1,845; self-service, n = 1,849 and facilitated, n = 1,858). There were no adverse events related to the study. CyberRwanda did not affect the primary outcomes of modern contraceptive use (prevalence ratio (PR) = 1.04; 95% confidence interval (CI) = 0.76, 1.42), childbearing (PR = 1.33; 95% CI = 0.71, 2.50) and HIV testing (PR = 1.00; 95% CI = 0.91, 1.11) in the full sample. Significantly higher modern contraceptive use observed in the CyberRwanda facilitated arm in a prespecified analysis of sexually active participants suggests that longer-term evaluation is needed to examine effects as more of the study population becomes sexually active and has increased demand for contraception.

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doi: 10.1016/S2214-109X(24)00373-5. Online ahead of print.

Effect of a community-based intervention for sexually transmitted infections on population-level prevalence among youth in Zimbabwe (STICH): a cluster-randomised trial

[Chido Dziva Chikwari¹](#), [Ethel Dauya²](#), [Victoria Simms³](#), [Katharina Kranzer⁴](#), [Tsitsi Bandason²](#), [Anna Machiha⁵](#), [Owen Mugurungi⁵](#), [Primrose Musiyandaka²](#), [Tinashe Mwaturura²](#), [Nkazimulo Tshuma⁶](#), [Sarah Bernays⁷](#), [Constancia Mavodza⁸](#), [Mandikudza Tembo⁹](#), [Kevin Martin¹⁰](#), [Constance R S Mackworth-Young¹¹](#), [Joanna Busza¹²](#), [Suzanna C Francis¹³](#), [Richard J Hayes¹³](#), [Rashida A Ferrand¹⁰](#)

Abstract

Background: Young people are at particularly high risk of acquiring sexually transmitted infections (STIs). We conducted a trial to investigate the effect of a community-based intervention that included STI screening among youth on population-level prevalence of STIs in Zimbabwe.

Methods: STICH was a parallel-arm, cluster-randomised controlled trial nested within CHIEDZA, a trial of community-based integrated HIV and sexual and reproductive health services for youth in Zimbabwe. STICH was conducted in Harare and Bulawayo provinces with eight clusters in each province, randomised 1:1 to control (existing health services) or to the intervention: community-based screening and treatment for Chlamydia trachomatis and Neisseria gonorrhoeae (males and females) and Trichomonas vaginalis (females only) offered over 12 months to intervention cluster residents aged 16-24 years who were attending CHIEDZA. Outcomes were ascertained through a population-level survey immediately after the intervention period, which included young people aged 18-24 years who lived in randomly selected households in each of the 16 clusters. The primary outcome was population prevalence of any (one or more) of the three STIs; secondary outcomes were prevalence of each of the three STIs. The STICH trial is registered with ISRCTN registry, ISRCTN15013425, and the CHIEDZA trial is registered with ClinicalTrials.gov, [NCT03719521](#).

Findings: From Oct 6, 2021, to March 8, 2022, 6361 randomly sampled young people were recruited into the outcome survey (median age 20 years [IQR 19-22], 3500 female and 2101 male, 3066 in intervention clusters and 3295 in control clusters). 5601 participants were included in the primary outcome analysis (2756 in intervention clusters and 2845 in control clusters). In the intervention clusters, 612 (22.2%) of 2756 participants reported that they had attended CHIEDZA and 298 (10.8%) had been tested for C trachomatis and N gonorrhoeae. In the control clusters, 113 (4.0%) of 2845 participants had attended CHIEDZA and 40 (1.4%) had been tested for C trachomatis and N gonorrhoeae. In the outcome survey, the cluster-level geometric mean prevalence of the primary outcome (any of C trachomatis, N gonorrhoeae, and T vaginalis) was 19.07% (geometric standard deviation [GSD] 1.20) in the intervention arm versus 19.95% (GSD 1.10) in the control arm (risk ratio [RR] 0.93 [95% CI 0.78-1.10]; p=0.35). There was no difference between arms in geometric mean prevalence of C trachomatis (12.86% [GSD 1.14] in the intervention arm vs 12.94% [GSD 1.15] in the control arm, RR 0.97 [95% CI 0.84-1.11]; p=0.60) or T vaginalis (7.06% [GSD 1.48] vs 6.20% [1.38], RR 1.09 [95% CI 0.74-1.60]; p=0.66). N gonorrhoeae prevalence was significantly lower in the intervention arm, with a 43% risk reduction (geometric mean 1.65% [GSD 1.77] vs 2.87% [1.43], RR 0.57 [95% CI 0.34-0.96]; p=0.036).

Interpretation: Our study showed high population prevalence of curable STIs. Community-based STI screening appeared to reduce population-level prevalence of N gonorrhoeae, but not of C trachomatis or T vaginalis, probably due to low intervention coverage. Future research is needed on the effects of screening interventions on morbidity, antimicrobial resistance, and re-infection rates.

BMC Womens Health. 2025 Mar 14;25(1):119.

doi: 10.1186/s12905-025-03647-w.

Effectiveness of an empowerment-based self-defense program among South African girls: results from a cluster-randomized control trial in schools

Miriam Hartmann^{1,2}, Shepherd Mutangabende³, Stephen Nash⁴, Erica N Browne⁵, Abigail Hatcher⁶, Anna E Kågesten⁷, Sarah T Roberts⁵

Abstract

Empowerment-based self-defense (ESD) programs have proven effective in preventing sexual violence (SV) among girls in diverse settings, yet their effectiveness in South Africa remains unexplored. In this hybrid type 1 cluster-randomized controlled trial, we assessed the impact and implementation of the COVID-adapted 'No Means No' intervention, an ESD program to prevent SV among girls aged 10-19 in Gqeberha, South Africa. Fifteen schools were randomly assigned to one of three trial arms: an arm receiving intervention delivered to girls-only, one receiving interventions delivered to girls and boys separately, or to serve as controls in a 1:1:1 ratio. Surveys were conducted at baseline, 3, 6, and 12 months. The primary outcome was past-year SV exposure among girls, including harassment or rape. Generalized Estimating Equation models compared the two intervention arms to the control, and each intervention arm to the control. Implementation data consisted of intervention attendance logs, quarterly implementation reports, and in-depth interviews with school stakeholders. We enrolled 1,540 from 14 schools, of whom 1,250 provided primary outcome data. The average age was 13 years and 83% identified as Black. At baseline, 35% of girls reported past-year SV, and 33% did during follow-up. The intervention did not significantly reduce SV compared to the control (adjRR 1.24, 95% CI 0.96, 1.69; $p = 0.08$). Exploratory analyses examined the effects on secondary outcomes (rape, offline, and online sexual harassment), and on intermediate outcomes (e.g., knowledge and attitudes) with only knowledge of self-defense differing between intervention and control (coefficient 0.42, 95% CI 0.16, 0.68; $p = 0.007$). Implementation data revealed barriers to implementing in schools post-COVID, including limitations on allotted time and lack of whole-school buy-in. Improved school awareness, willingness to disclose violence, and reductions in bullying were described as impacts of the intervention by stakeholders. While the lack of reduction in SV may point towards areas for improvement, numerous contextual and implementation factors may also have influenced results. Future trials should utilize implementation science methods to improve delivery and rigorously evaluate ESD interventions' impact on disclosure, acknowledging the complexity of assessing their effects on various facets of SV.

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The impact of the SKILLZ intervention on sexual and reproductive health empowerment among Zambian adolescent girls and young women: results of a cluster randomized controlled trial

[Lila A Sheira¹](#), [Chama Mulubwa²](#), [Calvin Chiu³](#), [Jenala Chipungu²](#), [Chelsea Coakley^{4,5}](#), [Helene Smith⁶](#), [Ushma D Upadhyay⁷](#), [Chansa Chilambe²](#), [Besa Chibwe²](#), [Jake M Pry^{2,8}](#), [Boyd Mkandawire⁹](#), [Maggie Musonda⁹](#), [Carolyn Bolton Moore²](#), [Jenny Liu³](#)

Abstract

Background: Zambian adolescent girls and young women (AGYW, age 15–24) experience a disproportionate burden of HIV and unintended pregnancy. Sports-based interventions, which affect sexual health behaviors via improving sexual and reproductive empowerment, may be an innovative and effective approach for promoting HIV and unintended pregnancy prevention. We sought to evaluate the impact of a peer-led, sports-based intervention on sexual and reproductive empowerment among in-school Zambian adolescent girls and young women.

Methods: Data come from the ‘SKILLZ’ study, a cluster randomized controlled trial evaluating the impact of a peer-led, sports-based health education program. Sexual and reproductive empowerment, a secondary outcome of SKILLZ, was measured via the 23-item Sexual and Reproductive Empowerment for adolescents and young adults scale (range 0–92, higher = more sexual and reproductive empowerment) three times over approximately 24 months. We conducted a difference-in-differences analysis to evaluate intervention impact over time.

Results: The study enrolled 2,153 AGYW (1134 intervention; 1019 control) across 46 secondary schools in Lusaka. Median age at baseline was 17; participants were largely unmarried (96%), with 20% reporting any sexual activity. By endline, nearly 40% reported being sexually active. Between baseline and midline, attending an intervention school was associated with a 6.21-point increase in overall score calculated using the imputed sample (standard error [SE]: 0.75, $p < 0.001$) compared to being in a control school (6.75% change). At endline, being in an intervention school was associated with a 5.12-point increase in the Sexual and Reproductive Empowerment overall score (SE: 0.71, $p < 0.001$; 5.57% change)). Among sexually active AGYW, being in an intervention school was associated with a 7.78-point (SE: 1.17, $p < 0.001$) and 4.64-point increase (SE: 0.93, $p < 0.001$) from the baseline to the midline and endline rounds, respectively (8.46% and 5.04% change, respectively).

Conclusion: The intervention moderately impacted Sexual and Reproductive Empowerment scores; results were magnified among sexually active AGYW. Given adolescence is a critical period for sexuality and gender programming, as well as for sexual debut, empowerment interventions at schools may support downstream sexual health behaviors that will impact the life-course of AGYW.

AIDS Educ Prev. 2025 Jul;37(3):218-236.

doi: 10.1521/aeap.2025.37.3.218.

Integrating a Nurse-Led Sexual and Reproductive Health Program Among Adolescents Living With HIV in Nigeria: Randomized Controlled Trial

[Gift Onyinye Christopher¹](#), [Candan Ozturk²](#)

Abstract

This study examines the impact of a nurse-led sexual and reproductive health (SRH) intervention on the knowledge and attitudes of adolescents living with HIV (ALHIV). Using a randomized controlled trial design, 50 participants (25 control, 25 intervention) were recruited, with 47 completing the study between October 2023 and April 2024. The intervention group received four interactive sessions covering personal hygiene, contraceptive use, STI prevention, and risky behaviors. Baseline assessments showed no significant difference between groups ($t = -1.411, p = .300$). However, post-intervention analysis revealed a significant improvement in SRH knowledge and attitudes in the intervention group ($t = 5.467, p < .001$). Participants also showed increased comfort discussing SRH with nurses ($\chi^2 = 22.17, p < .001$), greater willingness to disclose HIV status ($\chi^2 = 7.69, p = .021$), and better understanding of STI testing importance ($\chi^2 = 18.694, p < .001$). These findings support integrating nurse-led SRH programs into adolescent HIV care to improve outcomes.

PLoS One. 2024 Aug 22;19(8):e0302523.

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Menstrual hygiene management interventions and their effects on schoolgirls' menstrual hygiene experiences in low and middle countries: A systematic review

Balem Demtsu Betsu¹, Araya Abrha Medhanyie², Tesfay Gebregzabher Gebrehiwet², L Lewis Wall^{3,4,5}

Abstract

Background: Inadequate menstrual hygiene management can result in physical, social, psychological, and educational challenges for schoolgirls. To address these issues, researchers have conducted intervention studies, but the impact on school attendance has varied. This review has systematically collected and evaluated evidence about the effects of menstrual hygiene interventions on schoolgirls.

Method: A systematic search of the literature was done and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement). Both peer-reviewed journals and gray literature were searched using PubMed and Google Scholar. The search included individual, or cluster randomized controlled trials, and quasi-experimental studies, and covered the period from the date of indexing until January 3, 2023.

Result: A review of sixteen trial studies showed that menstrual hygiene interventions have a positive effect on schoolgirls' school attendance, performance, and dropout rates, as well as on their menstrual knowledge, attitudes, practices, and emotional well-being. There was a low to medium risk of bias in most of the studies. Additionally, the literature overlooked the impact of interventions that involve parental and male engagement, interventions correcting community misperceptions about menstruation, and the impact of infrastructure improvements on water, sanitation, and hygiene.

Conclusion: Interventions aimed at improving menstrual hygiene management can enhance schoolgirls' educational outcomes, and can improve their menstrual knowledge, attitudes, and practices by helping them manage their periods more effectively. Most interventions have focused on the provision of menstrual products and menstrual education but have neglected improvements in the physical environment at home and school and the social norms surrounding menstruation. Trial studies should take a holistic approach that

considers the total socio-cultural environment in which menstrual hygiene management takes place, thus enabling stakeholders and policymakers to develop sustainable, long-term solutions to these problems

J Adolesc Health. 2025 May;76(5):879-888.

doi: 10.1016/j.jadohealth.2024.12.018. Epub 2025 Feb 11.

Effect of a Multicomponent Intervention to Improve Menstrual Health and Hygiene and School Attendance Among Adolescent Girls in the Gambia (MEGAMBO Trial)

[Vishna Shah¹](#), [Wolf Schmidt¹](#), [Bakary Sonko²](#), [Edrisa Sinjanka²](#), [Francois Mendy³](#), [Julie Hennegan⁴](#), [Penelope Phillips-Howard⁵](#), [Belen Torondel⁶](#)

Abstract

Purpose: Evidence on the effect of menstrual health and hygiene (MHH) interventions on education is scarce. This trial assessed the effect of a multicomponent intervention on school attendance, urogenital health, and other wellbeing outcomes among schoolgirls in rural Gambia.

Methods: A cluster-randomised controlled trial was conducted between July 2019 and December 2020 in 50 villages across 2 regions of The Gambia, selecting one school per village. Using restricted randomisation, half of the villages received a 3-month NGO-led intervention, which included Peer education camps, Mother's outreach sessions, Community meetings and improving school water, sanitation, and hygiene (WASH). The other 25 villages received no intervention. The primary outcome was self-reported schoolgirls' absenteeism of at least one-day due to last period. Secondary outcomes included: urinary tract infections measured with symptoms and biochemical markers, reproductive tract infections symptoms, menstruation-related wellbeing, social support and knowledge, attitudes, and practices toward menstruation. All menstruating schoolgirls 13 years and older were eligible for outcome assessment. We analyzed data on an intention-to-treat basis.

Results: Outcome assessment included 3556 schoolgirls (1832 [51.5%] in the intervention group and 1724 [48.5%] in the control group). Self-reported school absenteeism was only slightly lower in the intervention arm than the control arm (15.6% vs. 17.1%, risk difference = -1.4%, 95% CI = -4.6%-1.9%). The intervention had no effect on urogenital health but had broad positive effects on menstrual knowledge, attitudes, wellbeing, and social support.

Discussion: The multicomponent MHH intervention had no effect on absence due to last period, but achieved improvements in MHH knowledge, experiences, and needs.

Reprod Health. 2025 Apr 7;22(1):48.

doi: 10.1186/s12978-025-02005-1.

Enhancing reproductive health among adolescent girls in India: results of an individualized RCT to study the efficacy of the go Nisha go mobile game

[Aparna Raj¹](#), [Lalita Shankar²](#), [Anvita Dixit^{2,3}](#), [Ananya Saha⁴](#), [Madhusudana Battala⁴](#), [Nizamuddin Khan⁴](#), [Kavita Ayyagari²](#), [Niranjan Saggurti⁴](#), [Susan Howard^{2,5}](#)

Abstract

Background: Adolescent girls in India face significant barriers to accessing sexual and reproductive health (SRH) information and services. Digital interventions, particularly mobile-based ones, promise to deliver SRH education in a fun and engaging manner. These

can be offered privately directly to the adolescent, allowing players to 'experience' the outcomes of their choices, receive tailored feedback, and the option to 'try again'.

Methods: This study evaluated the efficacy of "Go Nisha Go®" (GNG), a low-end smartphone-based digital game for adolescent girls in India, using a two-armed, encouragement-led, randomized controlled trial (RCT). The study involved 1950 participants from Patna, Jaipur, and Delhi NCR. The intervention group received encouragement to play GNG, while the control group did not. Key constructs measured included menstrual health management (MHM), contraception knowledge, and agency. Data were collected at baseline and a ten-week follow-up.

Results: The intervention group showed significant improvements in various MHM parameters, contraception knowledge, and agency outcomes compared to the control group. Overall, 1697 out of 1993 participants completed the study after ten weeks (85%). The intervention group's awareness of menstrual hygiene products increased from 33 to 92%, while comprehensive knowledge of oral contraceptive pills (OCPs) rose from 2 to 17% ($p < 0.0001$). Confidence in negotiating contraception use increased from 60 to 85% ($p < 0.0001$), and the attitude of refusing sex when not ready improved from 61 to 85% ($p < 0.0001$). The subjects in the game group showed high levels of satisfaction with the app, with 74% discussing the game with others and 66% recommending it. The belief in negotiating marriage decisions with parents also improved more in the intervention group than in the control group.

Conclusion: The findings of the first-ever RCT outcome evaluation for a digital mobile game app for enhancing SRH education among adolescent girls in low-resource settings support the efficacy of digital games for health like GNG. The game's engaging and interactive format effectively communicated complex and sensitive SRH information, empowered participants, and encouraged ($p < 0.0001$) critical health behaviors through informed decision-making. Future studies could explore the long-term sustainability of behavior changes induced by such interventions and their effectiveness across different settings and populations.

BMJ Open. 2024 Dec 5;14(12):e087438.

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Factors associated with declining a menstrual cup among female students and their parents in Ugandan secondary schools: a cross-sectional study

[Levicatus Mugenyi^{1,2}](#), [Mandikudza Tembo^{2,3}](#), [Kate Andrews Nelson²](#), [Katherine A Thomas²](#), [Catherine Kansiime⁴](#), [Stephen Lagony⁴](#), [Alex Muleyi Mpaata⁴](#), [Sophie Belfield⁵](#), [Shamirah Nakalema⁵](#), [Agnes Akech⁵](#), [Belen Torondel-Lopez⁶](#), [Helen A Weiss^{7,8}](#)

Abstract

Introduction: A greater choice of menstrual products may improve menstrual health (MH). This study assessed factors associated with declining consent to receive a menstrual cup by parents and female students participating in a MH intervention trial in Ugandan schools.

Methods: We analysed baseline data from a cluster-randomised trial evaluating the effectiveness of a multicomponent MH intervention among female students in 60 Ugandan secondary schools. Parental consent and student assent to receive a menstrual cup and training on its use was sought separately from consent from other trial activities. Random-effects logistic regression models were used to estimate adjusted OR (aOR) and 95% CIs for

factors associated with (i) parents or guardians declining the cup and (ii) students declining the cup using hierarchical conceptual frameworks.

Results: The baseline trial population comprised 3705 post-menarchal students (mean age 15.6 (SD 0.9 years), of whom 2048 (55.3%) were day students. Among the parents of the 3635 participants aged <18 years, 1566 (43.1%) declined consent for their student to receive the cup. This was higher in Wakiso District than in Kalungu District (52.9% vs 8.0%, $p<0.001$). Parental decline of the cup differed by ethnicity, and this association varied between districts ($p=0.004$). Overall, 20.5% students declined the cup (Kalungu 21.1%, Wakiso 20.2%, $p=0.62$). Student decline of the cup was higher among day than boarding students (aOR=1.40, 95% CI 1.07 to 1.84), those with academic performance above the median score (aOR=1.29, 95% CI 1.01 to 1.65), those whose menstrual practice needs score was above the median (aOR=1.36, 95% CI 1.08 to 1.72) and those with more negative attitudes to MH (aOR=1.46, 95% CI 1.16 to 1.83).

Conclusion: Among Ugandan students and their parents, declining consent to receive a menstrual cup varied by district and ethnicity as well as academic performance and menstrual-related factors. A contextual understanding of the barriers for uptake of the menstrual cup is needed to guide future interventions.

Lancet Glob Health. 2025 May;13(5):e888-e899.

doi: 10.1016/S2214-109X(25)00007-5.

Effects and costs of a multi-component menstrual health intervention (MENISCUS) on mental health problems, educational performance, and menstrual health in Ugandan secondary schools: an open-label, school-based, cluster-randomised controlled trial

[Kate A Nelson¹](#), [Stephen Lagony²](#), [Catherine Kansiime³](#), [Belen Torondel⁴](#), [Clare Tanton⁵](#), [Denis Ndekezi²](#), [Levicatus Mugenyi²](#), [Ratifah Batuusa²](#), [Christopher Baleke²](#), [Katherine A Thomas⁶](#), [Titus Ssesanga²](#), [Robert Bakanoma²](#), [Prossy Namirembe²](#), [Aggrey Tumuhimbise²](#), [Beatrice Nanyonga²](#), [Rodah Nambi²](#), [Edward Obicho²](#), [Denis Ssenyondwa²](#), [Daria Bucci⁵](#), [Sophie Belfield⁷](#), [Agnes Akech Ocen⁷](#), [Shamirah Nakalema⁷](#), [Connie Alezuyo⁸](#), [Fred Matovu⁹](#), [Stella Neema¹⁰](#), [Nambusi Kyegombe¹¹](#), [Giulia Greco⁵](#), [John Jerrim¹²](#), [Chris Bonell¹³](#), [Janet A Seeley⁵](#), [Helen A Weiss⁶](#)

Abstract

Background: Menstrual health is a human rights issue, affecting many aspects of life including mental health, wellbeing, and education. We assessed the effectiveness and costs of a school-based, multi-component menstrual health intervention (MENISCUS) to improve mental health problems and educational performance among in-school adolescents.

Methods: We conducted a parallel-arm, cluster-randomised trial in secondary schools in Wakiso and Kalungu districts in Uganda. Schools were eligible for inclusion if they had both male and female students; senior 1-4 classes; day or mixed day and boarding students; at least minimal water, sanitation, and hygiene (WASH) facilities; and enrolments of 50-125 female Senior 1 students in Wakiso district and 40-125 female Senior 1 students in Kalungu district. Schools were randomised (1:1) to the intervention or control condition, stratified by district and baseline mean school examination score. The intervention included creating action groups, strengthening teacher-delivered puberty education, distributing menstrual kits, supporting student-led drama skits, providing pain-management strategies, and improving school water and sanitation facilities. The control condition was provision of printed government menstrual health materials. Schools, participants, and implementors,

including the study clinician who monitored adverse events, could not be masked to allocation status. Primary outcomes were mental health problems using the Strength and Difficulties Questionnaire (SDQ) Total Difficulties Score and independently assessed educational performance at individual level, assessed in all female participants at endline. We estimated cluster-intention-to-treat intervention effects using mixed-effects models accounting for school clustering and adjusted for randomisation strata and baseline school-level means of outcomes. The study was registered at the ISRCTN registry, ISRCTN45461276 and is completed.

Findings: 60 randomly selected schools (44 from Wakiso and 16 from Kalungu) were randomly assigned (30 per group) to the intervention or the control group, and none withdrew. Between March 21 and July 5, 2022, 3841 female students participated in baseline assessments (89.7% of those eligible) and between June 5 and Aug 22, 2023, 3356 participated in endline assessments (1666 in the control group and 1690 in the intervention group). Female participants had a median age of 16 years (IQR 15-16). At endline, there was no evidence of a difference in mental health problems (mean SDQ score, 10.8 in the intervention group vs 10.7 in the control group; adjusted mean difference [aMD] 0.05 [95% CI -0.40 to 0.50]) nor educational performance (mean z score, 0.20 in the intervention group vs 0.12 in the control group; aMD 0.05 [95% CI -0.10 to 0.19]), despite improvements to menstrual health. The annual implementation cost was US\$85 per Senior 2 female student. One participant had a serious adverse event (severe anaemia secondary to excess vaginal bleeding), which was deemed to be possibly related to the intervention.

Interpretation: Improving multiple dimensions of menstrual health in secondary schools in Uganda is important for health and human rights but is not sufficient to improve mental health or educational performance over 1 year.

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doi: 10.1186/s12978-024-01901-2.

Acceptability of and experiences with menstrual hygiene cups among adolescent girls and young women aged 15-24 in two communities in Lusaka, Zambia: an exploratory study nested in the Yathu Yathu trial

[Melleh Gondwe¹](#), [Melvin Simuyaba²](#), [Mwelwa Phiri²](#), [Chisanga Mwansa²](#), [Albertus Schaap^{2,3}](#), [Lucheka Sigande²](#), [Kwame Shanaube²](#), [Sian Floyd³](#), [Sarah Fidler⁴](#), [Helen Ayles^{2,5}](#), [Musonda Simwinga²](#), [Bernadette Hensen^{5,6}](#)

Abstract

Background: Menstrual cups could be a sustainable menstrual material for adolescent girls and young women (AGYW) in sub-Saharan Africa. Yathu Yathu was a cluster-randomized trial of community-based delivery of HIV and sexual and reproductive health services to young people in Lusaka, Zambia. Among services available through the intervention were menstrual products, including menstrual cups. We explored knowledge of menstruation and menstrual products, acceptability, and experiences of using cups among AGYW aged 15-24. We share lessons learned on how to distribute cups through community-based strategies to AGYW in urban communities.

Methods: Through community-based, peer-led spaces (hubs), AGYW could access menstrual products, including pads and menstrual cups. We conducted four focus group discussions,

two with AGYW aged 15-19 (n = 9) and 20-21 (n = 8) who had accessed different menstrual products through Yathu Yathu and two with AGYW aged 15-19 (n = 5) and 20-24 (n = 9) who had accessed menstrual cups. Four interviews were conducted with four AGYW (15-19, n = 2; 20-24, n = 2) who had accessed cups, and four with two AGYW who were enrolled in a qualitative cohort. Data were analyzed thematically.

Results: 'Surprise' and 'fear' were initial reactions from most AGYW who saw the cups for the first time at Yathu Yathu hubs. Misconceptions that cups cause cancer and fears that they could get stuck in the vagina, cause sore, vagina enlargement, and loss of virginity were raised by AGYW. The desire to try the cup, use an alternative menstrual product and information gained at the hubs facilitated access. Use of the cup was comfortable, and cups were said to be cost-effective and durable. Advantages over pads included: the absence of odor, easy to maintain, and environmentally friendly: "it is hygienic, and it is even easy to maintain". Challenges included pain, discomfort, and failure to or incorrectly inserting the cup at initial use. When faced with challenges using the cup, AGYW reported going back to the hub for additional information and demonstrations on use.

Conclusion: Despite concerns, misconceptions and initial challenges, cups were acceptable among AGYW. Free distribution of cups provides an opportunity to address menstrual health challenges among AGYW. However, as a new product, there is need to increase awareness and provide detailed information on use.

Holist Nurs Pract. 2024 Nov-Dec;38(6):361-370.

doi: 10.1097/HNP.0000000000000661. Epub 2024 Jul 22.

The Effect of Yoga on Premenstrual Distress, Quality of Life, and Stress Level

Meryem Erdoğan^{1,2,3}, Şenay Ünsal Atan^{1,2,3}, İrem Şenyuva^{1,2,3}

Abstract

The study aims to evaluate the effect of yoga on the premenstrual syndrome, perceived stress level and the quality of life. The study was conducted as a randomized controlled trial at a university in Turkey. A yoga group = 39, a control group = 41, total of n = 80 female students participated in the study. In the study, firstly, the preview was made, then the yoga group was applied two days a week for eight weeks, the second follow-up was made after the application, and lastly, the last follow-up was made in the 24th week. Four questionnaire surveys were applied on students. When the yoga group compared with the control group in terms of premenstrual syndrome, the quality of life and perceived stress level in the 2nd follow-up, a statistically significant decrease was found in the mean between the menstrual and premenstrual period, and the quality of life increases in the yoga group compared to the control group students. Practicing yoga in university students with premenstrual syndrome reduced premenstrual symptoms and raised quality of life. Yoga can be recommended to girls with premenstrual syndrome (PMS) to reduce PMS and improve quality of life.

Reprod Health. 2025 Feb 21;22(1):28.

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Contraceptive decision-making and its association with contraceptive use among married adolescent girls in Niger

[Jay G Silverman¹](#), [Shweta Tomar²](#), [Mohamad I Brooks³](#), [Sani Aliou³](#), [Nicole E Johns²](#), [Sneha Challa²](#), [Holly Baker Shakya²](#), [Sabrina C Boyce^{2,4}](#), [Anita Raj^{2,5,6}](#)

Abstract

Objective: Niger has among the highest rates of child marriage and lowest rates of modern contraceptive use in the world. This study analyzes the association between contraceptive decision-making and contraceptive use among married adolescent girls in rural Niger, including multiple assessments of decision-making and consideration of overt vs. covert contraceptive use.

Methods: We analyzed cross-sectional survey data collected from married adolescent females (n = 823) participating in the third round of data collection (October-November 2019) for the cluster-randomized controlled trial of a family planning intervention study. Contraceptive decision-making measures assessed participants' (a) participation in contraceptive decision-making, (b) final say in decision-making in case of spousal disagreement, and (c) satisfaction with participation in decision-making. Outcomes include contraceptive use ever categorized based on whether use was overt (with husband's knowledge) or covert (without husband's knowledge). Adjusted multinomial logistic regression models were used to test the associations between each decision-making item and each type of contraceptive use.

Results: Over half of participants reported ever using a contraceptive (59%) and that their husbands were the sole decision-makers regarding contraceptive use (60%). Adolescents' participation in decision-making was negatively associated with overt contraceptive use (ARRR = 0.41; 95%CI = 0.19-0.91) and positively associated with covert contraceptive use (ARRR = 8.76; 95%CI = 2.45-31.30). Women reporting joint decision-making were more likely to report covert use vs. no use (ARRR = 3.20; 95%CI = 1.14-8.99). Women having final say in contraceptive decision-making in case of disagreements were more likely to report covert contraceptive use over no use (ARRR = 9.14; 95%CI = 3.17-26.40). Women's satisfaction with decision-making was positively associated with contraceptive use ever (AOR = 2.72; 95%CI = 1.80-4.16), and overt (ARRR = 2.68; 95%CI = 1.75-4.01) and covert contraceptive use (ARRR = 10.9; 95%CI = 2.16-54.80).

Conclusion: Male control over decision-making and female satisfaction with decision-making are associated with greater contraceptive use. Findings indicate that women's control over decision-making, and its relation to contraceptive use, is complex and requires more nuanced understanding for married adolescents.

Adolescent pregnancy and child marriage

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Effectiveness of a nurse-led family empowerment program to improve the quality of life among pregnant adolescents: A randomized controlled trial

[Shurouq Ghalib Qadous^{1,2}](#), [Sopen Chunuan¹](#), [Warangkana Chatchawet¹](#)

Abstract

Objective: The present study examined the effects of a nurse-led family empowerment program on the quality of life of Palestinian pregnant adolescents.

Methods: This was a randomized controlled trial with a two-group pre-/post-test design. The sample consisted of 58 pregnant adolescents recruited from six governmental primary health care clinics in Palestine. Participants were randomly allocated in equal numbers to either the control group (n = 29), which received routine care, or the experimental group (n = 29), which received both routine care and the study program. Data collection instruments included a demographic form and the WHO Quality of Life-BREF (WHOQoL-BREF). Data were collected twice: at 32 or 33 weeks' gestation to establish a baseline and at 36 or 37 weeks' gestation post-test. Statistical analyses were performed and included descriptive statistics, chi-square and t-tests.

Results: The study findings indicated a significant increase in the mean quality of life scores of the experimental group in the post-test compared to the pre-test ($P < 0.001$). Additionally, pregnant adolescents in the experimental group demonstrated significantly higher post-test QoL scores than those in the control group ($P < 0.001$).

Conclusion: The nurse-led family empowerment program emerges as a viable and efficacious alternative intervention for improving the quality of life among Palestinian pregnant adolescents.

EClinicalMedicine. 2024 Nov 15;78:102934.

doi: 10.1016/j.eclim.2024.102934. eCollection 2024 Dec.

Effectiveness of economic support, comprehensive sexuality education and community dialogue on early childbearing and sitting for grade nine exams among adolescent girls in rural Zambia: a cluster randomised trial

[Ingviold Fossgard Sandøy^{1,2}](#), [Mweetwa Mudenda^{1,2,3}](#), [Hanne Keyser Hegdahl^{1,2}](#), [Joseph Mumba Zulu^{1,4}](#), [Taran Grønvik^{1,2}](#), [Ecloss Munsaka^{1,5}](#), [Choolwe Jacobs^{1,4}](#), [Joar Svanemyr^{1,2,6}](#), [Bertil Tungodden^{1,6,7}](#), [Astrid Blystad^{1,2}](#), [Linda Kampata Olowski^{1,2,4}](#), [Mpundu Chikoya Makasa^{1,4}](#), [Karen Marie Moland^{1,2}](#), [Ottar Mæstad^{1,6}](#), [Amani Thomas Mori^{1,2,6}](#), [Knut Martin Fylkesnes^{1,2}](#), [Patrick Musonda^{1,2,4}](#)

Abstract

Background: Adolescent pregnancies pose a risk to young mothers and their babies. In Zambia, one third of 18-year-old girls have given birth. Poverty, low secondary school enrolment, misinformation, and community norms contribute to early childbearing. We assessed the effectiveness of economic support alone and combined with comprehensive sexuality education (CSE) and community dialogue on childbearing and sitting for grade nine exams among girls.

Methods: This cluster randomised trial had one control and two intervention arms. In 2016, 157 rural schools (units of randomisation) were included, and girls in grade seven were eligible. After recruitment, schools were stratified by district and randomised (ratio 31:63:63). In one arm, girls and their guardians were offered economic support. Another arm combined CSE and community dialogues with the economic support. The interventions were implemented for 27 months, and the participants were followed for another 2 years. The primary outcomes were *birth within 8 months of the end of the intervention period*, *birth before the 18 th birthday*, and *sitting for grade nine exams*. The trial is registered with ISRCTN (ISRCTN12727868).

Findings: Between 3rd March and 15th July 2016, 4922 girls were recruited, with 999 randomised to the control, 2004 to the economic and 1919 to the combined arm. The combined support gave a moderate reduction in the incidence of birth within eight months of the intervention period's end (risk difference (RD) -0.042 (95% CI -0.084, -0.0003), possibly a minimal reduction in birth before the 18th birthday (RD -0.010 (95% CI -0.053, 0.032), and a substantial increase in sitting for grade nine exams (RD 0.17 (95% CI 0.11, 0.22). The economic support alone tended to give slightly smaller effects.

Interpretation: Our findings suggest that a combination of economic support, CSE and community dialogue may give small reductions in adolescent childbearing. The same interventions can increase completion of basic education.

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doi: 10.1016/S0140-6736(25)00454-4. Online ahead of print.

Community-based mentoring to reduce maternal and perinatal mortality in adolescent pregnancies in Sierra Leone (2YoungLives): a pilot cluster-randomised controlled trial

Cristina Fernandez Turienzo¹, Lucy November², Mangenda Kamara³, Osman Conteh⁴, Philemon Kamara⁵, Appiah M Kingsford⁴, Peter J S Koroma⁴, Michael Munu⁴, Alexandra E Ridout², Betty Sam⁴, Paul T Seed², Suzanne Thomas⁴, Prince T Williams⁵, Andrew H Shennan², Jane Sandall²; CRIBS Collaborative Group

Abstract

Background: Sierra Leone has very high maternal and neonatal mortality rates, and a large proportion of these deaths occur in adolescents, a particularly vulnerable group, and is usually driven by poverty, lack of education, and sparse employment opportunities. We evaluated the feasibility and potential effects of a community-based mentoring intervention from pregnancy up to 1 year after birth to inform a subsequent larger trial aiming to reduce mortality among adolescent girls and their newborns (2YoungLives).

Methods: We conducted a parallel-arm, pilot, hybrid implementation-effectiveness cluster randomised controlled trial of the introduction of the 2YoungLives intervention as an adjunct to maternity care in rural and urban communities served by 12 peripheral health units in five districts of Sierra Leone. Clusters were randomly allocated 1:1. All pregnant adolescent girls aged younger than 18 years living in those cluster communities and presenting for maternity care were eligible. The primary outcome was a composite of maternal and perinatal deaths (including stillbirths and neonatal deaths), assessed in all randomly allocated participants who remained in follow-up. The trial was prospectively registered (ISRCTN32414369).

Findings: Between July 4, 2022, and Nov 30, 2023, 673 girls were included in the trial; six clusters with 372 girls were allocated to 2YoungLives (intervention group; 361 included in primary analysis) and six clusters with 301 girls were allocated to the control group (279 included in primary analysis). Loss to follow-up accounted for less than 10% in both groups. The incidence of the primary composite outcome by intention to treat was significantly lower in the intervention group (23 [6%] of 361 compared with 35 [13%] of 279 in the control group [adjusted risk ratio 0.52, 95% CI 0.34 to 0.81, $p=0.0034$; risk difference -0.05%, 95% CI -0.10 to -0.01]). The number needed to treat with 2YoungLives to prevent one maternal or perinatal death was 18 (95% CI 10 to 92).

Interpretation: 2YoungLives, a community-based mentoring intervention for adolescent girls from pregnancy up to 1 year after birth, was feasible to implement in urban and rural communities in Sierra Leone and significantly reduced a composite of maternal deaths, stillbirths and neonatal deaths.

Adolescents and HIV prevention and treatment

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The long-term impact of family economic empowerment on viral suppression and mental health outcomes among adolescents living with HIV in low-income settings: A cluster-randomized controlled trial in Southern Uganda

[Samuel Kizito¹](#), [Fred M Ssewamala¹](#), [Josephine Nabayinda¹](#), [Flavia Namuwonge²](#), [Torsten B Neilands²](#), [Proscovia Nabunya³](#), [Ozge Sensoy Bahar¹](#), [Vicent Ssentumbwe¹](#), [Jennifer Nattabi¹](#)

Abstract

Objectives: We examined the impact of a family-based economic empowerment intervention on viral suppression and mental health among ALHIV.

Study design: Between 2013 and 2014, 702 participants aged 10-16, living with HIV, and taking antiretroviral therapy, were recruited from 39 clinics in Uganda. Twenty clinics (n = 358 participants) were randomized to the intervention and 19 clinics (n = 344 participants) were randomized to the control conditions. The intervention comprised a matched savings account, financial literacy training, and microenterprise workshops. The primary outcome was viral suppression, while the secondary outcomes included depression, hopelessness, and self-concept. We ran mixed-effects models to determine the intervention effects.

Results: At enrollment, participants' mean age was 12 years. The intervention improved viral suppression, evidenced by significant intervention-by-time interaction effects [$\chi^2(5) = 12.81$, $p = 0.025$], further qualified by increased viral suppression in the intervention group at year two, OR = 1.89 (95% CI: 1.14-3.15), year three, OR = 2.31 (95% CI: 1.05-5.04), and year four, OR = 2.34 (95% CI: 1.03-5.33). Regarding mental health, we did not find significant intervention main effects or intervention-by-time interaction effects for depressive symptoms, hopelessness, or self-concept for the entire sample. However, for participants owning fewer assets, we found significant intervention-by-time interaction effects for hopelessness [$\chi^2(5) = 12.33$, $p = 0.031$], and self-concept [$\chi^2(5) = 27.26$, $p < 0.001$], suggesting beneficial intervention effect for this demographic.

Conclusions: Family EE interventions have the potential to improve viral suppression and mental health outcomes among ALHIV. These findings offer insights in designing programs and policies to improve outcomes among ALHIV.

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A community-based peer-facilitated psychological and social support model to improve retention in care among Cameroonian adolescents perinatally infected with human immunodeficiency virus: A randomized controlled trial

[Francis Ateba Ndongo¹](#), [Jean-Pierre Yves Awono Noah²](#), [Rogacien Kana²](#), [Justin Ndie³](#), [Marius Tchassep Nono⁴](#), [Patrice Ndzie⁵](#), [Mathurin Cyrille Tejiokem⁶](#), [Emmanuelle Hopp Biheng⁷](#), [Tatiana Avang Nkoa⁷](#), [Yacouba Aba Coulibaly⁸](#), [Joseph Fokam⁹](#), [Alice Ketchaji³](#), [Joëlle Nounouche Ngako³](#), [Calixte Ida Penda⁴](#), [Paul Olivier Koki Ndombo⁷](#), [Hubert Mbassi Hawa⁷](#), [Philippe Msellati¹⁰](#), [Albert Faye¹¹](#), [Marc Lallemand¹²](#), [Anne Cécile Zoung-Kani Bissek¹³](#)

Abstract

Background: Psychological and social support for adolescents living with HIV remains undocumented and unaddressed in Central Africa. This study aimed at assessing effectiveness of a peer-facilitated community-based support model in improving retention in care among adolescents living with HIV and attending care in Chantal Biya Foundation, Yaounde, Cameroon.

Materials and methods: We conducted an analysis of adolescents aged 10-19 years old, perinatally infected with HIV, on follow-up in the Day Care Unit of a reference hospital in Yaounde, Cameroon, and enrolled in the IAS-CIPHER-2021/1214-ATE-SMAVI, a individually randomized controlled trial. While the control arm only received routine care in the health facility, the intervention arm, in addition, was assigned to an HIV association for sustained support model, including support groups, leisure workshops and home visits. Structured questionnaires, including validated French versions of mental health scales, were quarterly administered to the study participants in both study arms by trained healthcare providers. The main outcome was maintaining retention in care beyond the first 15-month period of the study start. Kaplan-Meier and Cox regression models were fitted to assess association between intervention and outcome. Hazard Ratio (HR) across categories of exposure variables were compared using Wald's test. p-value <0.05 was considered significant.

Results: In total, 305 adolescents were recruited in the study at a median age of 15.2 years old, including 162 (53.1 %) females and 153 individuals in the intervention arm. Mental health troubles were prevalent: severe depression (26.9 %), high or very high anxiety (28.9 %), and low self-esteem (84.9 %). Noteworthy, all of the baseline characteristics were balanced irrelevant to the study arm. Probability of maintaining good retention in care beyond the first 15-month period of study start remained higher in the intervention arm (82.0 % [95 %CI: 73.7 %-88.4 %]) versus the control arm (71.0 % [95 %CI: 63.2 %-78.1 %]), [cHR (95 %CI): 2.0 (1.1-3.3), p=0.044].

Conclusions: Capacity should be built in terms of implementing community-based peer-facilitated support groups in local organizations providing care to adolescents living with HIV.

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Effectiveness of community-based peer facilitated psychological and social support interventions on improving mental health in Cameroonian adolescents with perinatal HIV: the IAS-CIPHER-2021/1214-ATE SMAVI controlled randomized trial (November 2021-May 2023)

[Francis Ateba Ndongo¹](#), [Rogacien Kana²](#), [Désiré Aminou Sambo³](#), [Alice Ketchaji⁴](#), [Jean-Pierre Yves Awono Noah²](#), [Justin Ndie⁴](#), [Marius Tchassep Nono⁵](#), [Patrice Ndzie⁶](#), [Alaine Fadimatou³](#), [Hélène Kamo³](#), [Edwige Christelle Naambow Anaba³](#), [Berthe Tchifam³](#), [Mathurin Cyrille Tejiokem⁷](#), [Emmanuelle Hopp Biheng⁸](#), [Tatiana Avang Nkoa⁴](#), [Yacouba Aba Coulibaly⁹](#), [Joseph Fokam¹⁰](#), [Roméo Bouba Yagai¹⁰](#), [Joëlle Nounouce Ngako⁴](#), [Calixte Ida Penda¹¹](#), [Jérôme Ateudjieu¹²](#), [Basile Keugoung¹³](#), [Christian Bayiha⁴](#), [Paul Olivier Koki Ndombo¹⁴](#), [Hubert Mbassi Awa¹⁴](#), [Anne Cécile Zoung-Kanyi Bissek¹⁵](#), [Albert Faye¹⁶](#), [Philippe Msellati¹⁷](#), [Marc Lallemant¹⁸](#)

Abstract

Background: Psychological and social support to adolescents living with HIV remains undocumented and unaddressed in Central Africa. This study aimed to assess effectiveness of a peer-facilitated community-based support in improving mental health among Cameroonian adolescents living with vertically acquired HIV (ALHIV).

Setting: The study was conducted in a national referral hospital in Yaounde, Cameroon.

Methods: This was a parallel randomized controlled trial in ALHIV. The control arm only received routine support in the health facility; the intervention arm benefited from community-based and peer-facilitated support. The endpoints were mean mental health scores' variations from month 0 to month 15, estimated based on validated French versions mental health scales and using independent samples' Student t test.

Results: In total, 305 ALHIV were recruited at a mean age of 15.0 years old, including 162 (53.1%) females, 153 individuals in the intervention arm; in whom symptoms of severe depression (26.9%), high or very high anxiety (28.9%), and low self-esteem (84.9%). From month 0 to month 15, there was increase in self-esteem (mean between-arm difference (M) (standard deviation (SD))=+0.5 (SD: 1.0) ;; significance degree (p)= 0.6543), decrease in symptoms of depression (M=-0.2 (SD: 1.4)); p= 0.9098) and decrease in symptoms of anxiety (M=-1.8 (SD: 3.4)); p= 0.7338), without significant differences between the 2 arms.

Conclusions: This study showed benefits in anxiety and depression reduction and improvement in self-esteem in both arms, without any significant difference, suggesting that regardless of whether psychosocial interventions are implemented in-clinic or in the community, both are of benefit to patients.

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[Integrating a mental health referral system within adolescent HIV clinics in Tanzania](#)

[Dana Chow¹](#), [Paul Pronyk²](#), [Rainald Mgimba³](#), [Winner Elimwaria⁴](#), [Regina Ndaki⁵](#), [Aloyce Ambokile⁶](#), [Blandina T Mmbaga^{7 8 9 10}](#), [Dorothy Dow^{9 10 11}](#)

Abstract

Objective: To evaluate the acceptability and feasibility of integrating a mental health (MH) stepped-care referral pathway for young people with HIV (YPWH) who screened positive for MH distress using task-sharing and stepped-care approaches.

Design: This is a longitudinal nested study within the Sauti ya Vijana (SYV: The Voice of Youth) randomised controlled trial, describing an integrated referral pathway created within adolescent HIV clinics. SYV is a peer-led, group-based MH intervention for YPWH. The study includes youth enrolled between March and September 2023 who completed a 6-month visit by March 2024.

Methods: YPWH who knew their HIV status, received antiretroviral therapy, and could attend 10-weekly intervention sessions were included. Enrolled youth responded to interviewer-guided MH screening questionnaires at every study visit. Automatic referral alerts were generated if a YPWH had a total score ≥ 10 on the Patient Health Questionnaire (PHQ-9) or General Anxiety Disorder (GAD-7) Questionnaire, reported sexual abuse, self-harm, or suicidal ideation. An interviewer could self-refer a participant if they had a separate MH concern. Site-specific MH referrals were tracked using a REDCap database. Data were analysed for incidence of MH referrals, attendance to referral appointment, and outcome.

Results: Of 349 YPWH included in this study, 62 (18%) generated referral alerts. Most attended their appointment ($n = 50$, 81%) and many ($n = 28$, 56%) experienced resolution of distress after one visit. Eight participants required stepped-up care to a MH professional.

Conclusions: The integration of a MH stepped-care referral pathway was acceptable and feasible for YPLW within existing primary adolescent HIV clinics in Tanzania.

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Randomized Pilot Trial of the Text-Based Adherence Game for Ghanaian Youth with HIV

Nicholas Tarantino¹, Betty Norman^{2,3}, Anthony Enimil^{2,4}, Shadrack Osei Asibey², Charles Martyn-Dickens², Kathleen O'Neill⁵, Kate M Guthrie^{6,7}, Awewura Kwara⁸, Beth Bock^{6,7}, Matthew J Mimiaga^{9,10}, Larry K Brown^{11,6}

Abstract

This study examined the feasibility, acceptability, and preliminary efficacy of a mobile intervention called the Text-Based Adherence Game (TAG). TAG aimed to improve HIV treatment adherence among young people with HIV (YPWH) in Ghana. Participants, YPWH aged 18 to 24, were recruited from an HIV clinic in Kumasi, Ghana where study procedures were conducted. A randomized controlled pilot trial was conducted to evaluate TAG (ClinicalTrials.gov Identifier [NCT03928717](#)). Participants were randomized to receive TAG or a standard-of-care (SOC) control. All completed quantitative assessments on outcomes preintervention and at two follow-up visits at 6- and 12-months. TAG participants received personalized, semi-automated, and game-based text messages over the six-month intervention period. Primary outcomes included viral load, antiretroviral medication adherence, and missed HIV clinic visits. Secondary outcomes were also explored. Two surveys measured intervention acceptability. 60 YPWH were enrolled. 51 completed all assessments. At the 12-month follow-up assessment, TAG had a significant and positive effect on a measure of antiretroviral adherence but not viral load or missed clinic visits. Positive intervention effects were also found at postintervention and 12 months for several secondary outcomes (e.g., adherence-related social support). Intervention acceptability was generally high. TAG is a novel and promising mobile health intervention approach. Results suggest the need to further develop TAG as it may have the potential to reach populations of YPWH and improve HIV continuum of care outcomes in settings where access to more advanced mobile technology (e.g., smartphones) and the internet is not universal.

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The 4 youth by youth (4YBY) crowdsourced HIV prevention intervention: A stepped-wedge longitudinal trial on HIV self-testing uptake among adolescents and young people in Nigeria

[Juliet Iwelunmor¹](#), [Chisom Obiezu-Umeh²](#), [Titilola Gbaja-Biamila³](#), [David Oladele³](#), [Ucheoma Nwaozuru⁴](#), [Adesola Z Musa⁵](#), [Olunike R Abodunrin⁶](#), [Folahanmi T Akinsolu⁷](#), [Temitope Ojo⁸](#), [Olufunto Olusanya⁸](#), [Tajudeen Bamidele⁹](#), [Nkiru Ezeama⁹](#), [Chinyere Okeke⁹](#), [Ifiok Johnny⁹](#), [Moses Ekene⁹](#), [Nurudeen Rahman⁹](#), [Tomilola Musari-Martins⁹](#), [Sola Ajibaye⁹](#), [Akeem Lateef⁹](#), [Victor Ojo⁹](#), [Yusuf Babatunde⁹](#), [Collins O Airhihenbuwa¹⁰](#), [Kathryn Muessig¹¹](#), [Nora Rosenberg¹¹](#), [Rhonda BeLue¹²](#), [Hong Xian¹³](#), [Donaldson F Conserve¹⁴](#), [Zhuoru Zou¹⁵](#), [Jason J Ong¹⁶](#), [Lei Zhang¹⁷](#), [Jamie Curley¹³](#), [Susan Nkengasong¹⁸](#), [Stacey Mason¹³](#), [Weiming Tang¹⁹](#), [Barry Bayus²⁰](#), [Gbenga Ogedegbe¹²](#), [Joseph D Tucker²¹](#), [Oliver Ezechi⁷](#)

Abstract

Adolescents and young adults (AYAs) participatory approaches for HIV control have increased across LMICs, but there are few trials to evaluate effectiveness. We assessed a crowdsourced HIV self-testing (HIVST) intervention among a cohort of AYA in Nigeria.

Methods: We conducted a pragmatic stepped-wedge cluster randomized control trial recruiting participants (aged 14-24 years) from 32 local government areas across four geopolitical zones in Nigeria. Eligible AYA were HIV negative or unknown HIV status, residing in study sites, spoke English, and consented. Areas were randomly assigned to one of four steps and AYA were followed for 24 months. AYA research facilitators implemented a 4YBY crowdsourced HIV prevention bundle. The primary outcome was self-reported HIVST uptake. We compared the probability of HIVST between the control and intervention periods using a generalized linear mixed model. We examined the fixed cost and per capita cost of the intervention. The protocol was registered with Clinical Trials.gov on January 15, 2021, under registration [NCT04710784](#).

Results: 2652 AYA were screened, and 1500 were enrolled in the study (March 10, 2021-August 31, 2023). 1333/1500 (89 %) were followed up at 24 months. The mean age of AYA was 20 ± 2.65 years old, most were students (1155/1500, 77 %), and unemployed (915/1500, 61 %). The intervention led to a 9.96-fold increase in HIV self-testing uptake compared to the control period (95 % CI: 8.36-11.85, $p < 0.0001$). The annual fixed cost of the intervention was estimated at US\$42,237, with a per capita testing cost of US\$14.8. No significant adverse events were reported.

Conclusion: A crowdsourced HIV prevention intervention increased HIVST uptake among Nigerian AYA. Greater participation of AYA in the design and implementation of clinical trials is needed to achieve UNAIDS targets.

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Using a cash transfer plus SMS nudge package to improve the wellbeing among caregivers of adolescents living with HIV during the COVID-19 epidemic in South Africa: A pilot randomised controlled trial

[Stanley Carries¹](#), [Zibuyisile Mkhwanazi¹](#), [Nokwanda Sithole¹](#), [Lovemore Sigwadhi¹](#), [Mosa Moshabela²](#), [Makandwe Nyirenda^{2,3}](#), [Jane Goudge⁴](#), [Eugene Lee Davids^{1,5}](#), [Darshini Govindasamy¹](#)

Abstract

Caregivers of adolescents living with HIV encounter multiple economic and psycho-social challenges which impair their wellbeing and provision of optimal care. Cash transfers combined with short message service (SMS) nudges may address the financial and mental barriers to caregiver wellbeing in sub-Saharan Africa. We examined the preliminary effectiveness and feasibility outcomes of this multipronged approach for improving caregiver wellbeing. We piloted the Caregiver Wellbeing intervention in the eThekweni municipality, KwaZulu-Natal, South Africa. Participants were randomly assigned to one of the following groups: (i) the intervention arm (n = 50) received three cash payments (of ZAR 350, approximately 21 USD), coupled with behaviourally-informed mobile SMS nudges over a 3-month period; (ii) the control arm (n = 50) received a standard SMS encouraging linkage to health services. The primary outcome was change in psychological wellbeing at four-months follow-up. Secondary outcomes were changes in depressive symptoms and caregiver burden scores, recruitment pace, retention, uptake, acceptability and costs. Trial Registration Number: PACTR202203585402090. The n = 100 caregivers (mean age = 42.3 years, 87% female) enrolled at baseline were recruited within six weeks. Compared to controls, there was a non-significant increase in psychological wellbeing ($\beta = 3.14$, $p = 0.319$). There was a 1.32 unit ($p = 0.085$) decrease in depressive symptoms and a reduction in caregiver burden ($\beta = -1.28$, $p = 0.020$) in the intervention arm. Participant retention was 85%, with high intervention uptake (95%). Caregivers expressed appreciation for the intervention as the cash component allowed them to fulfil their carer responsibilities and the SMS brought a sense of belonging and self-acceptance. Total societal cost of the intervention was US\$13,549, and the incremental cost per increase in wellbeing score was US\$1,080. Results suggest a cash transfer plus SMS nudge package, whilst feasible and acceptable, may require longer duration and an economic empowerment component to enhance caregiver wellbeing as part of post-pandemic recovery efforts.

Trials. 2024 Jul 3;25(1):448.

doi: 10.1186/s13063-024-08279-3.

[A mixed methods process evaluation: understanding the implementation and delivery of HIV prevention services integrated within sexual reproductive health \(SRH\) with or without peer support amongst adolescents and young adults in rural KwaZulu-Natal, South Africa](#)

[Thembelihle Zuma^{1,2,3}](#), [Jacob Busang⁴](#), [Sphesihle Hlongwane⁴](#), [Glory Chidumwa⁵](#), [Dumsani Gumede⁴](#), [Manono Luthuli⁴](#), [Jaco Dreyer⁴](#), [Carina Herbst⁴](#), [Nonhlanhla Okesola⁴](#), [Natsayi Chimbindi^{4,6,7}](#), [Nuala McGrath^{4,7,8}](#), [Lorraine Sherr⁶](#), [Janet Seeley^{4,9,7}](#), [Maryam Shahmanesh^{4,6,7}](#)

Abstract

Background: Combination prevention interventions, when integrated with community-based support, have been shown to be particularly beneficial to adolescent and young peoples' sexual and reproductive health. Between 2020 and 2022, the Africa Health Research Institute in rural South Africa conducted a 2 × 2 randomised factorial trial among young

people aged 16-29 years old (Isisekelo Sempilo) to evaluate whether integrated HIV and sexual and reproductive health (HIV/SRH) with or without peer support will optimise delivery of HIV prevention and care. Using mixed methods, we conducted a process evaluation to provide insights to and describe the implementation of a community-based peer-led HIV care and prevention intervention targeting adolescents and young people.

Methods: The process evaluation was conducted in accordance with the Medical Research Council guidelines using quantitative and qualitative approaches. Self-completed surveys and clinic and programmatic data were used to quantify the uptake of each component of the intervention and to understand intervention fidelity and reach. In-depth individual interviews were used to understand intervention experiences. Baseline sociodemographic factors were summarised for each trial arm, and proportions of participants who accepted and actively engaged in various components of the intervention as well as those who successfully linked to care were calculated. Qualitative data were thematically analysed.

Results: The intervention was feasible and acceptable to young people and intervention implementing teams. In particular, the STI testing and SRH components of the intervention were popular. The main challenges with the peer support implementation were due to fidelity, mainly because of the COVID-19 pandemic. The study found that it was important to incorporate familial support into interventions for young people's sexual health. Moreover, it was found that psychological and social support was an essential component to combination HIV prevention packages for young people.

Conclusion: The results demonstrated that peer-led community-based care that integrates SRH services with HIV is a versatile model to decentralise health and social care. The family could be a platform to target restrictive gender and sexual norms, by challenging not only attitudes and behaviours related to gender among young people but also the gendered structures that surround them.

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A Stepped-Wedge, Cluster-Randomized, Multisite Study of Text Messaging Plus Peer Navigation to Improve Adherence and Viral Suppression Among Youth on Antiretroviral Therapy

[Babafemi O Taiwo¹](#), [Lisa M Kuhns²](#), [Oche Agbaji³](#), [Agatha David⁴](#), [Sulaimon Akanmu⁵](#), [Akinyinka Akinbami⁶](#), [Olayinka Omigbodun⁷](#), [Folashade Adekanmbi⁸](#), [Esther Yiltok⁹](#), [Priscilla Ezemelue⁴](#), [Patricia Akintan¹⁰](#), [Olujimi Sodipo¹¹](#), [Olutosin Awolude¹²](#), [Kehinde Kutu¹³](#), [Gbenayon Mautin¹⁴](#), [Titilope Badru¹](#), [Marbella Cervantes²](#), [Patrick Janulis¹⁵](#), [Ogochuckwu Okonkwo¹](#), [Baiba Berzins¹](#), [Robert Garofalo²](#)

Abstract

Background: To address the need for improved virologic suppression among youth living with HIV (YLH) on antiretroviral treatment (ART), we evaluated peer navigation plus TXTXT daily text message ART reminders.

Setting: YLH aged 15-24 years on ART for at least 3 months at 6 research sites in 4 Nigerian cities.

Methods: Using a stepped-wedge design, cluster 1 was nonrandomized, whereas clusters 2 and 3 were randomized to sequences of routine care (control period) and 48 weeks of the

combination intervention (intervention period). The primary end point was viral suppression (HIV-1 RNA <200 copies/mL) at week 48 of the intervention. Secondary end points included adherence measured by self-report (90% considered adherent). Post hoc analysis assessed virologic control at <50 copies per milliliter and <1000 copies per milliliter. Generalized estimating equations determined the difference between intervention and control periods in the intention-to-treat population.

Results: We enrolled 558 YLH and followed 541 over time, mean age 18 years, 53.8% female, 71.7% perinatally infected, and 38.6% virologically nonsuppressed at enrollment. For the primary end point, the intervention periods displayed a small, nonsignificant increase in viral suppression < 200 copies per milliliter [odds ratio (OR) = 1.16 (0.88-1.54), P = 0.297]. There was a significant effect of the combination intervention on virologic control <1000 copies per milliliter (OR = 1.42 [1.03-1.94], P = 0.030). Self-reported adherence also improved (OR = 2.07 [1.46-2.95], P < 0.001).

Conclusions: Peer navigation plus daily text message ART reminders demonstrated limited benefit among ART-experienced, predominantly perinatally infected YLH, with no significant effect on viral suppression below 200 copies per milliliter despite improvement in self-reported adherence.

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Using FRAME to characterize provider-identified adaptations to a stepped care intervention for adolescents and youth living with HIV in Kenya: a mixed methods approach

[Nok Chhun¹](#), [Dorothy Oketch²](#), [Kawango Agot²](#), [Dorothy I Mangale¹³](#), [Jacinta Badia²](#), [James Kibugi²](#), [Wenwen Jiang⁴](#), [Mary Kirk¹](#), [Barbra A Richardson¹⁵](#), [Pamela K Kohler¹⁶](#), [Grace John-Stewart¹⁴⁷⁸](#), [Kristin Beima-Sofie¹](#)

Abstract

Introduction: The Data-informed Stepped Care (DiSC) study is a cluster-randomized trial implemented in 24 HIV care clinics in Kenya, aimed at improving retention in care for adolescents and youth living with HIV (AYLHIV). DiSC is a multi-component intervention that assigns AYLHIV to different intensity (steps) of services according to risk. We used the Framework for Reporting Adaptations and Modifications-Expanded (FRAME) to characterize provider-identified adaptations to the implementation of DiSC to optimize uptake and delivery, and determine the influence on implementation outcomes.

Methods: Between May and December 2022, we conducted continuous quality improvement (CQI) meetings with providers to optimize DiSC implementation at 12 intervention sites. The meetings were guided by plan-do-study-act processes to identify challenges during early phase implementation and propose targeted adaptations. Meetings were audio-recorded and analysed using FRAME to categorize the level, context and content of planned adaptations and determine if adaptations were fidelity consistent. Providers completed surveys to quantify perceptions of DiSC acceptability, appropriateness and feasibility. Mixed effects linear regression models were used to evaluate these implementation outcomes over time.

Results: Providers participated in eight CQI meetings per facility over a 6-month period. A total of 65 adaptations were included in the analysis. The majority focused on optimizing the

integration of DiSC within the clinic (83%, n = 54), and consisted of improving documentation, addressing scheduling challenges and improving clinic workflow. Primary reasons for adaptation were to align delivery with AYLHIV needs and preferences and to increase reach among AYLHIV: with reminder calls to AYLHIV, collaborating with schools to ensure AYLHIV attended clinic appointments and addressing transportation challenges. All adaptations to optimize DiSC implementation were fidelity-consistent. Provider perceptions of implementation were consistently high throughout the process, and on average, slightly improved each month for intervention acceptability ($\beta = 0.011$, 95% CI: 0.002, 0.020, $p = 0.016$), appropriateness ($\beta = 0.012$, 95% CI: 0.007, 0.027, $p < 0.001$) and feasibility ($\beta = 0.013$, 95% CI: 0.004, 0.022, $p = 0.005$).

Conclusions: Provider-identified adaptations targeted improved integration into routine clinic practices and aimed to reduce barriers to service access unique to AYLHIV. Characterizing types of adaptations and adaptation rationale may enrich our understanding of the implementation context and improve abilities to tailor implementation strategies when scaling to new settings.

Lancet HIV. 2024 Jul;11(7):e449-e460.

doi: 10.1016/S2352-3018(24)00119-X.

Effectiveness of integrating HIV prevention within sexual reproductive health services with or without peer support among adolescents and young adults in rural KwaZulu-Natal, South Africa (Isisekelo Sempilo): 2 × 2 factorial, open-label, randomised controlled trial

[Maryam Shahmanesh¹](#), [Natsayi Chimbindi²](#), [Jacob Busang³](#), [Glory Chidumwa⁴](#), [Nondumiso Mthiyani⁵](#), [Carina Herbst³](#), [Nonhlanhla Okesola³](#), [Jaco Dreyer³](#), [Thembelihle Zuma²](#), [Manono Luthuli³](#), [Dumsani Gumede³](#), [Siphesihle Hlongwane³](#), [Simphiwe Mdluli³](#), [Sithembile Msane³](#), [Theresa Smit³](#), [Jean-Michel Molina⁶](#), [Thandeka Khoza³](#), [Ngundu Osee Behuhuma³](#), [Nuala McGrath⁷](#), [Janet Seeley⁸](#), [Guy Harling⁹](#), [Lorraine Sherr¹⁰](#), [Andrew Copas¹⁰](#), [Kathy Baisley⁸](#)

Abstract

Background: Approximately 200 000 South Africans acquired HIV in 2021 despite the availability of universal HIV test and treat and pre-exposure prophylaxis (PrEP). The aim of this study was to test the effectiveness of sexual and reproductive health services or peer support, or both, on the uptake of serostatus neutral HIV services or reduction of sexually transmissible HIV.

Methods: We did an open-label, 2 × 2 randomised factorial trial among young people in a mostly rural area of KwaZulu-Natal, South Africa. Inclusion criteria included being aged 16-29 years, living in the mapped geographical areas that were accessible to the area-based peer navigators, being willing and able to provide informed consent, and being willing to provide a dried blood spot for anonymous HIV testing and HIV viral load measurement at 12 months. Participants were randomly allocated by computer-generated algorithm to one of four groups: those in the standard-of-care group were referred to youth-friendly services for differentiated HIV prevention (condoms, universal HIV test and treat with antiretroviral therapy, and PrEP if eligible); those in the sexual and reproductive health services group received baseline self-collected specimens for sexually transmitted infection (STI) testing and referral to integrated sexual and reproductive health and HIV prevention services; those in the peer support group were referred to peer navigators for health promotion, condom

provision, and facilitation of attendance for differentiated HIV prevention services; and those in the final group received a combination of sexual and reproductive health services and peer support. Coprimary outcomes were linkage to clinical services within 60 days of enrolment, proportion of participants who had sexually transmissible HIV at 12 months after enrolment, and proportion of sampled individuals who consented to participation and gave a dried blood spot for HIV testing at 12 months. Logistic regression was used for analyses, and adjusted for age, sex, and rural or peri-urban area of residence. This study is registered with ClinicalTrials.gov ([NCT04532307](https://clinicaltrials.gov/ct2/show/study/NCT04532307)) and is closed.

Findings: Between March 2, 2020, and July 7, 2022, 1743 (75.7%) of 2301 eligible individuals were enrolled and followed up. 12-month dried blood spots were collected from 1168 participants (67.0%). The median age of the participants was 21 years (IQR 18-25), 51.4% were female, and 51.1% had secondary level education. Baseline characteristics and 12-month outcome ascertainment were similar between groups. 755 (43.3%) linked to services by 60 days. 430 (49.8%) of 863 who were in the sexual reproductive health services group were linked to care compared with 325 (36.9%) of 880 who were not in the sexual and reproductive health services group (adjusted odds ratio [aOR] 1.68; 95% CI 1.39-2.04); peer support had no effect: 385 (43.5%) of 858 compared with 370 (43.1%) of 885 (1.02, 0.84-1.23). At 12 months, 227 (19%) tested ELISA-positive for HIV, of whom 41 (18%) had viral loads of 400 copies per mL; overall prevalence of transmissible HIV was 3.5%. 22 (3.7%) of 578 participants in the sexual and reproductive health services group had transmissible HIV compared with 19 (3.3%) of 590 not in the sexual and reproductive health services group (aOR 1.12; 95% CI 0.60-2.11). The findings were also non-significant for peer support: 21 (3.3%) of 565 compared with 20 (3.3%) of 603 (aOR 1.03; 95% CI 0.55-1.94). There were no serious adverse events or deaths during the study.

Interpretation: This study provides evidence that STI testing and sexual and reproductive health services create demand for serostatus neutral HIV prevention in adolescents and young adults in Africa. STI testing and integration of HIV and sexual health has the potential to reach those at risk and tackle unmet sexual health needs.

AIDS. 2024 Aug 1;38(10):1579-1588.

doi: 10.1097/QAD.0000000000003939. Epub 2024 Jun 10.

[A randomized trial of 'fresh start' text messaging to improve return to care in people with HIV who missed appointments in South Africa](#)

[Christine Njuguna](#)¹, [Lawrence Long](#)^{2,3}, [Preethi Mistri](#)³, [Candice Chetty-Makkan](#)³, [Brendan Maughan-Brown](#)⁴, [Alison Buttenheim](#)⁵, [Laura Schmucker](#)⁶, [Sophie Pascoe](#)³, [Harsha Thirumurthy](#)⁶, [Cara O'Connor](#)¹, [Chipo Mutyambizi](#)¹, [Barry Mutasa](#)¹, [Kate Rees](#)^{1,7}

Abstract

Objective: Treatment interruptions are a barrier to successful antiretroviral therapy (ART). 'Fresh start messages', which leverage significant days on the calendar (e.g., new year, public holiday) in order to prompt action, have the potential to encourage people with HIV (PWH) to return to care. We evaluated a 'fresh start' intervention (text messages) to increase return to care in PWH who had missed their last appointment.

Design: A three arm 1 : 1:1 individual randomised controlled trial.

Methods: We randomized adults in Capricorn District who had missed ART appointments by >28 days to: no text message; unframed messages (fresh start not mentioned); or framed messages (fresh start mentioned). Randomization was stratified by treatment interruption

duration and across two holidays (Youth Day, Mandela Day). The primary outcome was an ART-related clinic visit at ≤ 45 days of the first message.

Results: 9143 participants were randomised. For Youth Day, 1474 and 1468 were sent unframed and framed messages respectively, with 13.4% sent these messages having an ART visit vs. 11.9% not sent a message [adjusted odds ratio (aOR) 1.2; 95% confidence interval (CI): 1.0-1.4, P -value = 0.075]. For Mandela Day, 1336 and 1334 were sent unframed and framed messages respectively, with 6.7% sent these messages having an ART-related clinic visit vs. 5.4% not sent a message (aOR 1.2; 95% CI: 1.0-1.6; P -value = 0.100).

Conclusions: Low-cost text messages sent around a 'fresh start' date may increase the likelihood that patients who miss appointments return to care. This study suggests the potential of text messaging for motivating return to care.

AIDS Care. 2024 Jul;36(7):983-992.

doi: 10.1080/09540121.2024.2361240. Epub 2024 Jul 8.

Acceptability, feasibility and preliminary effectiveness of the mHealth intervention, InTSHA, on retention in care and viral suppression among adolescents with HIV in South Africa: a pilot randomized clinical trial

[Brian C Zanon^{1,2,3}](#), [Moherndran Archary^{4,5}](#), [Thobekile Sibaya⁴](#), [Nicholas Musinguzi⁶](#), [Casiel T Gethers^{1,2}](#), [Madeleine Goldstein^{1,2}](#), [Scarlett Bergam^{4,5}](#), [Christina Psaros^{7,8}](#), [Vincent C Marconi^{1,3}](#), [Jessica E Haberer^{7,8}](#)

Abstract

We describe the results of a pilot randomized clinical trial of a mobile phone-based intervention, InTSHA: Interactive Transition Support for Adolescents with HIV, compared to standard care. Encrypted, closed group chats delivered via WhatsApp provided peer support and improved communication between adolescents with HIV, their caregivers, and healthcare providers. We randomized 80 South African adolescents ages 15 to 19 years with perinatally-acquired HIV to receive either the intervention (n=40) or standard of care (n=40). We measured acceptability (Acceptability of Intervention Measure [AIM]) and feasibility (Feasibility of Intervention Measure [FIM]) as primary outcomes. We evaluated impact on retention in care and viral suppression six months after randomization as secondary endpoints. We performed bivariable and multivariable analyses using logistic regression models to assess the effect of the InTSHA intervention compared to standard of care. Among the adolescents randomized to the InTSHA intervention, the median AIM was 4.1/5.0 (82%) and median FIM was 3.9/5.0 (78%). We found no difference in retention in care or in viral suppression comparing intervention and control groups. Among adolescents who attended three or more sessions, retention in care was 100% at 6 months. InTSHA is an acceptable and feasible mHealth intervention warranting further study in a larger population.

Soc Sci Med. 2025 Jan;364:117546.

doi: 10.1016/j.socscimed.2024.117546. Epub 2024 Nov 26.

The long-term impact of family economic empowerment on viral suppression and mental health outcomes among adolescents living with HIV in low-income settings: A cluster-randomized controlled trial in Southern Uganda

[Samuel Kizito¹](#), [Fred M Ssewamala¹](#), [Josephine Nabayinda¹](#), [Flavia Namuwonge²](#), [Torsten B Neilands²](#), [Proscovia Nabunya³](#), [Ozge Sensoy Bahar¹](#), [Vicent Ssentumbwe¹](#), [Jennifer Nattabi¹](#)

Abstract

Objectives: We examined the impact of a family-based economic empowerment intervention on viral suppression and mental health among ALHIV.

Study design: Between 2013 and 2014, 702 participants aged 10-16, living with HIV, and taking antiretroviral therapy, were recruited from 39 clinics in Uganda. Twenty clinics (n = 358 participants) were randomized to the intervention and 19 clinics (n = 344 participants) were randomized to the control conditions. The intervention comprised a matched savings account, financial literacy training, and microenterprise workshops. The primary outcome was viral suppression, while the secondary outcomes included depression, hopelessness, and self-concept. We ran mixed-effects models to determine the intervention effects.

Results: At enrollment, participants' mean age was 12 years. The intervention improved viral suppression, evidenced by significant intervention-by-time interaction effects [$\chi^2(5) = 12.81$, $p = 0.025$], further qualified by increased viral suppression in the intervention group at year two, OR = 1.89 (95% CI: 1.14-3.15), year three, OR = 2.31 (95% CI: 1.05-5.04), and year four, OR = 2.34 (95% CI: 1.03-5.33). Regarding mental health, we did not find significant intervention main effects or intervention-by-time interaction effects for depressive symptoms, hopelessness, or self-concept for the entire sample. However, for participants owning fewer assets, we found significant intervention-by-time interaction effects for hopelessness [$\chi^2(5) = 12.33$, $p = 0.031$], and self-concept [$\chi^2(5) = 27.26$, $p < 0.001$], suggesting beneficial intervention effect for this demographic.

Conclusions: Family EE interventions have the potential to improve viral suppression and mental health outcomes among ALHIV. These findings offer insights in designing programs and policies to improve outcomes among ALHIV.

AIDS Behav. 2024 Aug;28(8):2769-2779.

doi: 10.1007/s10461-024-04353-8. Epub 2024 Apr 29.

[Preliminary Impact of Group-Based Interventions on Stigma and the Mental Health of Caregivers of Adolescents Living with HIV in Uganda](#)

[Proscovia Nabunya¹](#), [Samuel Kizito²](#), [Mitra Naseh³](#), [Atwebembere Raymond²](#), [Vicent Ssentumbwe²](#)

Abstract

This study examined the preliminary impact of group-cognitive behavioral therapy (G-CBT) and a family-strengthening intervention delivered via multiple family groups (MFG-FS) on HIV stigma, parenting stress, and the mental health of caregivers of adolescents living with HIV. We analyzed data from the Suubi4Stigma study (2020-2022), a two-year pilot randomized clinical trial for adolescents and their caregivers (N = 89 dyads), recruited from nine health clinics in Uganda. Adolescent-caregiver dyads were randomized to three intervention conditions delivered over three months, with data collected at baseline, three and six-months follow-up. We fitted mixed-effects linear regression models to test the effect of the interventions on caregiver outcomes over time. At six months, caregivers randomized to the MFG-FS condition reported lower levels of stigma by association (mean difference = -1.45, 95% CI = -2.52 - -0.38, $p = 0.008$), and stigma and discrimination attitudes (mean difference = -3.84, 95% CI = -4.63 - -3.05, $p < 0.001$), compared to Usual care condition. In addition,

caregivers of adolescents randomized to the G-CBT condition reported lower levels of stigma and discrimination attitudes at three months (mean difference = -5.18, 95% CI = -9.13 - -1.22, $p = 0.010$), and at six months (mean difference = -6.70, 95% CI = -9.28 - -4.12, $p < 0.001$). Caregiver mental health and parenting stress significantly reduced over time regardless of intervention condition. Findings point to the importance of incorporating stigma reduction components within psychosocial interventions targeting adolescents and families impacted by HIV.

Contemp Clin Trials. 2024 Nov 13:107733.

doi: 10.1016/j.cct.2024.107733. Online ahead of print.

Factors associated with HIV self-testing and PrEP use among Nigerian youth: Baseline outcomes of a pragmatic, stepped-wedge, cluster-randomized controlled trial

[Juliet Iwelunmor¹](#), [Ebenezer Adeoti²](#), [Titilola Gbaja-Biamila³](#), [Ucheoma Nwaozuru⁴](#), [Chisom Obiezu-Umeh²](#), [Adesola Z Musa⁵](#), [Hong Xian⁵](#), [Weiming Tang⁶](#), [David Oladele³](#), [Collins O Airhihenbuwa⁷](#), [Nora Rosenberg⁸](#), [Donaldson F Conserve⁹](#), [Franklin Yates¹⁰](#), [Temitope Ojo¹¹](#), [Oliver Ezechi⁵](#), [Joseph D Tucker¹²](#)

Abstract

Introduction: Adolescents and young adults (AYA, 14-24 years) bear a disproportionate burden of new HIV infections in Nigeria and are more likely to have worse HIV outcomes compared to other age groups. However, little is known about their access to recommended sexual health care services, including HIV self-testing (HIVST), sexually transmitted infections (STI) testing, sexual behavior patterns, awareness and or access to pre-exposure prophylaxis (PrEP), and overall risk for HIV.

Methods: We present a baseline analysis of the 4 Youth by Youth randomized controlled trial aimed to evaluate the uptake and sustainability of crowdsourced HIVST strategies led by and for young people across 14 states in Nigeria. None of the participants had received intervention at the time of completing this self-reported behavioral survey. We conducted a descriptive analysis to summarize participants' characteristics, sexual behavior, HIV testing, STI testing, and knowledge of PrEP and use across the study sample of the AYAs. We conducted a chi-square test, and the level of significance was set at ≤ 0.05 .

Results: A total of 1551 participants completed the baseline survey comprising males (777, 50.1 %) and females (774, 49.9 %). The majority (77 %) of the participants were students at enrollment. Very few of the participants had ever tested for syphilis, 47 (3.1 %), gonorrhea, 49 (3.2 %), chlamydia, 31 (2.0 %), and hepatitis B, 106 (6.9 %). 678 (43.8 %) of the participants reported to be sexually active at the time of enrolment into the study, of which about 38 % of them engaged in condomless sex. Paying for sex, alcohol use, and drug use are all significant sexual behaviors ($p < 0.01$). Only 14 (1 %) have ever used PrEP. 481 (31.4 %) have ever tested for HIV, and 104 (6.8 %) have ever used an HIV self-testing kit at baseline. 457 (38.6 %) were eligible for PrEP.

Conclusions: HIVST and STI uptake were low at baseline among the AYA in this study. Most AYAs also do not receive recommended sexual health care services, including STI testing services. This underlines the need for interventions to increase the uptake of HIV/STI prevention services among Nigerian AYA.

Public Health. 2025 Jul;244:105753.

doi: 10.1016/j.puhe.2025.105753. Epub 2025 May 13.

[A prediction model for virologic failure in adolescents living with HIV in Uganda: Findings from the Suubi+Adherence study](#)

[Samuel Kizito](#)¹, [Fred M Ssewamala](#)², [Torsten B Neilands](#)³, [Proscovia Nabunya](#)², [Phionah Namatovu](#)⁴, [Josephine Nabayinda](#)², [Mary M McKay](#)², [Kimberly J Johnson](#)², [Ross Brownson](#)²

Abstract

Objectives: Adolescents living with HIV (ALHIV) have low viral suppression levels, with 1 in 3 ALHIV experiencing virologic failure, calling for more efforts to reverse these trends. We developed and validated a model that predicts the risk of virologic failure (VF) among ALHIV.

Study design: Cross-sectional study.

Methods: We used baseline data from 702 ALHIV enrolled in the Suubi + Adherence cluster-randomized clinical trial. Participants were aged 10-16 years, living with HIV and aware of their HIV status, and are living with a family. We developed a risk-prediction model for VF (viral load of ≥ 200 copies/mL) using sociodemographic, behavioral, psychological, economic, and treatment-related factors. LASSO logistic regression using 10-fold cross-validation with bootstrapping was used to select the predictors for the final model. Model performance was assessed by determining the discrimination using the area under the curve and calibration by drawing a calibration plot.

Results: Using a lambda value of 0.007, the final model had 24 predictors (and interaction terms). The predictors included the participants' age, sex, work status, stigma, depressive symptoms, adherence self-efficacy, HIV knowledge, duration with HIV, time spent on ART, communication with the caregiver, family cohesion, social support, orphanhood status, number of people in the household, HIV disclosure, years spent at the current residence, and household asset ownership. The model predicted VF with AUC of 73.8 (95 % CI: 68.3-78.0) and calibration slope of 0.985.

Conclusions: We developed and validated a model to predict the risk of virologic failure among ALHIV in Uganda, demonstrating its potential utility in identifying individuals at elevated risk for VF. Future models could be refined by incorporating clinical characteristics such as CD4 count to further improve predictive accuracy.

Allergy

Pediatr Allergy Immunol. 2025 Mar;36(3):e70062.

doi: 10.1111/pai.70062.

[Daily egg intake may reduce sensitisation to common allergenic foods among six- to nine-month-old south African infants: A randomized controlled trial](#)

[Regina Nakiranda](#)¹, [Linda Malan](#)¹, [Hannah Ricci](#)^{1,2}, [Herculina S Kruger](#)¹, [Arista Nienaber](#)¹, [Marina Visser](#)¹, [Cecile Cooke](#)¹, [Cristian Ricci](#)², [Mieke Faber](#)^{1,3}, [Cornelius M Smuts](#)¹

Abstract

Background: This study aimed to investigate sensitization to eggs and other common allergenic foods, allergic symptoms, and fatty acid status among infants after introducing daily eggs as a complementary food for 6 months.

Methods: This secondary analysis used data from a randomized controlled trial of 500 infants aged 6-9 months in Jouberton, South Africa, who were randomly assigned to receive one egg daily, n = 250 (treatment) or no egg, n = 250 (control) for 6 months. Clinical allergy symptoms were assessed with the Childhood Allergy and Immunology Research questionnaire. Infants were tested with a skin prick test for egg sensitization at baseline and at the end of the study for additional food allergens. The fatty acid composition was analyzed in whole blood at the endpoint.

Results: At the endpoint, egg sensitization was 1.9% in the egg intervention group and 2.0% in the control group (aOR 0.936 [95% CI 0.229, 3.822]; p = .926) and all foods sensitization was 7.5% in the egg intervention group and 12.9% in the control group (aOR 0.515 [0.264, 1.005]; p = .052). There were no reported acute egg-related allergy symptoms at baseline and midpoint in the two groups. The incidence of allergic disease during the study was 7.5% in the egg intervention group and 13.4% in the control group (aOR = 0.545 [95% CI: 0.283, 1.048]; p = .069). The total and long-chain polyunsaturated fatty acid omega-6/omega-3 ratios were higher in the intervention group (β = .173 [0.291, 2.898], p = .021 and β = .198 [0.149, 0.902], p = .007) with no effect on omega-3 fatty acid composition.

Conclusion: Complementary feeding with daily eggs may reduce overall allergic sensitization to common allergenic foods.

Anaemia and iron deficiency

(See also Nutrition – micronutrients and food fortification)

Matern Child Nutr. 2025 May 20:e70033.

doi: 10.1111/mcn.70033. Online ahead of print.

Micronutrient Powders Combined With Malaria Chemoprevention to Improve Anaemia and Cognitive Function in Early Childhood in Mali: A Cluster-Randomised Trial

Niéle H Diarra¹, Yahia Dicko¹, Natalie Roschnik², Modibo Bamadio¹, Michael Boivin³, Yvonne Griffiths⁴, Rebecca Jones⁵, Sham Lal⁶, Helen Moestue², Hamidou Niangaly⁷, Lauren Pisani², Renion Saye⁸, Kalifa Sidibe¹, Karla Smuts⁶, Nia-An Philippe Thera¹, Josselin Thuilliez⁹, Hans Verhoef¹⁰, Moussa Sacko⁸, Siân E Clarke⁶

Abstract

A cluster-randomised controlled trial was conducted in 60 communities in southern Mali to evaluate the impact of micronutrient powders (MNP) combined with seasonal malaria chemoprevention (SMC) on anaemia (primary endpoint), Plasmodium infection, stunting and cognitive function in children < 5 years. The 60 communities were randomly allocated to the intervention or control arm, and cross-sectional biomedical and cognitive surveys were conducted after 1 and 3 years in a random sample of 3 and 5 years olds (1052 and 1081 children, respectively). All children aged 3-59 m in intervention and control communities received two rounds of SMC each year during the peak malaria season, and in intervention communities, all children aged 6-59 m additionally received 4 months of daily MNP after the peak malaria season. Despite a high baseline prevalence of anaemia and good fidelity to intervention, this trial found no evidence of impact on study outcomes. The prevalence of anaemia was similar in both arms for both age groups after 1 and 3 years of intervention-

after 3 years, the prevalence of anaemia amongst 3-year olds was 57.6% in the intervention arm versus 60.1% in the control group ($p = 0.352$). For 5-year olds, it was 51.3% and 53.0%, respectively ($p = 0.607$). No effect was observed on stunting or cognitive function either.

Indian J Hematol Blood Transfus. 2025 Apr;41(2):267-273.

doi: 10.1007/s12288-024-01880-1. Epub 2024 Sep 28.

Sesame Jaggery Ball Supplementation as a Dietary Adjunct Therapy in Treating Moderate Iron Deficiency Anemia Among Children Aged 6-11 Years in South India: An Open-Labeled Randomized Controlled Trial

[Yenduri Naimisha¹](#), [Dhandapany Gunasekaran¹](#), [Ramasamy Ramesh²](#), [D Madhavi Massilamani³](#)

Abstract

The prevalence of iron deficient anemia in Indian children has continued to be high for decades, despite drastic measures. Natural food dietary diversification with foodstuffs prepared at home using locally available ingredients could be helpful to counter childhood anemia. In this open-labelled randomized controlled trial, 82 consecutive children aged 6-11 years diagnosed with moderate iron deficiency anemia were randomized into two groups. Children in the control group received 3 mg/kg/day of elemental iron orally in a syrup form, for eight weeks. In addition to the oral iron syrup in the same dose, the intervention group received one sesame jaggery ball (containing 60 g of sesame seeds and jaggery each) for eight weeks. The increases in hemoglobin (Hb) at 4 and 8 weeks were estimated as the primary outcomes. The increases in serum ferritin and body weight at eight weeks were measured as the secondary outcomes. The increase in the median Hb levels of the intervention group at four weeks [0.9 (0.6, 1.5) Vs 0.8 (0.4, 1.2), $p=0.045$] and eight weeks [1.7 (1.0, 2.4) Vs 1.3 (0.6, 2.0), $p=0.013$] were statistically more significant than the control group. Likewise, the increase in the serum ferritin levels [10.7 (6.4, 16.7) Vs 6.2 (4.6, 13.3), $p=0.015$] and body weight [0.8 (0.3, 1.4) Vs 0.1 (-0.4, 0.6)] in the intervention group were significantly more than in the control group. Besides routine oral iron syrup, daily supplementation of sesame jaggery balls in moderate iron-deficient anemic children improves their iron status.

J Nutr. 2024 Dec;154(12):3740-3748.

doi: 10.1016/j.tjnut.2024.10.042. Epub 2024 Oct 30.

Vitamin C-Rich Guava Consumed with Mungbean Dal Reduces Anemia and Increases Hemoglobin but not Iron Stores: A Randomized Controlled Trial of Food-to-Food Fortification in Indian Children

[Varsha Rani¹](#), [Diego Moretti²](#), [Neelam Khetarpaul³](#), [Prashanth Thankachan⁴](#), [Michael B Zimmermann⁵](#), [Alida Melse-Boonstra⁶](#), [Inge D Brouwer⁷](#)

Abstract

Background: Adding vitamin C-rich fruit to staples containing iron could be an effective strategy to improve iron bioavailability and thereby reduce iron-deficiency anemia in children.

Objectives: We aimed to assess the effect of consuming a mungbean-based meal with or without guava fruit on body iron stores, hemoglobin concentration, and anemia of children as part of a school feeding program.

Methods: We conducted a 7-mo randomized, controlled trial with 6- to 10-y-old school children (n = 200; 46% anemic, 71% iron-deficient) from a rural community in Haryana, North India. Children were assigned to 2 treatment groups to daily receive either a meal of mungbean dal only (3.0 mg iron; vitamin C:iron molar ratio ~0.5:1), or mungbean dal with fresh guava (3.2 mg iron; ~170 mg vitamin C; molar ratio ~18:1). Meals were served every school day under supervision. The primary outcome was body iron stores, whereas concentrations of hemoglobin and other iron indicators were secondary outcomes.

Results: Daily consumption of mungbean dal along with guava did not result in an overall improvement of body iron stores [mean treatment effect: 0.65 mg/kg body weight; 95% confidence interval (CI): -0.34, 1.63; P = 0.197]. However, compared with children who consumed mungbean dal only, children in the guava group showed a larger increase in hemoglobin concentration (3.7 g/L; 95% CI: 1.6, 5.6; P = 0.001), and a larger drop in the prevalence of anemia (-51%; 95% CIs: -74, -10; P = 0.022) and iron-deficiency anemia (-56%, 95% CI: -83, 13; P = 0.087). These effects were more pronounced in children who were iron deficient at study start.

Conclusions: Addition of guava to a mungbean-based meal containing a moderate amount of iron increased hemoglobin and reduced anemia but did not provide enough additional absorbed iron to also increase body iron stores. Food-to-food fortification by inclusion of vitamin C-rich fruits in iron-containing school meals may help alleviate the burden of anemia in children.

Lancet Glob Health. 2025 Mar;13(3):e497-e507.

doi: 10.1016/S2214-109X(24)00559-X.

[Comparative effectiveness of daily therapeutic supplementation with multiple micronutrients and iron-folic acid versus iron-folic acid alone in children with mild-to-moderate anaemia in rural India: an open-label, randomised controlled trial](#)

[Ravi Prakash Upadhyay¹](#), [Ranadip Chowdhury¹](#), [Sudarshan Mundra¹](#), [Sunita Taneja²](#), [Molly Jacob³](#), [Umesh Kapil⁴](#), [Ashish Bavdekar⁵](#), [Nita Bhandari¹](#)

Abstract

Background: Anaemia is a major public health problem among children younger than 5 years and supplementation with iron-folic acid alone has not been found to result in desired improvements in haemoglobin concentrations. We aimed to compare the effect of supplementation with iron-folic acid plus multiple micronutrients versus iron-folic acid supplementation alone on haemoglobin concentration and cure rates in children with mild-to-moderate anaemia.

Methods: In this individually randomised controlled trial conducted in rural Haryana, India, children (aged 6-59 months) with mild-to-moderate anaemia (haemoglobin ≥ 7 to <11 g/dL) were randomly assigned (1:1) to receive either daily iron-folic acid plus multiple micronutrients or iron-folic acid alone for 90 days. The primary outcomes were mean haemoglobin concentration and the proportion of children cured of anaemia (haemoglobin ≥ 11 g/dL) at 90 days, assessed in the intention-to-treat population, which included all randomly assigned participants for whom primary outcome assessments were done. Safety

was assessed in all randomly assigned participants. The trial was registered with the Clinical Trial Registry-India, CTRI/2020/10/028298.

Findings: Between March 1, 2021, and March 7, 2022, 1300 children were randomly assigned to the iron-folic acid plus multiple micronutrients group (n=648) or the iron-folic acid alone group (n=652). At baseline, 93 (20%) of 472 children had vitamin B₁₂ deficiency (≤ 203 pg/mL), 16 (3%) of 475 children had serum folate deficiency (< 4 ng/mL), and 44 (9%) of 468 children had zinc deficiency (< 66 μ g/dL). 611 children in the iron-folic acid plus micronutrients group and 626 children in the iron-folic acid alone group had a blood sample collected at the end of the 90-day supplementation period and were included in the primary outcome assessment. At 90 days, no differences in mean haemoglobin concentration were identified between the treatment groups (mean difference 0.06 [95% CI -0.05 to 0.16]). 489 (80%) of 611 children in the iron-folic acid plus micronutrients group and 492 (79%) of 626 children in the iron-folic acid alone group were cured of anaemia (risk ratio 1.02 [95% CI 0.90 to 1.16]). Compliance rates in both groups exceeded 75%. Black stools were the most common side-effect observed in both groups (640 [99%] of 648 children in iron-folic acid plus micronutrients group and 643 [99%] of 652 children in the iron-folic acid alone group).

Interpretation: In children with mild-to-moderate anaemia, supplementation with multiple micronutrients and iron-folic acid did not result in significant benefits compared with iron-folic acid alone. Efforts that focus on ensuring high compliance with iron-folic acid supplementation alone might achieve satisfactory rates of anaemia recovery.

Nat Commun. 2024 Oct 5;15(1):8640.

doi: 10.1038/s41467-024-53013-x.

Effects of iron supplements and iron-containing micronutrient powders on the gut microbiome in Bangladeshi infants: a randomized controlled trial

[Andrew Baldi^{1,2}](#), [Sabine Braat^{3,4,5}](#), [Mohammed Imrul Hasan^{3,6,7}](#), [Cavan Bennett^{3,6}](#), [Marilou Barrios⁸](#), [Naomi Jones³](#), [Imadh Abdul Azeez^{3,6}](#), [Stephen Wilcox⁸](#), [Pradip Kumar Roy^{3,9}](#), [Mohammad Saiful Alam Bhuiyan⁷](#), [Ricardo Ataide^{3,5}](#), [Danielle Clucas^{3,6,10}](#), [Leila M Larson¹¹](#), [Jena Hamadani⁷](#), [Michael Zimmermann¹²](#), [Rory Bowden^{3,6,8}](#), [Aaron Jex^{3,6,9}](#), [Beverley-Ann Biggs^{5,13}](#), [Sant-Rayn Pasricha^{14,15,16,17}](#)

Abstract

Anemia is highly prevalent globally, especially in young children in low-income countries, where it often overlaps with a high burden of diarrheal disease. Distribution of iron interventions (as supplements or iron-containing multiple micronutrient powders, MNPs) is a key anemia reduction strategy. Small studies in Africa indicate iron may reprofile the gut microbiome towards pathogenic species. We seek to evaluate the safety of iron and MNPs based on their effects on diversity, composition, and function of the gut microbiome in children in rural Bangladesh as part of a large placebo-controlled randomized controlled trial of iron or MNPs given for 3 months (ACTRN12617000660381). In 923 infants, we evaluate the microbiome before, immediately following, and nine months after interventions, using 16S rRNA gene sequencing and shotgun metagenomics in a subset. We identify no increase in diarrhea with either treatment. In our primary analysis, neither iron nor MNPs alter gut microbiome diversity or composition. However, when not adjusting for multiple comparisons, compared to placebo, children receiving iron and MNPs exhibit reductions in

commensal species (e.g., Bifidobacterium, Lactobacillus) and increases in potential pathogens, including Clostridium. These increases are most evident in children with baseline iron repletion and are further supported by trend-based statistical analyses.

Am J Clin Nutr. 2025 May;121(5):1090-1098.

doi: 10.1016/j.ajcnut.2025.02.018. Epub 2025 Feb 19.

Role of hepcidin on benefits and risks of supplementation with iron syrup and multiple micronutrient powders in Bangladeshi children: a substudy to a randomized controlled trial

[Leila M Larson¹](#), [Andrew Baldi²](#), [Mohammed Imrul Hasan²](#), [Naomi Jones²](#), [Emily Owens Pickle³](#), [Ricardo Ataide⁴](#), [Cavan Bennett²](#), [Mohammad Saiful Alam Bhuiyan⁵](#), [Sm Mulk Uddin Tipu⁵](#), [Fahmida Tofail⁵](#), [Beverley-Ann Biggs⁶](#), [Jena Hamadani⁵](#), [Sant-Rayn Pasricha⁷](#), [Sabine Braat⁸](#)

Abstract

Background: Hepcidin can determine individuals' responses to iron supplementation, but limited evidence exists from pediatric trials.

Objectives: We aimed to examine the influence of hepcidin on the effects of supplementation with iron syrup and multiple micronutrient powders (MNPs) on hemoglobin and ferritin concentrations and the incidence of diarrhea in young children.

Methods: Participants included a subsample of 1281 8-mo-old children enrolled in a 3-arm, double-blind, double-dummy, individually randomized controlled trial examining the efficacy of 3 mo of universal supplementation with daily iron syrup (12.5 mg iron), MNPs (containing 12.5 mg iron), or placebo in children living in Bangladesh. In all participants at baseline, immediately postintervention (month 3), and after a further 9 mo of follow-up (month 12), serum hepcidin concentrations were measured by enzyme-linked immunosorbent assay, venous hemoglobin by HemoCue 301, and incidence of diarrhea by caregiver report. We used a likelihood-based longitudinal data analysis model to examine effect modification from baseline hepcidin on the effects of iron syrup or MNPs on hemoglobin and ferritin concentrations and a log-binomial model on the incidence of diarrhea at months 3 and 12.

Results: Hepcidin modified the effect of MNPs, but not iron syrup, compared with placebo on hemoglobin and ferritin concentrations immediately postintervention. The treatment effect of MNPs compared with placebo in the change from baseline to month 3 was larger among children with low compared with not-low baseline hepcidin [hemoglobin: mean difference 11.6 g/L (7.2, 15.9) compared with 4.3 (3.09, 5.7), P-interaction = 0.002; ferritin: geometric mean ratio 2.4 (1.6, 3.6) compared with 1.5 (1.3, 1.7), P-interaction = 0.024]. This effect modification was not sustained at month 12. Hepcidin did not modify the effects of either intervention on the incidence of diarrhea.

Conclusions: Immediate effects of MNPs on child hemoglobin and iron status are larger among those with low compared with not-low hepcidin, indicating that preintervention screening could help identify those who would benefit most from MNPs.

doi: 10.1016/S2352-3018(24)00238-8. Epub 2024 Oct 11.

Safety and efficacy of iron supplementation with 3 months of daily ferrous sulphate in children living with HIV and mild-to-moderate anaemia in Uganda: a double-blind, randomised, placebo-controlled trial

[Anne E P Frosch¹](#), [Victor Musiime²](#), [Christopher Staley³](#), [Andrea L Conroy⁴](#), [Diana Rutebarika⁵](#), [Gilbert Ategeka⁶](#), [Sarah E Cusick⁷](#)

Abstract

Background: Iron deficiency is the most common nutritional deficiency in the world, but iron supplementation can increase risk of opportunistic infections, especially in children living with HIV. We aimed to assess the effect of supplemental iron on haemoglobin concentration in children living with HIV and mild-to-moderate anaemia in Uganda.

Methods: We did a double-blind, randomised, placebo-controlled trial of iron supplementation in children aged 6 months to 12 years living with HIV at two sites (ie, Kampala and Fort Portal, Uganda). Inclusion criteria were confirmed diagnosis of HIV and stable treatment with antiretroviral therapy for at least 6 months. Exclusion criteria were already taking iron supplementation, acute illness, current opportunistic infection, fever, known sickle cell disease, severe undernutrition, or any chronic illness requiring medical attention. Children were randomly assigned (1:1) via simple randomisation to an 84-day course of either ferrous sulphate or identical placebo tablets once per day. Randomisation codes were computer-generated and stratified by age (ie, 6-23 months or 24 months and older) by the Toronto Institute of Pharmaceutical Technology, the tablet manufacturer. Participants and all individuals giving the interventions, assessing outcomes, and analysing data were masked to group assignment. Children aged 6-23 months received tablets of 12.5 mg ferrous sulphate or identical placebo; children aged 24 months or older received tablets of 30.0 mg ferrous sulphate or identical placebo. Caregivers were instructed to give the supplement after a meal, preferably after an evening meal. The primary outcome was mean haemoglobin concentration at day 84. All analyses were intention to treat. This trial is registered at ClinicalTrials.gov ([NCT03596996](#)).

Findings: Between May 5, 2018, and Nov 6, 2019, 973 children living with HIV were screened, of whom 200 (20%) met all inclusion criteria and were enrolled. 102 (51%) were randomly assigned to receive iron and 98 (49%) to receive placebo. In the iron group, 57 (56%) of 102 children were male and 45 (44%) were female. In the placebo group, 44 (45%) of 98 children were male and 54 (55%) were female. Iron supplementation was associated with improvement in haemoglobin in unadjusted analysis ($p=0.029$), but not adjusted analysis ($p=0.10$), and with improvement in ferritin and hepcidin in both adjusted ($p=0.0046$; $p=0.0079$) and unadjusted ($p<0.0001$; $p<0.0001$) analyses at day 84. There were four hospital admissions, all for children in the iron group; none were fatal: two children were admitted to hospital with pneumonia, one with severe malaria, and one with hepatitis. Frequency of admissions was not significantly different between groups ($p=0.12$).

Interpretation: Iron could have haematological benefit and improve iron status in children living with HIV in Uganda. Future studies powered for morbidity outcomes with longer follow-up are needed, as are those that evaluate the effects of iron supplementation on neurocognitive outcomes.

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The Effect of Vitamin B₁₂ Supplementation on Leukocyte Telomere Length in Mildly Stunted Nepalese Children: A Secondary Outcome of a Randomized Controlled Trial

[Manjeswori Ulak¹](#), [Ingrid Kvestad²](#), [Ram K Chandyo³](#), [Catherine Schwinger⁴](#), [Sudha Basnet⁵](#), [Merina Shrestha⁵](#), [Suman Ranjitkar⁵](#), [Linda Vy Nguyen⁶](#), [Diana Corona-Pérez⁶](#), [Immaculata De Vivo⁶](#), [Per M Ueland⁷](#), [Adrian McCann⁷](#), [Tor A Strand⁸](#)

Abstract

Background: Vitamin B₁₂ is essential for deoxyribonucleic acid synthesis and genome stability. A deficiency of vitamin B₁₂ is associated with telomere shortening, genomic aging, and increased risk of chronic disease and mortality.

Objectives: The study aims to determine the effect of vitamin B₁₂ supplementation on leukocyte telomere length (LTL) in infants at risk of vitamin B₁₂ deficiency.

Methods: The study was a predefined secondary analysis of a randomized controlled trial enrolling 600 Nepalese infants aged 6 -11 mo, who were supplemented with 2 µg (2-3 recommended daily allowances) vitamin B₁₂ or placebo daily for 1 y. At the end of the study, LTL was measured in 497 participants. Mean LTL was compared between the treatment arms in the full sample and predefined subgroups based on markers of vitamin B₁₂ status, hemoglobin, sex, and growth indices.

Results: LTL at end-study did not differ between the vitamin B₁₂ and placebo arm with a standardized mean difference (95% confidence interval) of 0.04 (-0.14, 0.21). There was no effect of vitamin B₁₂ on LTL in any of the subgroups.

Conclusions: Providing daily vitamin B₁₂ for 1 y during infancy in a population at risk of vitamin B₁₂ deficiency does not affect LTL

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Comparison of Efficacy and Safety of Parenteral vs Oral Route of Vitamin B12 Supplementation for the Treatment of Vitamin B12 Deficiency Anemia in Children: A Systematic Review

[Meenakshi Sachdeva¹](#), [Abhishek Purohit¹](#), [Meenakshi Malik¹](#), [Lovely Jain¹](#), [Pranita Pradhan¹](#), [Joseph L Mathew^{1,2}](#)

Abstract

Context: Vitamin B12 deficiency in children is treated with either parenteral or oral supplementation. Although the efficacy of supplementation is reportedly comparable for the 2 routes in adults, there is limited data for children.

Objective: The objective of this review was to compare the efficacy and safety of parenteral vs oral B12 supplementation in children with vitamin B12 deficiency anemia.

Data sources: A comprehensive literature search was conducted in PubMed, EMBASE, the Cochrane Library, Scopus, Web of Science, four Clinical Trials Registries, and 2 gray literature databases, for randomized controlled trials (RCTs) comparing the parenteral vs oral routes of administering B12 in children with vitamin B12 deficiency anemia.

Data extraction: Among 6467 citations screened, there was only 1 eligible RCT, in which children with vitamin B12 deficiency anemia received 1 dose of 1000 µg parenterally before being randomized to either parenteral or oral therapy.

Data analysis: After 3 months, the parenteral route resulted in higher B12 levels compared with the oral route (median [IQR]: 653 [459, 835] vs 506 [399, 726] pg/mL). The changes from baseline in vitamin B12 levels (median [IQR]: 600 [389, 775] vs 399 [313, 606] pg/mL, $P = .016$) and hemoglobin (2.7 [0.4, 4.6] vs 0.5 [-0.1, 1.2] g/dL, $P = .001$) were also significantly greater with the parenteral route. There was no data on safety. In terms of quality, the RCT was judged to be at "high risk of bias."

Conclusion: Limited evidence from a single, methodologically weak RCT suggested that the parenteral route is more efficacious than the oral route. However, considering the limitations in quality and quantity of the available evidence, this should be interpreted with caution.

Anaesthesia and intensive care

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[Comparison of intranasal dexmedetomidine and ketamine for paediatric premedication: A randomized study](#)

[N Kumari¹](#), [P K Dubey²](#), [S Singh¹](#)

Abstract

Introduction and objectives: Paediatric patients are given premedication in order to decrease preoperative anxiety, allow smooth induction, and prevent postoperative psychological insult and behavioural changes. A child friendly method of administration is desirable. We compared intranasal administration of dexmedetomidine and ketamine in the operating room environment, to evaluate the Faces, Legs, Activity, Cry and Consolability (FLACC) score at the time of establishing intravenous access for induction of general anaesthesia.

Methods: This prospective, double-blind, randomized controlled trial was conducted at a tertiary care center. One hundred patients, 2-10 years of age, ASA physical status 1 & 2, scheduled for general anaesthesia were enrolled. Patient's premedication behaviour was assessed by the modified Yale Preoperative Anxiety Scale Short Form (mYPAS-SF). Patients in Group D received Dexmedetomidine 1 mcg/kg intranasally, and patients in Group K received Ketamine 5 mg/kg intranasally. After 45 min, patients were transferred to the operating table where intravenous cannulation was carried out and the response to needle insertion was assessed by FLACC scale. Vital signs, including the pulse-oximetry, heart rate and respiratory rate were monitored. Side effects such as nausea, vomiting, and agitation were also recorded.

Results: A significantly higher FLACC score was seen in Group D as compared to Group K ($p = 0.001$). The mean heart rate between two groups was found to be significantly ($p = 0.001$) lower in Group D compared to Group K. However, the proportion of adverse events was 8% in patients who received ketamine.

Conclusions: Intranasal ketamine in a dose of 5 mg/kg is clinically more effective as premedication in children aged 2-10 years in comparison with intranasal dexmedetomidine in a dose of 1 mcg/kg.

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Evaluating the safety of procedural sedation in emergency department settings among the pediatric population: a systematic review and meta-analysis of randomized controlled trials

[Muhammad Taha Khan¹](#), [Ammar Ishaq²](#), [Samia Rohail¹](#), [Samia Aziz Sulaiman³](#), [Fatima Ali Raza¹](#), [Haris Habib²](#), [Aman Goyal⁴](#)

Abstract

Objective: Our meta-analysis aimed to evaluate the safety of procedural sedation and analgesia in pediatric emergency department (ED) settings by investigating the incidence of cardiac, respiratory, gastrointestinal, and neurological adverse events associated with different sedation medications.

Methods: In accordance with PRISMA guidelines, a comprehensive database search for randomized controlled trials was performed across ten databases from January 2005 to June 2024. Our inclusion criteria included randomized controlled trials involving children under 18 years old undergoing pediatric sedation and analgesia in the ED. Data on medication types, dosages, administration routes, and adverse events were extracted and analyzed. Primary endpoints included cardiac, respiratory, gastrointestinal, and neurological adverse events.

Results: Seventeen studies met the inclusion criteria, a total of 2,302 procedural sedations. The most common adverse events were vomiting, agitation, and hypoxia, which occurred in 104.9 [95% CI = 76.9-132.9], 37.5 [95% CI = 20.6-54.4], 38.3 [95% CI = 23.9-52.6] of each 1000 sedations, respectively. Other adverse events included apnea, hypotension, and the need for bag-valve mask ventilation, which occurred in 8.6 [95% CI: 3.5-13.6], 9.3 [95% CI: -1.4 to 20.1], and 13.5 [95% CI: 3.2-23.8] of each 1,000 sedations, respectively. Severe adverse events were rare, with no reported instances of intubation and only one case of laryngospasm. Subgroup analyses revealed varying incidence rates of adverse events across different sedation protocols, with ketamine and its combinations showing higher rates of specific respiratory complications.

Conclusions: Procedural sedation in pediatric EDs is generally safe, with a low incidence of adverse events, such as vomiting, agitation, and hypoxia. Life-threatening respiratory adverse events are extremely rare. Our findings thus support the careful selection and monitoring of sedation protocols to minimize risks.

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Comparison of a Besdata Video Laryngoscope With a Direct Laryngoscope in Neonates and Infants of 6 Months of Age-A Randomized Controlled Trial

[Vedha Venkatesh¹](#), [Gnanasekaran Srinivasan¹](#), [Prasanna Udupi Bidkar¹](#), [Priya Rudingwa¹](#)

Abstract

Introduction: Airway management of infants is challenging, and video laryngoscopes can help reduce intubation attempts and improve glottic visualization. In this study, we compared the Besdata video laryngoscope with the Miller laryngoscope in neonates and infants 6 months of age.

Methods: After obtaining informed written consent from the parents, we randomized 80 infants scheduled for elective surgery requiring endotracheal intubation into two groups, Group DL and Group VL. We used a direct laryngoscope with a Miller blade in group DL and a Besdata video laryngoscope with a Miller blade in group VL. We compared the time taken for intubation, glottis visualization time, percentage of glottic opening (POGO) score, Cormack Lehane (CL) grades, first attempt success rate, need for external laryngeal manipulation, and complications between the two groups.

Results: The median (interquartile range, IQR) time taken for intubation was 36.0 s (30.5-39.0) versus 35.0 s (28.0-40.0) ($p = 0.35$), similar in both groups. The median difference (95% confidence interval, CI) was 0.0 s [-4.0 to 5.0]. The median (IQR) time for glottic visualization was 13.0 s (10.0-15.5) versus 10.0 s (8.0-12.0), and the median difference (95% CI) was 2.0 s [1-6] in group DL and group VL, respectively, showing shorter time with a video laryngoscope. We also found better POGO scores and decreased need for optimal external laryngeal manipulation with a Besdata video laryngoscope. The first attempt intubation success rate, use of bougie, and complications were similar in both groups.

Conclusion: The Besdata video laryngoscope with a zero-size Miller blade has shown a similar intubation time when compared with a conventional laryngoscope in neonates and infants of 6 months of age. The first attempt intubation success rate was also comparable between the two groups. However, the Besdata video laryngoscope is associated with comparatively better glottic visualization.

Intensive care

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Evaluation of the use of telemedicine in pediatric intensive care units: a cluster-randomized trial

[Gabriela de Oliveira Laguna Silva¹](#), [Emanuele König Klever¹](#), [Jacqueline Castro da Rocha¹](#), [Mariana Motta Dias da Silva²](#), [Jerusa da Rosa de Amorim¹](#), [Vanessa Cristina Jacovas¹](#), [Bárbara Marina Simionato¹](#), [Luciane Gomes da Cunha¹](#), [Ana Paula Berni Zaupa¹](#), [João Ronaldo Mafalda Krauzer¹](#), [Aristóteles de Almeida Pires¹](#), [Felipe Cezar Cabral¹](#), [Taís de Campos Moreira¹](#), [Hilda Maria Rodrigues Moleda Constant¹](#)

Abstract

Introduction: Telemedicine has shown promising results, allowing specialists to provide rapid and effective care in remote locations. However, to our knowledge, current evidence is not robust enough to prove the effectiveness of this tool. This cluster-randomized trial (CRT) aimed to evaluate the impact of telemedicine on clinical care indicators in pediatric intensive care units (PICUs).

Methods: An open-label CRT was conducted in 16 PICUs within the Brazilian public health system. The trial took place from August 2022 to December 2023 and compared an intervention group, which received telemedicine support, with a control group, which received usual PICU care. The primary outcome was the PICU length of stay. The main secondary outcomes were mortality rate and ventilator-free days.

Results: A total of 1393 participants were included, 657 in the control group and 736 in the intervention group. The mean PICU length of stay was 10.42 (SD, 10.71) days for the control group and 11.52 (SD, 10.80) days for the intervention group. The overall mean of ventilator-free days was 6.82 (SD, 7.71) days. Regarding mortality, 7.54% of participants died in total. No significant difference was found in the outcomes between the groups.

Conclusion: Despite the potential benefits of telemedicine, its effective implementation in the Brazilian public health system faces considerable challenges, highlighting the continued importance of investigating and improving the role of telemedicine in pediatric critical care.

Indian J Pediatr. 2024 Aug 5.

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High Flow Nasal Cannula Versus Conventional Oxygen Therapy and Incidence of Post-Extubation Airway Obstruction in PICU: An Open-Label Randomized Controlled Trial (HiFloCOT-PICU Trial)

[K C Sudeep¹](#), [Suresh Kumar Angurana²](#), [Karthi Nallasamy¹](#), [Arun Bansal¹](#), [Muralidharan Jayashree¹](#)

Abstract

Objectives: To study the impact of high flow nasal cannula (HFNC) vs. conventional oxygen therapy (COT) (by simple nasal cannula) as respiratory support after extubation on the rates of post-extubation airway obstruction (PEAO) among mechanically ventilated critically ill children.

Methods: This open-label randomized controlled trial was conducted in pediatric intensive care unit (PICU) of a tertiary care teaching hospital in North India over a period of 7 mo (11 August 2021 to 10 March 2022). Children aged 3 mo to 12 y who required invasive mechanical ventilation for > 72 h and had passed spontaneous breathing trial (ready for extubation) were enrolled and randomized by computer generated block randomization to receive HFNC or COT after extubation. Primary outcome was rate of PEAO (assessed by modified Westley croup score, mWCS) within 48 h of extubation; and secondary outcomes were rate and number of adrenaline nebulization, treatment failure (requiring escalation of respiratory support), extubation failure, adverse events, and length of PICU stay in two groups.

Results: During the study period, 116 children were enrolled (58 each in HFNC and COT groups). There was no difference in rate of PEAO (55% vs. 51.7%, respectively), need of adrenaline nebulization, extubation failure, adverse events, and duration of PICU stay in two groups. However, the HFNC group had significantly lower rates of treatment failure (27.6% vs. 48.3%, $p = 0.02$).

Conclusions: The rate of PEAO was similar in HFNC and COT groups. However, HFNC group had significantly lower rate of treatment failure requiring escalation of respiratory support.

Indian J Pediatr. 2025 Mar 5.

doi: 10.1007/s12098-025-05447-4. Online ahead of print.

Sedative and Analgesic Drug Rotation Protocol Versus Non-Rotation Protocol in Mechanically Ventilated Children: A Randomised Controlled Trial

[Uppaluri Naga Pradeep Babu¹](#), [Nisha Toteja²](#), [Bharat Choudhary³](#), [Kuldeep Singh¹](#), [Siyaram Didel¹](#), [Daisy Khara⁴](#)

Abstract

Objectives: To compare the proportion of children with withdrawal syndrome in sedoanalgesic drug rotation protocol vs. sedoanalgesia with no rotation using Withdrawal Assessment Tool Version-1 (WAT-1).

Methods: Sixty children one mo to 18 y admitted to the Pediatric Intensive Care Unit (PICU) for mechanical ventilation were randomized into two groups in a 1:1 ratio. The intervention group received a protocolized rotation of sedative and analgesic drugs combination. In contrast, the control group received sedative and analgesic drugs without any rotation for the entire duration of ventilation. In both groups, adequate depth of sedation was achieved by titrating the sedatives using COMFORT-Behavioural (COMFORT-B) scores. The primary outcome assessed was the incidence of withdrawal syndrome as defined by a WAT-1 score ≥ 3 . Secondary outcomes included cumulative doses of midazolam needed as rescue therapy, mechanical ventilation (MV) duration, need for inotropic support, and the length of stay (LOS) in the PICU.

Results: In the present study, median (IQR) age of patients was 24 (7, 93) mo. There was a reduced incidence (20% vs. 53.3%; $P = 0.004$) and median duration of withdrawal syndrome (WAT-1 score ≥ 3) [1 (IQR 0, 2) vs. 0 (IQR 0, 0); $P = 0.012$] in the intervention group compared to the control group. The need for inotropic support was higher in the intervention group (62.5% vs. 37.5%; $P = 0.038$). No other statistically significant outcomes were seen.

Conclusions: The present study showed that protocolised rotation of sedoanalgesic drugs in mechanically ventilated children can result in lower incidence as well as the duration of withdrawal syndrome.

Indian Pediatr. 2025 Jun;62(6):407-413.

doi: 10.1007/s13312-025-00035-3. Epub 2025 Apr 11.

[Role of Proton Pump Inhibitor as Stress Ulcer Prophylaxis in Sick Children: A Randomized Controlled Trial](#)

[Ananya Kavilapurapu¹](#), [A V Lalitha²](#), [Santu Ghosh³](#)

Abstract

Objective: To evaluate the efficacy of intravenous pantoprazole as a stress ulcer prophylaxis in sick children to prevent gastrointestinal (GI) bleeding.

Methods: A randomized controlled trial included children aged one-month to 18 years requiring intensive care. Participants were randomly assigned to receive intravenous pantoprazole or a placebo (normal saline) daily. The primary outcome was the incidence of GI bleeding (clinically significant or overt). Secondary outcomes were the median time of onset of GI bleeding, incidence of ventilator-associated pneumonia (VAP), duration of hospitalization, organ dysfunction scores, and all-cause mortality.

Results: A total of 151 and 150 children were allocated to group A (pantoprazole) and group B (placebo), respectively. No significant difference was observed in the incidence of GI bleeding between the groups (group A: 21/151 vs group B: 19/150 [RR (95% CI) 1.03 (0.18, 5.82), $P = 0.985$]. Comparable results were observed for clinically significant GI bleeding (1.3% vs 0.6%; RR (95% CI) 0.54 (0.21, 1.28); $P = 0.653$ and overt GI bleeding [12.6% vs 12%; RR (95% CI) 0.98 (0.39, 2.23); P value = 0.313]. On multivariate analysis, there was a reduced

incidence of GI bleeding in children with coagulopathy in pantoprazole group (n = 29) as compared to placebo (n = 25) [RR (95%CI) 0.52 (0.32, 0.87); P = 0.022].

Conclusion: Among critically ill children, pantoprazole prophylaxis did not reduce the incidence of gastrointestinal bleeding, although, a notable decrease in gastrointestinal bleeding was observed in children with coagulopathy.

Procedural sedation

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doi: 10.1007/s43678-024-00809-x. Epub 2024 Nov 10.

[Evaluating the safety of procedural sedation in emergency department settings among the pediatric population: a systematic review and meta-analysis of randomized controlled trials](#)

[Muhammad Taha Khan¹](#), [Ammar Ishaq²](#), [Samia Rohail¹](#), [Samia Aziz Sulaiman³](#), [Fatima Ali Raza¹](#), [Haris Habib²](#), [Aman Goyal⁴](#)

Abstract

Objective: Our meta-analysis aimed to evaluate the safety of procedural sedation and analgesia in pediatric emergency department (ED) settings by investigating the incidence of cardiac, respiratory, gastrointestinal, and neurological adverse events associated with different sedation medications.

Methods: In accordance with PRISMA guidelines, a comprehensive database search for randomized controlled trials was performed across ten databases from January 2005 to June 2024. Our inclusion criteria included randomized controlled trials involving children under 18 years old undergoing pediatric sedation and analgesia in the ED. Data on medication types, dosages, administration routes, and adverse events were extracted and analyzed. Primary endpoints included cardiac, respiratory, gastrointestinal, and neurological adverse events.

Results: Seventeen studies met the inclusion criteria, a total of 2,302 procedural sedations. The most common adverse events were vomiting, agitation, and hypoxia, which occurred in 104.9 [95% CI = 76.9-132.9], 37.5 [95% CI = 20.6-54.4], 38.3 [95% CI = 23.9-52.6] of each 1000 sedations, respectively. Other adverse events included apnea, hypotension, and the need for bag-valve mask ventilation, which occurred in 8.6 [95% CI: 3.5-13.6], 9.3 [95% CI: -1.4 to 20.1], and 13.5 [95% CI: 3.2-23.8] of each 1,000 sedations, respectively. Severe adverse events were rare, with no reported instances of intubation and only one case of laryngospasm. Subgroup analyses revealed varying incidence rates of adverse events across different sedation protocols, with ketamine and its combinations showing higher rates of specific respiratory complications.

Conclusions: Procedural sedation in pediatric EDs is generally safe, with a low incidence of adverse events, such as vomiting, agitation, and hypoxia. Life-threatening respiratory adverse events are extremely rare. Our findings thus support the careful selection and monitoring of sedation protocols to minimize risks.

doi: 10.1111/aas.14583.

Comparison of plasma concentration and sedative effect of sublingual and intranasal dexmedetomidine in children: A double-blind randomised controlled study

Armanullah Khan¹, Renu Sinha¹, Kanil Ranjith Kumar¹, Trimurty Velpandian¹, Souvik Maitra¹, Bikash Ranjan Ray¹

Abstract

Background: Pharmacokinetics and sedative effects of sublingual dexmedetomidine have not been established in children. The primary aim was to compare peak plasma concentration, time to reach peak plasma concentration and area under the curve with 2 µg/kg sublingual and intranasal dexmedetomidine. The secondary aims were to compare the depth of sedation, parental separation anxiety, mask acceptance, heart rate changes, analgesic requirements and recovery time with 2 µg/kg sublingual and intranasal dexmedetomidine in children.

Method: Thirty children between 2 and 12 years, weighing 10-30 kg, scheduled for surgeries were divided into two groups. Thirty minutes before the induction of anaesthesia, children were premedicated with 2 µg/kg dexmedetomidine either by intranasal drops (Group N) or sublingual wafer (Group S). Five venous blood samples were collected to measure dexmedetomidine plasma concentrations at 15, 30, 45, 60 and 120 min from dexmedetomidine administration. Sedation, parental separation anxiety, mask acceptance and heart rate were recorded. Recovery, pain and fentanyl requirements were assessed.

Results: Demographic data was comparable. Median interquartile range (IQR) dexmedetomidine peak plasma concentration in Group N (0.764 [0.650-0.820]) ng/mL was significantly higher than in Group S (0.593 [0.364-0.754]) ng/mL ($p = .014$). Plasma concentration was significantly higher at 30 and 45 min in Group N as compared to Group S ($p < .05$). The median (IQR) time to reach peak plasma concentration was shorter in Group N (45 [45-120]) minutes than in Group S (60 [45-60]) minutes, ($p = .814$). The median (IQR) area under the concentration-time curve was significantly higher in Group N (1.062 [0.848-1.20]) ng/mL.h in comparison to Group S (0.866 [0.520-1.05]) ng/mL.h ($p = .031$). Comparable sedation was achieved at 25 min in both groups. No child required treatment for decreased heart rate. Parental separation anxiety, mask acceptance, recovery and analgesic requirements were comparable.

Conclusions: Intranasal 2 µg/kg dexmedetomidine resulted in significantly higher peak plasma concentration and time to reach peak plasma concentration than sublingual wafers. Sublingual and intranasal dexmedetomidine resulted in comparable sedation, parental separation and mask acceptance.

Editorial comment: This study compared the pharmacokinetics and sedative effects of sublingual versus intranasal dexmedetomidine in children, finding that intranasal administration resulted in significantly higher peak plasma concentration and faster time to peak concentration. Both routes achieved comparable sedation, parental separation anxiety scores and mask acceptance, with no significant adverse effects observed.

Antibiotics

Antibiotic resistance and stewardship

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doi: 10.1186/s12879-024-09787-y.

[Impact of a package of point-of-care diagnostic tests, a clinical diagnostic algorithm and adherence training on antibiotic prescriptions for the management of non-severe acute febrile illness in primary health facilities during the COVID-19 pandemic in Burkina Faso](#)

[Francois Kiemde¹](#), [Juvenal Nkeramahame²](#), [Ana Belen Ibarz²](#), [Sabine Dittrich^{2,3,4}](#), [Piero Olliaro⁵](#), [Daniel Valia⁶](#), [Toussaint Rouamba⁶](#), [Berenger Kabore⁶](#), [Alima Nadine Kone⁶](#), [Seydou Sawadogo⁶](#), [Antonia Windkouni Bere⁶](#), [Diane Yirgnur Some⁶](#), [Athanase Mwinessobaonfou Some⁶](#), [Adelaide Compaore⁶](#), [Philip Horgan^{2,7,8}](#), [Stephan Weber⁹](#), [Thomas Keller⁹](#), [Halidou Tinto⁶](#)

Abstract

Objective: To assess the impact of an intervention package on the prescription of antibiotic and subsequently the rate of clinical recovery for non-severe acute febrile illnesses at primary health centers.

Methods: Patients over 6 months of age presenting to primary health care centres with fever or history of fever within the past 7 days were randomized to receive either the intervention package constituted of point-of-care tests including COVID-19 antigen tests, a diagnostic algorithm and training and communication packages, or the standard practice. The primary outcomes were antibiotic prescriptions at Day 0 (D0) and the clinical recovery at Day 7 (D7). Secondary outcomes were non-adherence of participants and parents/caregivers to prescriptions, health workers' non-adherence to the algorithm, and the safety of the intervention.

Results: A total of 1098 patients were enrolled. 551 (50.2%) were randomized to receive the intervention versus 547 (49.8%) received standard care. 1054 (96.0%) completed follow-up and all of them recovered at D7 in both arms. The proportion of patients with antibiotic prescriptions at D0 were 33.2% (183/551) in the intervention arm versus 58.1% (318/547) under standard care, risk difference (RD) -24.9 (95% CI -30.6 to -19.2, $p < 0.001$), corresponding to one more antibiotic saved every four (95% CI: 3 to 5) consultations. This reduction was also statistically significant in children from 6 to 59 months (RD -34.5; 95% CI -41.7 to -27.3; $p < 0.001$), patients over 18 years (RD -35.9; 95% CI -58.5 to -13.4; $p = 0.002$), patients with negative malaria test (RD -46.9; 95% CI -53.9 to -39.8; $p < 0.001$), those with a respiratory diagnosis (RD -48.9; 95% CI -56.9 to -41.0, $p < 0.001$) and those not vaccinated against COVID-19 (-24.8% 95% CI -30.7 to -18.9, p -value: < 0.001). A significant reduction in non-adherence to prescription by patients was reported (RD -7.1; 95% CI -10.9 to -3.3; $p < 0.001$).

Conclusion: The intervention was associated with significant reductions of antibiotic prescriptions and non-adherence, chiefly among patients with non-malaria fever, those with respiratory symptoms and children below 5 years of age. The addition of COVID-19 testing did not have a major impact on antibiotic use at primary health centers.

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Point-of-care C-reactive protein measurement by community health workers safely reduces antimicrobial use among children with respiratory illness in rural Uganda: A stepped wedge cluster randomized trial

Emily J Ciccone¹, Di Hu², John S Preisser², Caitlin A Cassidy³, Lydiah Kabugho⁴, Baguma Emmanuel⁴, Georget Kibaba⁴, Fred Mwebembezi⁴, Jonathan J Juliano^{1,3}, Edgar M Mulogo⁴, Ross M Boyce^{1,3,4}

Abstract

Background: Acute respiratory illness (ARI) is one of the most common reasons children receive antibiotic treatment. Measurement of C-reaction protein (CRP) has been shown to reduce unnecessary antibiotic use among children with ARI in a range of clinical settings. In many resource-constrained contexts, patients seek care outside the formal health sector, often from lay community health workers (CHW). This study's objective was to determine the impact of CRP measurement on antibiotic use among children presenting with febrile ARI to CHW in Uganda.

Methods and findings: We conducted a cross-sectional, stepped wedge cluster randomized trial in 15 villages in Bugoye subcounty comparing a clinical algorithm that included CRP measurement by CHW to guide antibiotic treatment (STAR Sick Child Job Aid [SCJA]; intervention condition) with the Integrated Community Care Management (iCCM) SCJA currently in use by CHW in the region (control condition). Villages were stratified into 3 strata by altitude, distance to the clinic, and size; in each stratum, the 5 villages were randomly assigned to one of 5 treatment sequences. Children aged 2 months to 5 years presenting to CHW with fever and cough were eligible. CHW conducted follow-up assessments 7 days after the initial visit. Our primary outcome was the proportion of children who were given or prescribed an antibiotic at the initial visit. Our secondary outcomes were (1) persistent fever on day 7; (2) development of prespecified danger signs; (3) unexpected visits to the CHW; (4) hospitalizations; (5) deaths; (6) lack of perceived improvement per the child's caregiver on day 7; and (7) clinical failure, a composite outcome of persistence of fever on day 7, development of danger signs, hospitalization, or death. The 65 participating CHW enrolled 1,280 children, 1,220 (95.3%) of whom had sufficient data. Approximately 48% (587/1,220) and 52% (633/1,220) were enrolled during control (iCCM SCJA) and intervention periods (STAR SCJA), respectively. The observed percentage of children who were given or prescribed antibiotics at the initial visit was 91.8% (539/587) in the control periods as compared to 70.8% (448/633) during the intervention periods (adjusted prevalence difference -24.6%, 95% CI: -36.1%, -13.1%). The odds of antibiotic prescription by the CHW were over 80% lower in the intervention as compared to the control periods (OR 0.18, 95% CI: 0.06, 0.49). The frequency of clinical failure (iCCM SCJA 3.9% (23/585) v. STAR SCJA 1.8% (11/630); OR 0.41, 95% CI: 0.09, 1.83) and lack of perceived improvement by the caregiver (iCCM SCJA 2.1% (12/584) v. STAR SCJA 3.5% (22/627); OR 1.49, 95% CI: 0.37, 6.52) was similar. There were no unexpected visits or deaths in either group within the follow-up period.

Conclusions: Incorporating CRP measurement into iCCM algorithms for evaluation of children with febrile ARI by CHW in rural Uganda decreased antibiotic use. There is evidence that this decrease was not associated with worse clinical outcomes, although the number of

adverse events was low. These findings support expanded access to simple, point-of-care diagnostics to improve antibiotic stewardship in rural, resource-constrained settings where individuals with limited medical training provide a substantial proportion of care.

Antibiotics – mass drug administration with Azithromycin

N Engl J Med. 2024 Aug 22;391(8):699-709.

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[Azithromycin to Reduce Mortality - An Adaptive Cluster-Randomized Trial](#)

[Kieran S O'Brien¹](#), [Ahmed M Arzika¹](#), [Abdou Amza¹](#), [Ramatou Maliki¹](#), [Bawa Aichatou¹](#), [Ismael Mamane Bello¹](#), [Diallo Beidi¹](#), [Nasser Galo¹](#), [Naser Harouna¹](#), [Alio M Karamba¹](#), [Sani Mahamadou¹](#), [Moustapha Abarchi¹](#), [Almou Ibrahim¹](#), [Elodie Lebas¹](#), [Brittany Peterson¹](#), [Zijun Liu¹](#), [Victoria Le¹](#), [Emily Colby¹](#), [Thuy Doan¹](#), [Jeremy D Keenan¹](#), [Catherine E Oldenburg¹](#), [Travis C Porco¹](#), [Benjamin F Arnold¹](#), [Thomas M Lietman¹](#); [AVENIR study group](#)

Abstract

Background: Twice-yearly mass distribution of azithromycin to children is a promising intervention to reduce childhood mortality in sub-Saharan Africa. The World Health Organization recommended restricting distribution to infants 1 to 11 months of age to mitigate antimicrobial resistance, although this more limited treatment had not yet been tested.

Methods: We randomly assigned rural communities in Niger to four twice-yearly distributions of azithromycin for children 1 to 59 months of age (child azithromycin group), four twice-yearly distributions of azithromycin for infants 1 to 11 months of age and placebo for children 12 to 59 months of age (infant azithromycin group), or placebo for children 1 to 59 months of age. Census workers who were not aware of the group assignments monitored mortality twice yearly over the course of 2 years. We assessed three primary community-level mortality outcomes (deaths per 1000 person-years), each examining a different age group and pairwise group comparison.

Results: A total of 1273 communities were randomly assigned to the child azithromycin group (1229 were included in the analysis), 773 to the infant azithromycin group (751 included in the analysis), and 954 to the placebo group (929 included in the analysis). Among 382,586 children, 419,440 person-years and 5503 deaths were recorded. Lower mortality among children 1 to 59 months of age was observed in the child azithromycin group (11.9 deaths per 1000 person-years; 95% confidence interval [CI], 11.3 to 12.6) than in the placebo group (13.9 deaths per 1000 person-years; 95% CI, 13.0 to 14.8) (representing 14% lower mortality with azithromycin; 95% CI, 7 to 22; $P < 0.001$). Mortality among infants 1 to 11 months of age was not significantly lower in the infant azithromycin group (22.3 deaths per 1000 person-years; 95% CI, 20.0 to 24.7) than in the placebo group (23.9 deaths per 1000 person-years; 95% CI, 21.6 to 26.2) (representing 6% lower mortality with azithromycin; 95% CI, -8 to 19). Five serious adverse events were reported: three in the placebo group, one in the infant azithromycin group, and one in the child azithromycin group.

Conclusions: Azithromycin distributions to children 1 to 59 months of age significantly reduced mortality and was more effective than treatment of infants 1 to 11 months of age. Antimicrobial resistance must be monitored

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Effect of biannual azithromycin on respiratory pathogens among symptomatic children: results from the randomised Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance (MORDOR) I trial

[Jie Liu¹](#), [Stephanie A Brennhof²](#), [Jixian Zhang²](#), [Suzanne Stroup²](#), [Suporn Pholwat²](#), [Ahmed M Arzika^{3,4}](#), [Ramatou Maliki⁴](#), [Amza Abdou⁵](#), [Elodie Lebas⁶](#), [Kieran S O'Brien^{6,7}](#), [Benjamin F Arnold^{6,7}](#), [Jeremy D Keenan^{6,7}](#), [Thomas M Lietman^{6,7}](#), [James A Platts-Mills²](#), [Elizabeth T Rogawski McQuade⁸](#), [Eric R Houpt⁹](#)

Abstract

Introduction: Biannual (ie, every 6 months) mass drug administration of azithromycin has reduced childhood mortality in Niger, but its effects on specific respiratory pathogens are not fully elucidated.

Methods: Across 2 years of the Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance (MORDOR) study in Niger, we evaluated 1468 nasopharyngeal swabs from children who presented for care with respiratory symptoms. Swabs were tested by quantitative PCR using a customised TaqMan Array Card that included assays for 19 respiratory pathogens.

Results: Nasopharyngeal detection of *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* was common in both azithromycin and placebo communities. The prevalence was reduced in children from azithromycin communities for just two pathogens: *Bordetella pertussis* and *H. influenzae* type b (Hib). These children had a 49% and 65% reduction in the prevalence of *B. pertussis* and Hib in nasopharyngeal swabs, respectively, compared with children from the control communities (prevalence ratios 0.51, 95% CI 0.35, 0.75; and 0.35, 95% CI 0.17, 0.71).

Conclusions: Biannual administration of azithromycin to communities in Niger was associated with lower prevalence of *B. pertussis* and Hib compared with placebo. These reductions may explain some of the childhood mortality benefit of azithromycin.

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Costs, Coverage, and Acceptability of Azithromycin Mass Administration to Children 1-11 Versus 1-59 Months Old to Reduce Mortality: A Cluster-Randomized Trial in Niger

[Ahmed M Arzika¹](#), [Ramatou Maliki¹](#), [Abdou Amza²](#), [Alio Karamba¹](#), [Nasser Gallo¹](#), [Bawa Aichatou¹](#), [Ismael I Sara¹](#), [Diallo Beidi¹](#), [Laminou M Haroun¹](#), [Farissatou Oumarou¹](#), [Carolyn Brandt³](#), [Brittany Peterson³](#), [Elodie Lebas³](#), [Emily Colby³](#), [William Nguyen³](#), [Zijun Liu³](#), [Benjamin F Arnold^{3,4,5}](#), [Thomas M Lietman^{3,4,5,6}](#), [Meagan C Fitzpatrick⁷](#), [Kieran S O'Brien^{3,4,5,6}](#)

Abstract

Azithromycin mass drug administration (MDA) for 1- to 59-month-olds reduces child mortality. However, guidelines restrict eligibility to 1- to 11-month-olds because of concerns about antimicrobial resistance. This cluster-randomized implementation trial was

conducted in parallel with a larger efficacy trial and compared implementation outcomes between these approaches. Rural communities in Niger were randomly assigned to receive biannual azithromycin MDA for either 1- to 59-month-olds or 1- to 11-month-olds over 1 year. The primary outcome was the community-level cost per dose delivered. Secondary outcomes included reach (coverage), as well as acceptability, appropriateness, and feasibility according to participants and providers. In November 2020, 40 eligible communities were randomly assigned to each arm, with 37 communities in the 1- to 59-month arm and 39 communities in the 1- to 11-month arm contributing to analyses. The mean cost per dose delivered was \$6.50 lower (95% CI -\$10.40 to -\$3.70; P-value <0.001) in the 1- to 59-month arm (\$1.60; 95% CI \$1.00 to \$2.30) compared with the 1- to 11-month arm (\$8.20; 95% CI \$7.60 to \$8.80). Treatment coverage was similar by arm and exceeded 90% in both distributions. More caregivers in the 1- to 59-month arm found the intervention acceptable (mean difference 4.2%; 95% CI 0 to 8.4%; P-value 0.04) and appropriate (3.4%; 95% CI 0.1 to 6.8%; P-value 0.04) compared with the 1- to 11-month arm. When combining arms, all groups indicated that including 1- to 59-month-olds was more acceptable, appropriate, and feasible than restricting to 1- to 11-month-olds. No serious adverse events were reported. Overall, including 1- to 59-month-olds resulted in a lower cost per dose delivered than restricting to 1- to 11-month-olds. Community groups perceived both interventions to be acceptable, appropriate, and feasible, but they strongly preferred the 1- to 59-month treatment.

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Cause-Specific Mortality among Infants in a Randomized Controlled Trial of Azithromycin Compared to Placebo for Prevention of Mortality

Mamadou Ouattara¹, Ali Sié¹, Mamadou Bountogo¹, Valentin Boudo¹, Thierry Ouedraogo¹, Clarisse Dah¹, Elodie Lebas², Huiyu Hu², Aimee Lansdale³, Ian Fetterman², Benjamin F Arnold^{2,4}, Thomas M Lietman^{2,3,4}, Catherine E Oldenburg^{2,3,4}

Abstract

Although community randomized trials have found a reduction in all-cause child mortality in communities receiving mass azithromycin distribution compared with placebo, individually randomized trials have not found similar protective effects. If a direct effect of azithromycin for prevention of child mortality exists, it is likely due to reduction in infectious mortality. Here, we assessed cause-specific mortality in a large randomized controlled trial of azithromycin administered during well-infant visits in Burkina Faso for prevention of mortality. Among 32,877 enrolled infants, the most common causes of death by 6 months of age were malaria, acute respiratory infections, and diarrheal disease. We found no evidence of a difference in the distribution of cause of death by randomized treatment assignment (P = 0.42) or in any infectious-specific cause of death. The results of this analysis are consistent with no direct effect of azithromycin on infant mortality when administered during well-infant visits.

doi: 10.1136/bmjopen-2024-097916.

Mass distribution of azithromycin and child mortality among underweight infants in rural Niger: a subgroup analysis of the AVENIR cluster-randomised trial

[Brittany Peterson](#)^{1,2}, [Ahmed Arzika](#)³, [Ramatou Maliki](#)³, [Amza Abdou](#)⁴, [Bawa Aichatou](#)³, [Ismael M Bello](#)³, [Diallo Beidi](#)³, [Nasser Galo](#)³, [Nasser Harouna](#)³, [Alio M Karamba](#)³, [Sani Mahamadou](#)³, [Moustapha Abarchi](#)³, [Almou Ibrahim](#)⁴, [Elodie Lebas](#)¹, [Zijun Liu](#)¹, [Carolyn Brandt](#)¹, [Emily Colby](#)¹, [Catherine E Oldenburg](#)^{1,2,5,6}, [Travis C Porco](#)^{1,2,5}, [Benjamin Arnold](#)^{1,5,6}, [Thomas M Lietman](#)^{1,2,5,6}, [Kieran Sunanda O'Brien](#)^{7,2,5,6}

Abstract

Objective: Azithromycin has been shown to reduce all-cause child mortality. This subgroup analysis investigates azithromycin's mortality impact by underweight status using *Azithromycine pour la Vie des Enfants au Niger: Implementation et Recherche* (AVENIR) trial data.

Design: The AVENIR trial randomised communities into three arms: azithromycin for children aged 1-59 months, azithromycin for infants aged 1-11 months or placebo. Weight-for-age z-score was used to categorise children into subgroups of either moderate to severe underweight or not and severe underweight or not.

Setting: 2880 communities with a population of less than 2500 people in the Dosso and Tahoua regions of Niger that participated in the AVENIR trial were included.

Participants: 97 572 children aged 1-59 months who had weight captured during at least one census participated.

Results: Underweight subgroups had higher overall mortality compared with non-underweight subgroups. IRDs of deaths in children aged 1-11 months comparing communities receiving azithromycin to children 1-59 months of age to placebo were -6.2 deaths per 1000 person-years (95% CI -9.3 to -2.6) overall, -8.0 (95% CI -15.9 to -0.4) in the moderate to severe subgroup and -11.2 (95% CI -26.0 to -2.1) in the severe subgroup. Similar trends were noted in the azithromycin 1-11 month comparison. Malnutrition was not a statistically significant effect modifier for either comparison.

Conclusions: Although analyses suggest the potential for stronger effects in more severe underweight subgroups, we were unable to demonstrate underweight status as an effect modifier. In fact, azithromycin mass drug administration to children 1-59 months old reduced mortality in all subgroups, and, especially as the number of lives saved would be the highest by treating all subgroups, our results do not support restricting eligibility for this intervention.

Am J Clin Nutr. 2025 Mar;121(3):597-609.

doi: 10.1016/j.ajcnut.2024.12.027. Epub 2025 Jan 7.

Protein supplementation delivered alone or in combination with presumptive azithromycin treatment for enteric pathogens did not improve linear growth in Bangladeshi infants: results of a cluster-randomized controlled trial

[Amanda C Palmer](#)¹, [Md Iqbal Hossain](#)², [Hasmot Ali](#)³, [Kaniz Ayesha](#)³, [Saijuddin Shaikh](#)³, [Md Tanvir Islam](#)³, [Fatema-Tuz Johura](#)², [Monica M Pasqualino](#)⁴, [Hafizur Rahman](#)³, [Rezwanul Haque](#)³, [Kelsey Alland](#)⁴, [Lee Shu-Fune Wu](#)⁴, [Kerry J Schulze](#)⁴, [Subhra Chakraborty](#)⁴, [Keith P West Jr](#)⁴, [Munirul Alam](#)², [Tahmeed Ahmed](#)², [Alain B Labrique](#)⁴

Abstract

Background: Protein requirements established for healthy populations may be insufficient to support healthy growth in infants consuming largely cereal-based complementary foods and frequently exposed to enteric pathogens.

Objectives: This study aimed to assess independent and combined effects of protein supplementation and antibiotic treatment on linear growth of infants aged 6-12 mo.

Methods: We conducted a 2×4 factorial cluster-randomized trial in northwestern Bangladesh, allocating 566 clusters to masked azithromycin (10 mg/kg $\times$ 3 d) or placebo at 6 and 9 mo of age and unmasked delivery of an egg white protein-rich blended food supplement (250 kcal; 10 g added protein), a rice-based isocaloric supplement, egg, or nutrition education from 6 to 12 mo. We measured length at 6 and 12 mo. For this cluster-level intention-to-treat analysis of the 2×2 antibiotic and protein interventions, we used multiple linear or log-binomial regression with generalized estimating equations to assess changes in length-for-age z (LAZ) score and stunting (LAZ < -2), respectively.

Results: We enrolled 2055 infants (283 clusters) and included 1821 infants (281 clusters) with complete anthropometry data at 6 and 12 mo in our analysis. There were no significant interactions between the protein and antibiotic interventions for any outcomes.

Independently, protein supplement did not improve LAZ (β : 0.05; 95% CI: 0.00, 0.11; $P = 0.07$) or reduce stunting (prevalence ratio: 1.12; 95% CI: 0.85, 1.49; $P = 0.41$) compared with the isocaloric supplement. The antibiotic intervention had no effect on LAZ (β : -0.05; 95% CI: -0.11, 0.01; $P = 0.09$) or stunting (prevalence ratio: 0.99; 95% CI: 0.75, 1.31; $P = 0.96$), relative to the placebo.

Conclusions: Supplementation to increase intakes of high-quality protein, provided with or without presumptive treatment for enteric pathogens, did not improve linear growth from 6 to 12 mo of age.

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doi: 10.1093/cid/ciae267.

Assessment of Spillover of Antimicrobial Resistance to Untreated Children 7-12 Years Old After Mass Drug Administration of Azithromycin for Child Survival in Niger: A Secondary Analysis of the MORDOR Cluster-Randomized Trial

[Brittany Peterson](#)^{1,2}, [Ahmed M Arzika](#)³, [Abdou Amza](#)⁴, [Ramatou Maliki](#)³, [Alio Mankara Karamba](#)³, [Mariama Moussa](#)³, [Mariama Kemago](#)³, [Zijun Liu](#)¹, [Eric Houpt](#)⁵, [Jie Liu](#)⁶, [Suporn Pholwat](#)⁵, [Thuy Doan](#)^{1,7}, [Travis C Porco](#)^{1,2,7,8}, [Jeremy D Keenan](#)^{1,7}, [Thomas M Lietman](#)^{1,2,7,8}, [Kieran S O'Brien](#)^{1,2,7,8}

Abstract

Background: The risk of antibiotic resistance is complicated by the potential for spillover effects from one treated population to another. Azithromycin mass drug administration programs report higher rates of antibiotic resistance among treatment arms in targeted groups. This study aimed to understand the risk of spillover of antibiotic resistance to nontarget groups in these programs.

Methods: Data were used from a cluster-randomized trial comparing the effects of biannual azithromycin and placebo distribution to children 1-59 months old on child mortality rates. Nasopharyngeal samples from untreated children 7-12 years old were tested for genetic determinants of macrolide resistance (primary outcome) and resistance to other antibiotic

classes (secondary outcomes). Linear regression was used to compare the community-level mean difference in prevalence by arm at the 24-month time point, adjusting for baseline prevalence.

Results: A total of 1103 children 7-12 years old in 30 communities were included in the analysis (15 azithromycin, 15 placebo). The adjusted mean differences in the prevalence of resistance determinants for macrolides, β -lactams, and tetracyclines were 3.4% (95% confidence interval, -4.1% to 10.8%; $P = .37$), -1.2% (-7.9% to 5.5%; $P = .72$), and -3.3% (-9.5% to 2.8%; $P = .61$), respectively.

Conclusions: We were unable to demonstrate a statistically significant increase in macrolide resistance determinants in untreated groups in an azithromycin mass drug administration program. While the result might be consistent with a small spillover effect, this study was not powered to detect such a small difference. Larger studies are warranted to better quantify the potential for spillover effects within these programs.

J Infect Dis. 2024 Jul 25;230(1):239-249.

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Minimal Impact on the Resistome of Children in Botswana After Azithromycin Treatment for Acute Severe Diarrheal Disease

[Allison K Guiton¹²³](#), [Anna Katyukhina¹²³](#), [Margaret Mokomane⁴⁵](#), [Kwana Lechiile⁶](#), [David M Goldfarb⁶⁷](#), [Gerard D Wright¹²³](#), [Andrew G McArthur¹²³](#), [Jeffrey M Pernica²⁸⁹](#)

Abstract

Background: Macrolide antibiotics, including azithromycin, can reduce under 5 years of age mortality rates and treat various infections in children in sub-Saharan Africa. These exposures, however, can select for antibiotic-resistant bacteria in the gut microbiota.

Methods: Our previous randomized controlled trial (RCT) of a rapid-test-and-treat strategy for severe acute diarrheal disease in children in Botswana included an intervention (3-day azithromycin dose) group and a control group that received supportive treatment. In this prospective matched cohort study using stools collected at baseline and 60 days after treatment from RCT participants, the collection of antibiotic resistance genes or resistome was compared between groups.

Results: Certain macrolide resistance genes increased in prevalence by 13%-55% at 60 days, without differences in gene presence between the intervention and control groups. These genes were linked to tetracycline resistance genes and mobile genetic elements.

Conclusions: Azithromycin treatment for bacterial diarrhea for young children in Botswana resulted in similar effects on the gut resistome as the supportive treatment and did not provide additional selective pressure for macrolide resistance gene maintenance. The gut microbiota of these children contains diverse macrolide resistance genes that may be transferred within the gut upon repeated exposures to azithromycin or coselected by other antibiotics.

iScience. 2024 Aug 3;27(9):110626.

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Effect of intrapartum azithromycin on gut microbiota development in early childhood: A post hoc analysis of a double-blind randomized trial

[Bakary Sanyang¹](#), [Thushan I de Silva^{1,2}](#), [Bully Camara¹](#), [Nathalie Beloum¹](#), [Abdoulie Kanteh¹](#), [Jarra Manneh¹](#), [Wouter A A de Steenhuijsen Piters^{3,4}](#), [Debby Bogaert^{3,5}](#), [Abdul Karim Sesay¹](#), [Anna Roca¹](#)

Abstract

Intrapartum azithromycin prophylaxis has shown the potential to reduce maternal infections but showed no effect on neonatal sepsis and mortality. Antibiotic exposure early in life may affect gut microbiota development, leading to undesired consequences. Therefore, we here assessed the impact of 2 g oral intrapartum azithromycin on gut microbiota development from birth to the age of 3 years, by 16S-rRNA gene profiling of rectal samples from 127 healthy Gambian infants selected from a double-blind randomized placebo-controlled clinical trial (PregnAnZI-2). Microbiota trajectories showed, over the first month of life, a slower community transition and increase of *Enterobacteriaceae* ($p = 0.001$) and *Enterococcaceae* ($p = 0.064$) and a decrease of *Bifidobacterium* ($p < 0.001$) in the azithromycin compared to the placebo arm. Intrapartum azithromycin alters gut microbiota development and increases proinflammatory bacteria in the first month of life, which may have undesirable effects on the child.

Clin Infect Dis. 2024 Dec 17;79(6):1338-1345.

doi: 10.1093/cid/ciae280.

Impact of Intrapartum Azithromycin on the Carriage and Antibiotic Resistance of *Escherichia coli* and *Klebsiella pneumoniae* in Mothers and Their Newborns: A Substudy of a Randomized, Double-Blind Trial Conducted in The Gambia and Burkina Faso

[Pauline Getanda¹](#), [Isatou Jagne¹](#), [Joel D Bognini²](#), [Bully Camara¹](#), [Bakary Sanyang¹](#), [Saffiatou Darboe¹](#), [Ellen Sambou¹](#), [Momodou Barry¹](#), [Kady Kassibo¹](#), [Aminata Cham¹](#), [Harriet Mendy¹](#), [Bintou K J Singateh¹](#), [Ebrahim Ndure¹](#), [Toussaint Rouamba²](#), [Abdoulie Bojang¹](#), [Christian Bottomley³](#), [Benjamin P Howden⁴](#), [Umberto D'Alessandro¹](#), [Halidou Tinto²](#), [Anna Roca¹](#); [PregnAnZI-2 Carriage Study Group](#)

Abstract

Background: Limited data exist on the effects of intrapartum azithromycin on the prevalence of carriage and antibiotic resistance of Enterobacterales.

Methods: We conducted a randomized trial in The Gambia and Burkina Faso where women received intrapartum azithromycin (2 g) or placebo. We determined the impact of treatment on the prevalence of carriage and antibiotic resistance of *Escherichia coli* and *Klebsiella pneumoniae* by analyzing rectal swabs (RS), nasopharyngeal swabs (NPS), breast milk, and rectovaginal swabs (RVS). Bacteria were isolated microbiologically; antibiotic susceptibility was confirmed with an E-test. Prevalence ratios (PRs) with 95% confidence intervals (CIs) were used for comparison between arms.

Results: In infants, *E. coli* carriage in RS was lower in the intervention than in the placebo arm at day 6 (63.0% vs 75.2%; PR, 0.84; 95% CI, .75-.95) and day 28 (52.7% vs 70.4%; 0.75; 0.64-0.87) post-intervention. Prevalence of azithromycin-resistant *E. coli* was higher in the azithromycin arm at day 6 (13.4% vs 3.6%; 3.75; 1.83-7.69) and day 28 (16.4% vs 9.6%; 1.71; 1.05-2.79). For *K. pneumoniae*, carriage in RS was higher in the intervention than in the placebo arm at day 6 (49.6% vs 37.2%, 1.33; 1.08-1.64) and day 28 (53.6% vs 32.9%, 1.63; 1.31-2.03). Prevalence of azithromycin-resistant *K. pneumoniae* was higher in the azithromycin arm at day 28 (7.3% vs 2.1%; 3.49; 1.30-9.37). No differences were observed for other sample types.

Conclusions: Intrapartum azithromycin decreased *E. coli* carriage but increased both *K. pneumoniae* carriage and azithromycin resistance in both bacteria. These data need to be considered together with efficacy results to balance the potential short- and long-term impact of the intervention.

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Biannual azithromycin mass drug administration for reduction of childhood mortality: a systematic review and meta-analysis

Meenalotchini Prakash Gurunthalingam¹, Madhusudan Prasad Singh¹, Nitin Rewaram Gaikwad¹

Abstract

Background: Biannual mass drug administration of azithromycin (MDA-azithromycin) has been proposed as a strategy to reduce childhood mortality in high-mortality regions, particularly sub-Saharan Africa. However, its effectiveness across different age groups and potential risks, including antibiotic resistance, require further evaluation.

Methods: We systematically searched PubMed, Cochrane CENTRAL, Web of Science and ClinicalTrials.gov through September 2024 for randomized controlled trials (RCTs) comparing biannual MDA-azithromycin to placebo in children aged 1-59 months. The primary outcomes were mortality in children <1 year and 12-59 months. Secondary outcomes included adverse events and antibiotic resistance. Data were analysed using a random-effects model in Review Manager 5.4, with heterogeneity assessed via I². Trial sequential analysis (TSA) evaluated cumulative evidence reliability, and the Cochrane RoB2 tool assessed risk of bias. PROSPERO registration: CRD42024589170.

Results: Five RCTs (691 235 children) were included. Among children <1 year, azithromycin showed a non-significant mortality reduction (RR: 0.90 [0.78, 1.04]; P = 0.14; I² = 55%), with TSA indicating inconclusive evidence. Among children 12-59 months, MDA-azithromycin significantly reduced mortality (RR: 0.85 [0.79, 0.91]; P < 0.00001; I² = 26%), with TSA confirming sufficient evidence. Adverse events were rare, but antibiotic resistance data were limited, warranting further monitoring. Evidence quality ranged from moderate to very low, with one trial at high risk of bias.

Conclusion: Biannual MDA-azithromycin significantly reduces mortality in children 12-59 months, supporting its use in high-mortality settings per WHO recommendations. Its impact on infants remains uncertain. Adverse events were minimal, but continued resistance surveillance is essential.

Cash transfers and family economic support

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doi: 10.7189/jogh.14.04186.

The cost-effectiveness of a cash-based transfer, specialised nutritious food, and social and behaviour change communication intervention package to prevent undernutrition among children 6-23 months in Pakistan: A cluster randomised controlled trial

[Michael N Onah¹](#), [Gul Nawaz Khan²](#), [Sumra Kureishy³](#), [Jessica Bourdair³](#), [Saskia de Pee³](#), [Cecilia Garzon³](#), [Yasir Ihtesham³](#), [Naveed Akbar⁴](#), [Sajid Bashir Soofi^{5,2}](#)

Abstract

Background: There is mixed evidence on the cost-effectiveness of cash transfers, along with food supplements and behaviour change communication interventions in improving child nutrition outcomes. To add to existing literature, we examined the cost-effectiveness of medium-quantity lipid-based nutrient supplement (LNS) and social and behaviour change communication (SBCC) messaging, separately and combined, compared to an existing unconditional cash transfers (UCT) programme in children 6-23 months of age in the district Rahim Yar Khan, Pakistan.

Methods: This was a four-arm, community-based cluster randomised controlled trial. The UCT provided a quarterly sum of USD 32, the medium-quantity LNS contained a daily ration of 50 g of LNS, and the SBCC included monthly and quarterly messaging on nutrition, health, and hygiene to eligible households. Cost data were collected from a provider perspective through the review of procurement invoices and budgets, as well as interviews with stakeholders. We examined cost-effectiveness via statistically significant differences between the intervention and control arms, and estimated as cost per case of stunting, and disability-adjusted life years (DALYs) averted at six and 18 months of intervention.

Results: Costs were higher for SBCC intervention combinations (UCT + SBCC and UCT + LNS + SBCC) due to high training costs for lady health workers. UCT + LNS achieved a reduction in stunting at a per-case cost of USDS 278.74 at six months and USD 897.15 at 18 months. UCT + LNS + SBCC achieved a reduction in stunting at per case cost of USD 846.48 at six months and USD 2324.58 at 18 months. The cost per DALYs averted for preventing stunting was USD 234 to USD 557.42 at six months, and USD 787.73 to USD 1537 at 18 months without discounting and age-weights.

Conclusions: Although the affordability of such interventions is arguable, combining UCTs with LNS appears to be very cost-effective for reducing undernutrition and averting DALYs, while combining cash transfers with LNS and SBCC showed limited cost-effectiveness when targeting stunting.

SSM Popul Health. 2025 Jan 31:29:101760.

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[Post-intervention gendered impacts and moderating factors of a government cash plus intervention for adolescents in Tanzania](#)

[Jennifer Waidler¹](#), [Leah Prencipe²](#), [Nyasha Tirivayi³](#), [Tumpe Mnyawami Lukongo⁴](#), [Paul Luchemba⁴](#), [Frank Eeataama⁵](#), [Jennifer Matafu⁵](#), [Tia Palermo⁶](#); [Tanzania Adolescent Cash Plus Evaluation Team](#)

Abstract

Introduction: Reducing poverty (including multidimensional poverty) and gender inequality can improve social development outcomes. Studies have sought to understand how poverty reduction and intersectoral programming targeted to adolescents can facilitate safe transitions to adulthood among adolescents. However, most intersectoral interventions for adolescents to date have been implemented by non-governmental actors with limited generalizability and potential for scale-up. In the current study, we examine 22-month post intervention impacts of the "plus components" of a cash plus intervention, Ujana Salama

(Swahili for "Safe Youth") targeted to adolescents ages 14-19 years (males and females) in households participating in a government social protection program in Tanzania. The government-implemented cash plus intervention, comprised of livelihoods and life skills training, a productive grant, mentoring, and linkages to adolescent-friendly health services, was implemented over 18 months in 2018 and 2019.

Methods: Using a cluster randomized controlled trial, we estimated post-intervention impacts in 2021 on the following domains: relationships, modern contraception, health seeking and HIV knowledge and risk, psychosocial outcomes and attitude, and violence. We further examined whether contextual factors, including gender norms and quality of health services, moderated these post-intervention impacts.

Results: Few impacts found at earlier rounds were still evident post-intervention. Exceptions include protective impacts on lifetime sexual violence risk among females and increases in sexual and reproductive health services utilization among males. Moreover, newly detected adverse impacts on mental health contrasted with earlier protective impacts.

Conclusion: While external factors such as lengthy delays of cash transfer payments to adolescents' households and the COVID-19 pandemic may have mitigated the potential for sustained impacts of this intervention, findings suggest that future programs may need to provide different combinations of programming, provide support longer-term, or intervene at more levels of the social ecological model to influence many of the outcomes examined and to effect more lasting change.

AIDS Behav. 2025 May 15.

doi: 10.1007/s10461-025-04750-7. Online ahead of print.

The Impact of a Family Economic Empowerment Intervention on Cultural Gender Norm Beliefs Among HIV-Orphaned Adolescents in Southern Uganda

[Portia B Nartey¹](#), [Vicent Ssentumbwe²](#), [Proscovia Nabunya³](#), [Samuel Kizito¹](#), [Mitra Naseh⁴](#), [Fred M Ssewamala¹](#)

Abstract

Sub-Saharan Africa (SSA) ranks lowest on the UNDP's Gender Inequality Index (GII), with a score of 0.56 out of 1 (1 being the worst), while Uganda scores 0.53, reflecting high gender inequality between males and females. These gender disparities are deeply rooted in longstanding inequitable gender norms and worsened by poverty. This study assessed a family economic empowerment intervention's impact on gender norm beliefs among HIV-orphaned adolescents in Uganda using three time-points data from the Suubi-Maka study, a cluster-randomized trial with 346 adolescent-caregiver dyads. Participants were randomized to control (n = 167) or treatment (n = 179) groups, with data collected at baseline, 12, and 24 months. We used mixed effects linear regression to assess the effect of the economic empowerment intervention on gender norms. Results indicated significant group-by-time interaction effects but non-significant independent group or time effects. Social support was positively significantly associated with equitable gender norms, emphasizing the role of supportive networks in facilitating change in gender norm beliefs. These findings suggest that economic interventions alone may not be sufficient for altering deeply entrenched gender norms, and future efforts should include more targeted, gender-transformative approaches.

Community child health

Bull World Health Organ. 2024 Sep 1;102(9):639-649.

doi: 10.2471/BLT.23.290975. Epub 2024 Jun 25.

[Home visits versus fixed-site care by community health workers and child survival: a cluster-randomized trial, Mali](#)

[Jenny Liu](#)¹, [Emily Treleaven](#)², [Caroline Whidden](#)³, [Saibou Doumbia](#)³, [Naimatou Kone](#)³, [Amadou Beydi Cisse](#)³, [Aly Diop](#)⁴, [Mohamed Berthé](#)⁴, [Mahamadou Guindo](#)⁴, [Brahima Mamadou Koné](#)⁴, [Michael P Fay](#)⁵, [Ari D Johnson](#)⁶, [Kassoum Kayentao](#)⁷

Abstract

Objective: To test the effect of proactive home visits by trained community health workers (CHWs) on child survival.

Methods: We conducted a two arm, parallel, unmasked cluster-randomized trial in 137 village-clusters in rural Mali. From February 2017 to January 2020, 31 761 children enrolled at the trial start or at birth. Village-clusters received either primary care services by CHWs providing regular home visits (intervention) or by CHWs providing care at a fixed site (control). In both arms, user fees were removed and primary health centres received staffing and infrastructure improvements before trial start. Using lifetime birth histories from women aged 15-49 years surveyed annually, we estimated incidence rate ratios (IRR) for intention-to-treat and per-protocol effects on under-five mortality using Poisson regression models.

Findings: Over three years, we observed 52 970 person-years (27 332 in intervention arm; 25 638 in control arm). During the trial, 909 children in the intervention arm and 827 children in the control arm died. The under-five mortality rate declined from 142.8 (95% CI: 133.3-152.9) to 56.7 (95% CI: 48.5-66.4) deaths per 1000 live births in the intervention arm; and from 154.3 (95% CI: 144.3-164.9) to 54.9 (95% CI: 45.2-64.5) deaths per 1000 live births in the control arm. Intention-to-treat (IRR: 1.02; 95% CI: 0.88-1.19) and per-protocol estimates (IRR: 1.01; 95% CI: 0.87-1.18) showed no difference between study arms.

Conclusion: Though proactive home visits did not reduce under-five mortality, system-strengthening measures may have contributed to the decline in under-five mortality in both arms.

BMJ Glob Health. 2024 Dec 27;9(12):e014940.

doi: 10.1136/bmjgh-2023-014940.

[Cost-effectiveness analysis of proactive home visits compared with site-based community health worker care on antenatal care outcomes in Mali: a cluster-randomised trial](#)

[Osondu Ogbuoji](#)^{1,2}, [Minahil Shahid](#)³, [Armand Zimmerman](#)³, [Jenny X Liu](#)⁴, [Kassoum Kayentao](#)^{5,6}, [Caroline Whidden](#)^{6,7}, [Emily Treleaven](#)⁸, [Coumba Traoré](#)⁶, [Mahamadou Sogoba](#)⁶, [Saibou Doumbia](#)⁶, [David Charles Boettiger](#)^{4,9}, [Amadou Beydi Cissé](#)⁶, [Youssef Keita](#)⁶, [Mohamed Berthé](#)¹⁰, [Ari Johnson](#)^{6,11}

Abstract

Introduction: Despite recommendations from the WHO, antenatal care (ANC) coverage remains low in many low-income and middle-income countries (LMICs). Community health workers (CHWs) can play an important role in expanding ANC coverage through pregnancy identification, provision of health education, screening for complications, delivery of

therapeutic care and referral to higher levels of care. However, despite the success of CHW programmes in various countries, WHO has called for additional research to develop evidence-based models that optimise CHW service delivery and that can be replicated across geographies.

Methods: The ProCCM Trial was a cluster-randomised controlled trial to compare proactive home visits by CHWs (intervention, 69 village clusters) to the provision of CHW care at community fixed sites only (control, 68 village clusters) in the Bankass health district in Central Mali. In this study, we conducted a cost-effectiveness analysis of proactive CHW home visits in improving ANC utilisation, a secondary outcome of the ProCCM trial. We analysed five ANC outcomes: (1) number of ANC contacts, (2) at least one ANC contact, (3) at least four ANC contacts, (4) at least eight ANC contacts and (5) ANC initiated in the first trimester. We assumed two perspectives, a CHW programme's and the Full ANC programme's perspective, which included facility-based as well as community-based ANC. We estimated programme costs, incremental cost-effectiveness ratios (ICERs) and probabilities of the intervention being more cost-effective than the control at different willingness-to-pay (WTP) thresholds.

Results: Proactive home visits were cost-saving from the CHW programme's perspective (ICERs: -\$21.39 to -\$79.20 per ANC utilisation outcome) and from the Full ANC programme perspective (ICERs: -\$1.70 to -\$6.30 per ANC utilisation outcome) compared with the fixed-site CHW care. The likelihood of the intervention being more cost-effective than the control was 100% at WTP thresholds \$0 per ANC utilisation outcome and between \$12.5 and \$50.00 per ANC utilisation outcome in the CHW- and Full ANC programme perspectives, respectively.

Conclusion: Our results provide evidence that proactive home visits produce more value per dollar spent as a means of improving the uptake of ANC services compared with fixed-site CHW services.

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[The effect of an interactive mobile health intervention to improve community-based essential neonatal care practices among postpartum women in northeast Ethiopia: a cluster randomized controlled trial](#)

[Niguss Cherie](#)¹², [Muluemebet Abera Wordofa](#)², [Gurmesa Tura Debelew](#)²

Abstract

Background: Despite global declines in child mortality rates, Africa's reduction is lagging behind other regions. Neonatal survival remains a key priority in the sustainable development agenda. Promoting neonatal care practices at the individual and community levels is essential, and technology-based interventions can effectively reach potential future mothers. This study aimed to evaluate the effect of an interactive mobile health intervention on improving community-based essential neonatal care practices among postpartum women in northeast Ethiopia.

Methods: This study was conducted in Dessie and Kombolcha city zones, in northeast Ethiopia. A cluster randomized controlled trial was implemented among 743 participants (376 intervention and 367 control) from 2 January to 15 June 2023. Pregnant women at 30-weeks' gestation in selected clusters were enrolled and followed up to 45 days after childbirth. Data were collected using Open Data Kit and analysed with Stata version 17. Structural equation modelling through confirmatory factor analysis was employed. Model

fitness was evaluated using the χ^2 :degree of freedom ratio, root mean square error of approximation and standardized root mean square residual, indicating a good model fit. Statistical significance was declared at a level <0.05 with a 95% confidence interval.

Results: The study revealed high narrow birth-to-pregnancy intervals of <24 months in both groups (48.5% control, 49.5% intervention). Awareness of neonatal care increased markedly in the intervention group, increasing from 62.0% to 85.9%, compared with an increase from 57.8% to 67.6% in the control group. Disagreement regarding immediate newborn bathing was more prevalent in the intervention group (73.9%) than in the control group (58.9%). Initiating breastfeeding within 1 h after birth was higher in the intervention group (85.4%) compared with the control group (74.4%). Postnatal visits to health facilities were more frequent in the intervention group (79.6%) than in the control group (54.8%). Mobile health intervention ($\beta=0.393$, $p=0.007$) and knowledge of neonatal care ($\beta=0.347$, $p=0.012$) had a significant positive effect on neonatal care practices. There were no significant indirect pathways between the variables analysed. Mobile health intervention and knowledge of neonatal care remain significant predictors with a total effect of $\beta=0.382$, $p=0.009$ and $\beta=0.347$, $p=0.012$, respectively, in enhancing neonatal care practices.

Conclusions: This study underscores the significant role of mobile health interventions and maternal knowledge in enhancing neonatal care practices. These findings should inform the design and implementation of maternal and child health programs, emphasizing the integration of technology and education to improve neonatal outcomes in resource-limited settings.

Health Policy Plan. 2024 Sep 10;39(8):864-877.

doi: 10.1093/heapol/czae066.

Community case management to accelerate access to healthcare in Mali: a realist process evaluation nested within a cluster randomized trial

[Caroline Whidden](#)^{1,2}, [Amadou Beydi Cissé](#)³, [Faith Cole](#)^{4,5}, [Saibou Doumbia](#)², [Abdoulaye Guindo](#)⁶, [Youssouf Karambé](#)⁷, [Emily Treleaven](#)⁵, [Jenny Liu](#)⁸, [Oumar Tolo](#)³, [Lamine Guindo](#)², [Bréhima Togola](#)², [Calvin Chiu](#)⁹, [Aly Tembely](#)¹⁰, [Youssouf Keita](#)³, [Brian Greenwood](#)¹, [Daniel Chandramohan](#)¹, [Ari Johnson](#)^{3,11}, [Kassoum Kayentao](#)^{2,12}, [Jayne Webster](#)¹

Abstract

The Proactive Community Case Management (ProCCM) trial in Mali reinforced the health system across both arms with user fee removal, professional community health workers (CHWs) and upgraded primary health centres (PHCs)-and randomized village-clusters to receive proactive home visits by CHWs (intervention) or fixed site-based services by passive CHWs (control). Across both arms, sick children's 24-hour treatment and pregnant women's four or more antenatal visits doubled, and under-5 mortality halved, over 3 years compared with baseline. In the intervention arm, proactive CHW home visits had modest effects on children's curative and women's antenatal care utilization, but no effect on under-5 mortality, compared with the control arm. We aimed to explain these results by examining implementation, mechanisms and context in both arms We conducted a process evaluation with a mixed method convergent design that included 79 in-depth interviews with providers and participants over two time-points, surveys with 195 providers and secondary analyses of clinical data. We embedded realist approaches in novel ways to test, refine and consolidate theories about how ProCCM worked, generating three context-intervention-actor-

mechanism-outcome nodes that unfolded in a cascade. First, removing user fees and deploying professional CHWs in every cluster enabled participants to seek health sector care promptly and created a context of facilitated access. Second, health systems support to all CHWs and PHCs enabled equitable, respectful, quality healthcare, which motivated increased, rapid utilization. Third, proactive CHW home visits facilitated CHWs and participants to deliver and seek care, and build relationships, trust and expectations, but these mechanisms were also activated in both arms. Addressing multiple structural barriers to care, user fee removal, professional CHWs and upgraded clinics interacted with providers' and patients' agency to achieve rapid care and child survival in both arms. Proactive home visits expedited or compounded mechanisms that were activated and changed the context across arms.

Lancet Glob Health. 2025 Jan;13(1):e121-e133.

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An innovative Community Mobilisation and Community Incentivisation for child health in rural Pakistan (CoMIC): a cluster-randomised, controlled trial

Jai K Das¹, Rehana A Salam², Zahra Ali Padhani³, Arjumand Rizvi⁴, Mushtaq Mirani⁴, Muhammad Khan Jamali⁴, Imran Ahmed Chauhadry⁵, Imtiaz Sheikh⁴, Sana Khatoon⁴, Khan Muhammad⁴, Rasool Bux⁴, Anjum Naqvi⁴, Fariha Shaheen⁵, Rafey Ali⁵, Sajid Muhammad⁵, Simon Cousens⁶, Zulfiqar A Bhutta⁷

Abstract

Background: Infectious diseases remain the leading cause of death among children younger than 5 years due to disparities in access and acceptance of essential interventions. The Community Mobilisation and Community Incentivisation (CoMIC) trial was designed to evaluate a customised community mobilisation and incentivisation strategy for improving coverage of evidence-based interventions for child health in Pakistan.

Methods: CoMIC was a three-arm cluster-randomised, controlled trial in rural areas of Pakistan. Clusters were formed by grouping villages based on geographical proximity, ethnic consistency, and ensuring a population between 1500 to 3000 per cluster. Clusters were randomly assigned (1:1:1) to either community mobilisation, community mobilisation and incentivisation, or the control arm. Community mobilisation included formation of village committees which conducted awareness activities, while clusters in the community mobilisation and incentivisation group were provided with a novel conditional, collective, community-based incentive (C3I) in addition to community mobilisation. C3I was conditioned on serial incremental targets for collective improvement in coverage at cluster level of three key indicators (primary outcomes): proportion of fully immunised children, use of oral rehydration solution, and sanitation index, assessed at 6 months, 15 months, and 24 months, and village committees decided on non-cash incentives for people in the villages. Data were analysed as intention-to-treat by an independent team masked to study groups. The trial is registered at ClinicalTrials.gov, [NCT03594279](https://clinicaltrials.gov/ct2/show/study/NCT03594279), and is completed.

Findings: Between Oct 1, 2018 and Oct 31, 2020, 21 638 children younger than 5 years from 24 846 households, with a total population of 139 005 in 48 clusters, were included in the study. 16 clusters comprising of 152 villages and 7361 children younger than 5 years were randomly assigned to the community mobilisation and incentivisation group; 16 clusters comprising of 166 villages and 7546 children younger than 5 years were randomly assigned to the community mobilisation group; and 16 clusters comprising of 139 villages and 6731

children younger than 5 years were randomly assigned to the control group. Endline analyses were conducted on 3812 children (1284 in the community mobilisation and incentivisation group, 1276 in the community mobilisation group, and 1252 in the control group). Multivariable analysis indicates improvements in all primary outcomes including a higher proportion of fully immunised children (risk ratio [RR] 1.3 [95% CI 1.0-1.5]), higher total sanitation index (mean difference 1.3 [95% CI 0.6-1.9]), and increased oral rehydration solution use (RR 1.5 [1.0-2.2]) in the community mobilisation and incentivisation group compared with the control group at 24 months. There was no evidence of difference between community mobilisation and control for any of the primary outcomes.

Interpretation: Community mobilisation and incentivisation led to enhanced acceptance evidenced by improved community behaviours and increased coverage of essential interventions for child health. These findings have the potential to inform policy and future implementation of programmes targeting behaviour change but would need evaluation for varying outcomes and different contexts.

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[Assessing the value-added contributions of community health workers and communities to early child development: a longitudinal study in a low-income setting](#)

[Caitlin Hemlock](#)^{1,2}, [Maria Dieci](#)³, [Lia C H Fernald](#)⁴, [Emanuela Galasso](#)⁵, [Lisy Ratsifandrihamanana](#)⁶, [Ann M Weber](#)⁷

Abstract

Background: Early child development (ECD) programs in low-resource settings can be effective when delivered through community health workers (CHWs), but there are significant challenges when moving to scale. This analysis aimed to determine the value-added, or relative effectiveness, of CHWs and communities on ECD outcomes within a home-visiting trial and examine associations between observable characteristics of the CHW or community and value-added.

Methods: We analysed data from the four treatment arms of a cluster-randomised trial conducted in 100 communities in rural Madagascar from 2014 to 2016. CHWs (one per cluster) and enrolled children (0-12 months) were surveyed at baseline and 2 years later. Child development scores were assessed using the Ages and Stages Questionnaire-Inventory (ASQ-I) and were internally age-standardised. We determined value-added by estimating CHW/community-level fixed effects on ASQ-I Z-score trajectories (change from baseline to endline), conditional on baseline ASQ-I Z-score and child and household characteristics. We also assessed associations between value-added and observable CHW and community-level characteristics.

Results: We analysed data from 1456 children present at baseline and endline. CHW/community fixed effects explained 26% of ASQ-I trajectory variance and estimates ranged from -1.68 SD to 1.31 SD. CHWs who had another income-generating position were associated with a 0.54 SD (95% CI 0.22, 0.87) increase in ASQ-I Z-score from baseline to endline. Greater increases in children's ASQ-I Z-scores were also associated with communities that had better healthcare, education and transportation infrastructure and were less geographically dispersed.

Conclusions: Children gained or lost over one standard deviation of ASQ-I Z-score depending on the community and CHW where they lived. Children's development trajectories benefitted from CHWs involved in an external income-generating activity and communities with better access to healthcare, education, and transportation. Careful consideration of the contexts in which child development interventions are implemented and potential correlates of improved CHW performance are crucial for improved outcomes.

Lancet Glob Health. 2024 Dec;12(12):e2035-e2048.

doi: 10.1016/S2214-109X(24)00369-3. Epub 2024 Oct 17.

Effect of a participatory whole-systems approach on mortality in children younger than 5 years in Jigawa state, Nigeria (INSPIRING trial): a community-based, parallel-arm, pragmatic, cluster randomised controlled trial and concurrent mixed-methods process evaluation

[Carina King¹](#), [Rochelle Ann Burgess²](#), [Ayobami A Bakare³](#), [Funmilayo Shittu⁴](#), [Julius Salako⁴](#), [Damola Bakare⁴](#), [Obioma C Uchendu⁵](#), [Agnese Iuliano²](#), [Nehla Djellouli²](#), [Adamu Isah⁶](#), [Ibrahim Haruna⁶](#), [Samy Ahmar⁷](#), [Tahlil Ahmed⁷](#), [Paula Valentine⁷](#), [Temitayo Folorunso Olowookere⁸](#), [Matthew MacCalla⁹](#), [Hamish R Graham¹⁰](#), [Eric D McCollum¹¹](#), [James Beard¹²](#), [Adegoke G Falade¹³](#), [Tim Colbourn²](#); [INSPIRING Project Consortium](#)

Abstract

Background: In 2019, Nigeria reported the highest mortality rate in children younger than 5 years globally. We aimed to assess a whole-systems approach to improving child mortality in northern Nigeria.

Methods: We conducted a community-based, parallel-arm, pragmatic, cluster randomised controlled trial in Kiyawa local government area, Jigawa state, Nigeria, and a concurrent mixed-methods process evaluation using ethnography and quantitative implementation monitoring. Trial clusters were population catchment areas of 32 government primary health-care facilities. Compounds were randomly sampled, proportional to cluster size, and all women aged 16-49 years and children younger than 5 years who were permanent residents were eligible for inclusion and recruited as the evaluation population. Children younger than 7 days were recruited but excluded from analysis. Evaluation clusters were allocated to intervention or control via simple randomisation with a 1:1 ratio. Cluster names were written on paper, folded, and placed in a container by community representatives. Different community representatives took out names one by one, with the first half assigned to receive the intervention. The intervention consisted of three components: participatory learning and action (PLA) groups for men and women (including compound heads [ie, the member of the compound that residents deemed most senior]), partnership defined quality scorecard (PDQS), and health-care worker capacity building; it was delivered from March 1, 2021, to Dec 31, 2022. We could not mask participants, field staff, or intervention-delivery staff to cluster allocation but baseline, endline, and follow-up data excluded information on cluster allocation. PLA groups involved separate groups of up to 25 men or women from all villages in the intervention clusters. The primary outcome was all-cause mortality in children aged 7 days to 59 months between Oct 1, 2021, and Sept 20, 2022, referred to as the evaluation period. The trial was prospectively registered (ISRCTN 39213655) and the protocol has been published.

Findings: We recruited 3800 compounds at baseline, with 12 893 children contributing to analysis of the primary outcome (7316 [56·8%] of 12 893 in the intervention group and 5577 [43·3%] in the control group). 6617 (51·3%) of 12 893 children were male, 6275 (48·7%) were female, and one (<0·1%) child had missing sex data. Sampled compounds randomly came from 388 (91·3%) of 425 villages in the 32 clusters. We conducted verbal autopsies for 1182 deaths, of which 369 (31·2%) were children aged 7 days to 59 months during the evaluation period. Of these 369, 91 (24·7%) were classified as pneumonia deaths. Children contributed a median 361 days (IQR 236-365) to the analysis, with 369 (2·9%) of 12 893 children censored on their date of death, 1545 (12·0%) on their 5th birthday, and 3392 (26·3%) on the date of the most recent follow-up in which their residence or survival status was known. We found no significant decrease in all-cause mortality (hazard ratio 0·95, 95% CI 0·68-1·33; $p=0·79$) or suspected pneumonia mortality (0·79, 0·43-1·46; $p=0·46$) in the intervention group. The process evaluation showed low coverage and issues in reach of the intervention, but qualitative data highlighted mechanisms for positive effects on health and relationships.

Interpretation: Our intervention did not affect mortality. However, due to the high child mortality in this region, further efforts should be made to adapt our participatory whole-systems approach to use communities of action within compounds.

Child development and parenting programs

BMJ Glob Health. 2025 Jun 8;10(6):e017866.

doi: 10.1136/bmjgh-2024-017866.

[Four-year follow-up to a home-visiting intervention to promote early childhood development and prevent family violence in rural Rwanda: the Sugira Muryango cluster randomised trial](#)

[Sarah G K Jensen](#)¹, [Matias Placencio-Castro](#)^{2,3}, [Shauna M Murray](#)⁴, [Jess Littman](#)⁵, [Stephanie M Bazubagira](#)⁶, [Dieudonne Uwizeye](#)⁷, [Vincent Sezibera](#)⁸, [Theresa S Betancourt](#)⁹

Abstract

Background: Sugira Muryango (SM) is a home-visiting intervention designed to promote early childhood development (ECD) and prevent violence in families with young children living in extreme poverty in rural Rwanda.

Methods: We present 4-year follow-up data collected in 2022 in $n=1009$ households (93%) from a cluster randomised trial. We compare outcomes in SM and usual care (UC) families using mixed-effect models. Results are reported as the average difference in change over time in the SM versus UC group for longitudinal outcomes and the average difference in SM versus UC groups for new outcomes.

Results: Compared with UC caregivers, caregivers who participated in SM report engaging in more stimulating interaction with their children ($b=0.531$; 95% CI: 0.468, 0.594) and are less likely to report use of harsh discipline ($b=-0.189$; 95% CI: -0.292, -0.087). The SM caregivers also provide more learning materials ($b=0.218$; 95% CI: 0.0219, 0.414), language stimulation ($b=0.159$; 95% CI: 0.080, 0.240), more varied interactions ($b=0.147$; 95% CI: 0.030, 0.260), fathers are reported to be more engaged in play ($b=0.253$; 95% CI: 0.039, 0.467) and SM households

have better hygiene practices ($b=0.189$; 95% CI: 0.052, 0.326) compared with UC households. We do not observe treatment effects on children's cognitive outcomes, self-regulation or behavioural problems. There is a small negative association between SM and height-for-age ($b=-0.038$; 95% CI: -0.062, -0.012).

Conclusions: SM resulted in changes in caregivers' behaviours to support children's health and development. Despite positive caregiver effects, we did not observe effects on child development or behavioural outcomes. Programme updates may be required to support children's continued cognitive growth.

J Exp Child Psychol. 2025 Jun;254:106216.

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Participation in a home visiting program predicted maternal but not child vocabulary diversity: A pragmatic randomized trial in Brazil

[Gabriela Vescovi¹](#), [Tiago N Munhoz²](#), [Meredith L Rowe³](#), [Elisa Rachel Pisani Altafim⁴](#), [Iná S Santos⁵](#), [Alicia Matijasevich⁶](#), [Cristiane Salum⁷](#), [Luciano Lima Correia⁸](#), [Pedro Israel Cabral de Lira⁹](#), [Letícia Marques Dos Santos¹⁰](#), [Marta Rovey de Souza¹¹](#), [Hernane Guimarães Dos Santos Junior¹²](#), [Esmeralda Correa Macana¹³](#), [Cauane Blumenberg¹⁴](#), [Caroline Bortolotto¹⁵](#), [Raquel Barcelos¹⁵](#), [Giana Bitencourt Frizzo¹⁶](#)

Abstract

The Criança Feliz (Happy Child) parenting program is a home visiting intervention serving over a million low-income Brazilian families. The current study assessed its longitudinal associations with maternal and child speech and gestures in a subsample ($n = 145$) from the program's impact evaluation research. We performed a between-participants pragmatic randomized trial. Mothers (79.7% Black) and children (17-25 months of age; 50.3% female) were randomly assigned to control ($n = 73$) and intervention ($n = 72$) groups. One year later, mother-child pairs were recorded playing at home, and the videos were transcribed and analyzed for speech (quantity, vocabulary diversity, sentence complexity, and number of questions) and gestures (quantity). Intention-to-treat analysis revealed that the intervention was associated with the mother's vocabulary diversity ($d = .35$) regardless of schooling level. No direct or indirect (via maternal speech) associations were observed with the child's speech or gestures. This preliminary evidence suggests that participation in the Criança Feliz program is related to mothers' vocabulary diversity but not to children's speech or gesture measures. The program could focus on maternal gestures, questions, and book reading (complexity feature). Future research evaluating the impact of the program on language outcomes should include pretesting and child follow-up assessments.

Lancet Child Adolesc Health. 2024 Dec 2;S2352-4642(24)00304-3.

doi: 10.1016/S2352-4642(24)00304-3. Online ahead of print.

Effect of a youth-led early childhood care and education programme on children's development and learning in rural Sindh, Pakistan (LEAPS): a stepped-wedge cluster-randomised implementation trial

[Aisha K Yousafzai¹](#), [Saima Siyal²](#), [Emily E Franchett³](#), [Quanyi Dai⁴](#), [Karima Rehmani⁵](#), [Christopher R Sudfeld⁵](#), [Shelina Bhamani⁶](#), [Shahnaz Hakro²](#), [Chin R Reyes⁷](#), [Günther Fink⁸](#), [Liliana A Ponguta⁷](#)

Abstract

Background: In low-income and middle-income countries, an estimated 181·9 million (74·6%) preschool-aged children do not receive adequate nurturing care in health, nutrition, protection, learning, and responsive care, thus jeopardising their healthy development across the life course. Working alongside the health sector, multisectoral actions including social protection and education are necessary to achieve child health and development outcomes. Innovations are needed to expand access to high-quality early childhood care and education (ECCE) for young children and opportunities for youth development. Youth Leaders for Early Childhood Assuring Children are Prepared for School (LEAPS) is a two-generation programme that trains female youth aged 18-24 years to deliver ECCE. We evaluated the effectiveness of LEAPS to improve children's school readiness when delivered at scale in rural Pakistan.

Methods: We implemented a stepped-wedge cluster-randomised trial with three steps from Dec 3, 2018, to June 30, 2021. 99 villages (clusters) in four districts in rural Sindh, Pakistan, were randomly assigned (1:1:1) to introduce LEAPS across three steps. Eligible clusters were those that had a feeder primary school run by the National Commission for Human Development, a department of the Ministry of Federal Education and Professional Training; were safe; had space for a LEAPS preschool; could identify a female youth to deliver the ECCE service; and had not previously participated in the pilot study. Government partners trained female youth, aged 18-24 years, to provide community-based ECCE, enrolling up to 20 children, aged 3·5-5·0 years, per class. Population-based cross-sectional surveys were conducted at baseline and after each step for children who were eligible if they resided in the cluster, were aged 4·5-5·5 years at the time of the survey, and without any severe clinical health conditions or disability. The primary outcome was children's school readiness using the International Development and Early Learning Assessment (IDELA) composite score comprising emergent numeracy, emergent literacy, socio-emotional development, and motor skills. An intention-to-treat analysis was conducted, using linear mixed models accounting for clustering and the stepped-wedge design. The trial is registered with ClinicalTrials.gov ([NCT03764436](https://clinicaltrials.gov/ct2/show/study/NCT03764436)).

Findings: LEAPS was implemented in 91 of 99 villages. In eight clusters, a LEAPS preschool could not be set up. For the intervention programme, the average enrolment of children in a LEAPS preschool was 19 (SD 3, range 12-20). A total of 3858 children (n=3852 with complete IDELA data) were assessed across the four survey rounds conducted between Jan 1, 2019, and March 31, 2021. LEAPS increased school readiness (standardised mean difference: 0·30 [95% CI 0·20-0·40]; p<0·0001) as compared with the control condition.

Interpretation: LEAPS offers a scalable solution to expand access to high-quality ECCE and promote children's school readiness while providing employment for female youth in rural Pakistan and settings with similarly low ECCE participation.

Child Dev. 2025 May-Jun;96(3):1128-1147.

doi: 10.1111/cdev.14225. Epub 2025 Feb 14.

Impacts of the Preschool Safe Program on Marginalized Girls in Northern Nigeria
[Sharon Wolf¹](#), [Johanna Bernard¹](#), [Chika R Ezeugwu²](#), [Lubabatu Ahmad³](#), [Khadijah Bello Gurin³](#)

Abstract

Quality early childhood education (ECE) can improve children's learning and development in low- and middle-income countries, but little evidence exists of programs targeting marginalized girls in vulnerable rural communities. This study used a matched-pair mixed-methods community-randomized trial to evaluate a preschool program for marginalized girls (N = 466, M_{age} = 5-years; W₁ = 2022; W₂ = 2023) from 16 rural Hausa-ethnic communities in Nigeria. The program yielded considerably large impacts on every domain of school readiness assessed (dt = 0.89-1.52). In qualitative interviews (N = 30, data collected in 2023), parents discussed witnessing their daughters' learning and development as well as their future educational and life goals for their daughters. Results demonstrate that access to high-quality ECE in highly disadvantaged communities can dramatically improve girls' learning and potentially change parental perceptions about girl-child education.

J Child Health Care. 2024 Oct 3:13674935241261744.

doi: 10.1177/13674935241261744. Online ahead of print.

Acceptability and feasibility of a group-based intervention to improve outcomes for children at risk for developmental delays in Kenya: A piloted randomized trial

[Megan S McHenry^{1,2}](#), [Brianna Alex¹](#), [Anna Roose¹](#), [Catherine Raciti³](#), [Eren Oyungu⁴](#), [Ananda R Ombitsa²](#), [Cleophas Cherop²](#), [Beatrice Kaniaru²](#), [Carolyn Cherop²](#), [Chandy C John¹](#), [Rachel C Vreeman^{2,5}](#)

Abstract

The Care for Child Development (CCD) program may improve child development outcomes in resource-limited settings, but has not yet been adapted to group-based settings to facilitate sustainable dissemination. In this study, we determined the acceptability and feasibility of a group-based CCD program, with evaluation of program outcomes for child development, home environment, and symptoms of maternal depression as secondary outcomes. We evaluated this adapted program using a 2 × 2 crossover-designed pilot study administered over 10 bi-weekly sessions. Acceptability and feasibility were assessed through focus group discussions using qualitative methods. Child development, home observations, and symptoms of maternal depression were evaluated at baseline, 6 months, and 12 months and assessed quantitatively. Twenty-six mother-child dyads participated. Overall, they perceived CCD as acceptable and feasible, and especially beneficial within its group-based format. Although there were no measured improvements in child development, improvements in stimulating home environments (mean difference 2.5, 95% C.I. [0.37, 4.72]) were found. Further scale-up of this intervention is needed to determine effectiveness.

Lancet Reg Health Southeast Asia. 2025 Jan 16:33:100526.

doi: 10.1016/j.lansea.2024.100526. eCollection 2025 Feb.

Effectiveness of a universal film intervention in reducing violence against children and increasing positive parenting among migrant and displaced caregivers from Myanmar: a community-based cluster randomised trial

[Amanda Sim¹](#), [Khaing Zar Lwin²](#), [Stephanie Eagling-Peche³](#), [G J Melendez-Torres⁴](#), [Seema Vyas³](#), [Francisco Calderon³](#), [Tawanchai Jirapramukpitak²](#), [Jamie Lachman³](#), [Sureeporn Punpuing²](#), [Andrea Gonzalez¹](#), [Mary Soan⁵](#), [Nway Nway Oo⁶](#), [Ivet Castello Mitjans⁷](#), [Greg Tyrosvoutis⁸](#), [Eve Puffer⁹](#)

Abstract

Background: Parenting interventions have been shown to reduce violence against children and promote positive parenting, but evidence on interventions to achieve population-level reach and impact is limited in low-resource settings. We assessed the impact of a universal film intervention for migrant and displaced caregivers from Myanmar living in Thailand.

Methods: We implemented a two-arm, cluster randomised trial in Tak province, Thailand, on the border with Myanmar. 44 communities were stratified by district and randomly allocated to intervention or control (1:1) using a computer-generated list of random numbers.

Intervention group participants received a screening of a 66-min narrative drama film about parenting, followed by a 30-40-min discussion and a 5-min video and poster summarising key messages. Control group participants received information about local health and social services. Eligible participants were primary caregivers aged 18 years or older with a child aged 4-17 years at enrolment. Participants were surveyed at baseline, endline approximately 4 weeks post-intervention, and follow-up approximately 4 months post-intervention.

Primary outcomes were caregiver self-reported use of physical and psychological violence and positive parenting, analysed using both imputed and non-imputed multilevel models estimating differences between study arms at endline and follow-up. Due to the nature of the intervention, participants and assessors were not masked. The trial was prospectively registered with Thai Clinical Trials Registry TCTR20230222005.

Findings: Between February and June 2023, 2249 participants in 44 communities completed baseline assessments and were randomly assigned to intervention ($n = 1116$) and control ($n = 1133$). 2023 caregivers ($n = 998$ in intervention and $n = 1025$ in control) completed the four-week endline survey and 1909 caregivers ($n = 961$ in intervention and $n = 948$ in control) completed the four-month follow-up. Intention to treat analyses showed the intervention reduced physical violence (IRR 0.91, 95% CI 0.85-0.97) and increased positive parenting (β 0.46, 95% CI -0.03 to 0.95). No meaningful differences were observed for psychological violence between intervention and control groups, with imprecisely estimated effects close to zero (β 0.47, 95% CI -0.62 to 1.57). Small effects were observed for the secondary and exploratory outcomes of parenting knowledge, belief in the need for harsh punishment, engagement in early learning, family functioning, and social support. Subgroup analyses suggest that the intervention may be more effective at reducing physical violence among female caregivers and caregivers of female children and younger children. There were no reported adverse effects.

Interpretation: Universal parenting interventions using a film-based entertainment-education approach can effectively reduce physical violence against children and increase positive parenting, with potential for scalability in low-resource settings.

J Exp Child Psychol. 2025 Jun;254:106216.

doi: 10.1016/j.jecp.2025.106216. Epub 2025 Mar 4.

Participation in a home visiting program predicted maternal but not child vocabulary diversity: A pragmatic randomized trial in Brazil

[Gabriela Vescovi¹](#), [Tiago N Munhoz²](#), [Meredith L Rowe³](#), [Elisa Rachel Pisani Altafim⁴](#), [Iná S Santos⁵](#), [Alicia Matijasevich⁶](#), [Cristiane Salum⁷](#), [Luciano Lima Correia⁸](#), [Pedro Israel Cabral de Lira⁹](#), [Letícia Marques Dos Santos¹⁰](#), [Marta Rovey de Souza¹¹](#), [Hernane Guimarães Dos Santos Junior¹²](#), [Esmeralda Correa Macana¹³](#), [Cauane Blumenberg¹⁴](#), [Caroline Bortolotto¹⁵](#), [Raquel Barcelos¹⁵](#), [Giana Bitencourt Frizzo¹⁶](#)

Abstract

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Prev Sci. 2024 Jul;25(5):823-833.

doi: 10.1007/s11121-024-01682-x. Epub 2024 May 17.

[Parenting for Lifelong Health for Young Children in Montenegro: Preliminary Outcomes, Dissemination, and Broader Embedding of the Program](#)

[Judy Hutchings¹](#), [Ida Ferdinandi²](#), [Roselinde Janowski^{3,4}](#), [Catherine L Ward³](#), [Amalee McCoy⁵](#), [Jamie Lachman⁴](#), [Frances Gardner⁴](#), [Margiad Elen Williams⁶](#)

Abstract

The quality of parenting program implementation significantly affects the extent to which a program is delivered effectively as well as the likelihood of it becoming embedded in everyday services. The group based Parenting for Lifelong Health for Young Children (PLH-YC) program for parents of children aged 2-9 years was developed specifically for implementation in low- and middle-income contexts, has been tested in five randomized trials, and incorporates a number of strategies to encourage fidelity of delivery. This paper reports on the introduction of PLH-YC to Montenegro, including initial work to engage government agencies and service providers, adapt the program and, following initial evidence of effectiveness, implement strategies to promote effective delivery and embed the program. Following program adaptation and initial facilitator training, eight groups were run, supported with resources and supervision and independently evaluated. The successful pilot led to program training accreditation by national professional agencies and a series of steps to successfully further embed it into routine settings in Montenegro, including by recognizing the program in national policy documents. This led to further facilitator trainings, now numbering 97 facilitators and the certification of ten coaches and two trainers. By the end of 2023, 1278 parents, across 13 municipalities (half of all municipalities in Montenegro) and a range of service providers, have received the program. The paper describes the project phases and key fidelity components that underpinned the successful introduction and embedding of the program in Montenegro. The plan has resulted in

Montenegro having its own domestic resources to continue to implement the program effectively and further plan for widespread dissemination.

J Exp Child Psychol. 2025 Jun;254:106216.

doi: 10.1016/j.jecp.2025.106216. Epub 2025 Mar 4.

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[Gabriela Vescovi¹](#), [Tiago N Munhoz²](#), [Meredith L Rowe³](#), [Elisa Rachel Pisani Altafim⁴](#), [Iná S Santos⁵](#), [Alicia Matijasevich⁶](#), [Cristiane Salum⁷](#), [Luciano Lima Correia⁸](#), [Pedro Israel Cabral de Lira⁹](#), [Letícia Marques Dos Santos¹⁰](#), [Marta Rovey de Souza¹¹](#), [Hernane Guimarães Dos Santos Junior¹²](#), [Esmeralda Correa Macana¹³](#), [Cauane Blumenberg¹⁴](#), [Caroline Bortolotto¹⁵](#), [Raquel Barcelos¹⁵](#), [Giana Bitencourt Frizzo¹⁶](#)

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Glob Health Action. 2024 Dec 31;17(1):2426784.

doi: 10.1080/16549716.2024.2426784. Epub 2024 Nov 19.

Parenting with nutrition education and unconditional cash reduce maternal depressive symptoms and improve quality of life: findings from a cluster randomised controlled trial in urban Bangladesh

[Sheikh Jamal Hossain^{1,2}](#), [Fahmida Tofail³](#), [Anisur Rahman²](#), [Jane Fisher⁴](#), [Jena Derakhshani Hamadani²](#), [Syed Moshfiqur Rahman¹](#)

Abstract

Background: Maternal post-natal depression is a global public health problem. Parenting interventions targeting children's development may also bring benefits to mothers, but few parenting interventions have been studied thoroughly.

Objectives: The study aimed to measure the effect of a parenting intervention using culturally appropriate and locally made toys, along with nutrition education and unconditional cash, on maternal depressive symptoms (MDS) and quality of life (QoL).

Methods: The study was a cluster randomised controlled trial with two arms: i) intervention: parenting with nutrition education and unconditional cash and ii) comparison: unconditional cash in an urban setting in Bangladesh. Twenty clusters were randomised to either the intervention or control group. Community Health Workers (CHWs) delivered parenting and nutrition education sessions fortnightly in households for one year. The participants were mother-child (6-16 months) dyads. The MDS and QoL were measured using the Self-Reporting Questionnaire-20 and a brief version of the QoL questionnaire. Linear regression analysis was used to assess the treatment effects.

Results: After one year of intervention, 547 mothers (93%) completed the study. The mothers in the intervention group had lower MDS [Regression coefficient (β)=-1.53, Confidence interval (95% CI)=-2.28, -0.80] and higher QoL scores in physical health [β = 4.21 (95% CI = 1.71, 6.73)], psychological health [β = 3.14 (95% CI = 1.10, 5.19)], social relationships [β = 3.21 (95% CI = 0.76, 5.66)] and environment [β = 3.40 (95% CI = 1.37, 5.44)] compared with the comparison group.

Conclusion: Parenting interventions including nutrition education and unconditional cash, aimed at improving children's development, resulted in a reduction in maternal depressive symptoms and improvement in quality of life.

BMC Public Health. 2024 Sep 27;24(1):2583.

doi: 10.1186/s12889-024-20149-w.

Integrating early child development into an existing health and nutrition program: evidence from a cluster-randomized controlled trial

[Caitlin Hemlock](#)^{1,2}, [Emanuela Galasso](#)³, [Ann M Weber](#)⁴, [Tsirery Christian Randriamiarisoa](#)⁵, [Mathilde Col](#)^{6,7}, [Maria Dieci](#)⁸, [Lisy Ratsifandrihamanana](#)⁹, [Lia C H Fernald](#)¹⁰

Abstract

Introduction: In low-resource settings, introducing child health programs into community services may compete for caregiver time. We analyzed the impact of a new early childhood development (ECD) program in rural Madagascar on family attendance at other health services and of adding at-home play materials on program attendance.

Methods: We randomized 75 communities where community health workers (CHWs) implement an existing child health and nutrition program (Projet d'Amélioration des Résultats Nutritionnels or PARN), the status quo. We offered two 6-month cycles of 12 ECD sessions to eligible caregiver-child dyads (6-30 months) in 25 sites [T]; we added take-home play materials in Cycle 2 to 25 sites [T+]. We used differences-in-differences with administrative data to analyze the effect of offering ECD sessions on monthly PARN attendance (T+/T vs. C) among age-eligible children and the impact of toy boxes/libraries on monthly ECD session attendance (T + vs. T). We used random intercept models to analyze characteristics associated with program registration.

Results: We analyzed data for 9,408 dyads; 30% and 32% registered for the program in Cycle 1 and 2 (respectively). On average, CHWs delivered 11.4 sessions (SD: 1.5). Children from wealthier households who already attended PARN sessions were more likely to register, and

we found no effect of T or T + on PARN attendance. Adding play materials did not affect monthly ECD session attendance. Children from more populated sites were less likely to participate in both ECD and PARN sessions.

Conclusions: Integrating new services for ECD into the health system was feasible and did not reduce dyad participation in existing services. Investment in health services in more populated areas is needed to provide coverage to all eligible children. Novel strategies should be explored to engage the most vulnerable children in new and existing health services.

Matern Child Nutr. 2024 Jul 3:e13698.

doi: 10.1111/mcn.13698. Online ahead of print.

Understanding modifiable caregiver factors contributing to child development among young children in rural Malawi

[Lilia Bliznashka^{1,2}](#), [Odiche Nwabuikwu¹](#), [Marilyn Ahun³](#), [Karoline Becker⁴](#), [Theresa Nnensa⁵](#), [Natalie Roschnik⁶](#), [Monice Kachinjika⁷](#), [Peter Mvula⁷](#), [Alister Munthali⁷](#), [Victoria Ndolo⁸](#), [Mangani Katundu⁸](#), [Kenneth Maleta⁵](#), [Agnes Quisumbing¹](#), [Melissa Gladstone⁹](#), [Aulo Gelli¹](#)

Abstract

This study examined modifiable caregiver factors influencing child development in Malawi using baseline data from 1,021 mothers and their children <2 years of age participating in a cluster-randomized controlled trial implemented in rural Malawi (2022-2025). We fit an evidence-based theoretical model using structural equation modelling examining four caregiver factors: (1) diet diversity (sum of food groups consumed in the past 24 h), (2) empowerment (assessed using the project-level Women's Empowerment in Agriculture Index), (3) mental health (assessed using the Self-Reported Questionnaire, SRQ-20), and (4) stimulation (number of stimulation activities the mother engaged in the past 3 days). Child development was assessed using the Malawi Development Assessment Tool (norm-referenced aggregate Z-score). The model controlled for child, caregiver, and household socioeconomic characteristics. Results showed that caregiver dietary diversity was directly associated with higher child development scores (standardized coefficient 0.091 [95% CI 0.027, 0.153]) and lower SRQ-20 scores -0.058 (-0.111, -0.006). Empowerment was directly associated with higher child development scores (0.071 [0.007, 0.133]), higher stimulation score (0.074 [0.013, 0.140]), higher dietary diversity (0.085 [0.016, 0.145]), and lower SRQ-20 scores (-0.068 [-0.137, -0.002]). Further, higher empowerment was indirectly associated with improved child development through enhancement of caregiver dietary diversity, with an indirect effect of 0.008 (0.002, 0.018). These findings highlight the important role that caregiver diet and empowerment play in directly influencing child development and other aspects of caregiver well-being. Interventions aimed at enhancing child development should consider these factors as potential targets to improve outcomes for children and caregivers.

Trauma Violence Abuse. 2024 Jul;25(3):2128-2142.

doi: 10.1177/15248380231207965. Epub 2023 Nov 18.

Parenting Interventions That Promote Child Protection and Development for Preschool-Age Children with Developmental Disabilities: A Global Systematic Review and Meta-Analysis

[Zuyi Fang¹](#), [Xinran Liu¹](#), [Cheng Zhang²](#), [Jamie M Lachman^{3,4}](#), [Dongping Qiao¹](#)

Abstract

Global guidelines emphasize the critical role of responsive caregiving in terms of reducing violence against children and promoting early childhood development. However, there is an absence of global evidence synthesis on the effects of early childhood parenting programs for children with developmental disabilities. This systematic review and meta-analysis aims to investigate the effectiveness of parenting interventions delivered for preschool-age children with developmental disabilities in reducing violence against children, altering violence-related factors, and promoting child development. We searched for randomized controlled trials with inactive control. Estimates were pooled using robust variance estimations. Meta-regressions were conducted to explore sources of heterogeneity. In all, 33 studies met the inclusion criteria. The results showed that parenting programs improved child behavior, parental mental health, parenting practices, parental self-efficacy, parent-child interaction, child language skills, and child social skills post-intervention. No studies provided data on the actual occurrence of violence against children. Effects might vary by diagnosis, delivery modality, and world region. The findings supported the delivery of parenting programs to alter factors associated with violence against children and promote child language and social skills for families of young children with developmental disabilities, especially attention deficit hyperactivity disorder, autism, intellectual disability, and language disorders. More research using rigorous methods, long-term follow-ups, and transparent reporting is needed, particularly within more low- and middle-income countries.

J Nutr. 2024 Aug;154(8):2590-2598.

doi: 10.1016/j.tjnut.2024.06.012. Epub 2024 Jun 25.

The Relationship of Preterm and Small for Gestational Age with Child Cognition During School-Age Years

[Phuong Thi Nguyen¹](#), [Phuong Hong Nguyen²](#), [Lan Mai Tran³](#), [Long Quynh Khuong⁴](#), [Son Van Nguyen¹](#), [Melissa F Young³](#), [Ann DiGirolamo⁵](#), [Usha Ramakrishnan³](#)

Abstract

Background: Children born preterm and/or small for gestational age (SGA) are at increased risk of poor cognitive outcomes, particularly in low and middle-income countries (LMICs).

Objectives: This study aimed to examine the cognitive and academic deficits during the school-age years in children born preterm or SGA compared with those in children born term adequate for gestational age (AGA) in rural Vietnam.

Methods: Children born to women in a preconception micronutrient supplementation trial in Vietnam were classified into 3 groups: preterm AGA (n = 138), term SGA (n = 169), and term AGA (n = 1134). Cognitive abilities were assessed using the Wechsler Intelligence Scale for Children, measuring 4 domains [verbal comprehension index (VCI), perceptual reasoning index (PRI), working memory index (WMI), and processing speed index (PSI) scores] and full-scale intelligence quotient (FSIQ) at 6-7 and 10-11 y. Academic achievement was assessed with mathematic and language tests. Analysis of variance and multiple regression models were used to analyze differences in cognitive function and academic achievement at 6-7 and 10-11 y by birth phenotypes.

Results: Compared with term AGA children, those born SGA had lower cognitive scores at both 6-7 y (VCI, -2.3; PRI, -3.7; PSI -2.1; and FSIQ, -2.9) and 10-11 y (VCI, -3.7; PRI, -3.5; WMI, -2.7; PSI, -1.9; and FSIQ, -3.9). Children born SGA also had poorer academic achievement with lower language (5.3) and mathematic (2.5) scores. Adjustments for maternal factors and home environment attenuated the associations, but the differences in VCI, PRI, FSIQ, and language at 10-11 y remained significant. There were no differences in cognitive function and academic achievement between children born preterm and AGA.

Conclusions: Our findings highlight the enduring association of birth phenotype on cognitive functioning and academic achievement during the school years, despite adjustments for maternal education and family environment. Further research is needed to implement effective interventions to improve birth outcomes and optimize child health and development in LMICs

J Glob Health. 2024 Nov 8:14:04063.

doi: 10.7189/jogh.14.04063.

[Access to affordable daycare and women's mental health in Rajasthan, India: Evidence from a cluster-randomised social intervention](#)

[Arijit Nandi](#)¹, [Parul Agarwal](#)², [Anoushaka Chandrashekar](#)², [Shannon Maloney](#)³, [Robin Richardson](#)⁴, [Laxmi Thakur](#)⁵, [Sam Harper](#)¹

Abstract

Background: Women in India are often responsible for unpaid household work, family caregiving, and paid work, which can contribute to poorer mental health. The provision of childcare has the potential to improve women's mental health, but evidence on the effects of providing access to daycare is limited.

Methods: We designed a cluster-randomised trial and used data from a sample of 2858 mothers with age-eligible children from 160 village hamlets in rural Rajasthan, India, to evaluate the impact of providing access to a community-based daycare programme on social and emotional aspects of women's mental health. We conducted a baseline survey in early 2016, randomised hamlets to intervention or control groups approximately six months later, and delivered the final post-intervention survey approximately two years thereafter.

Results: Treatment assignment increased the probability that a respondent used a daycare over the two-year follow-up by 40.9 percentage points. Providing randomised access to a daycare resulted in 0.2 (95% confidence interval (CI) = -0.1, 0.4) fewer symptoms of mental distress, representing a 9.5% decline compared to the baseline mean of 2.1 symptoms, as well as a 3.7 (95% CI = -0.8, 8.3) percentage point increase in the proportion of women who reported feeling very happy, equivalent to an 11.0% increase relative to the baseline mean of 33.6%. Among social indicators, treatment assignment was associated with a 5.6 (95% CI = -1.2, 12.4) percentage point increase in membership in an association, a relative increase of 43.4% compared to the baseline mean of 12.9%. The intervention did not have an appreciable impact on measures of life satisfaction or trust in institutions. Two-stage least squares instrumental variable analyses showed that daycare use decreased mental distress by 0.4 (95% CI = -0.1, 0.8) symptoms, increased the proportion of women who were very happy by 9.4 (95% CI = 0.0, 17.6) percentage points, and increased membership in an organisation by 15.9 (95% CI = 8.4, 23.7) percentage points.

Conclusions: The provision of affordable, community-based daycare was associated with substantial uptake and showed potential for improving mothers' mental health in a rural context where most women were not employed in the formal labour force.

Child protection and domestic violence

BMC Psychiatry. 2024 Nov 11;24(1):787.

doi: 10.1186/s12888-024-06209-w.

[Task-sharing to promote caregiver mental health, positive parenting practices, and violence prevention in vulnerable families in Sierra Leone: a pilot feasibility study](#)

[Alethea Desrosiers¹](#), [Indrani Saran²](#), [Ariana M Albanese³](#), [Cara M Antonaccio³](#), [Sarah E Neville³](#), [Rebecca Esliker⁴](#), [Musu Jambai⁵](#), [Mahmoud Feika⁵](#), [Theresa S Betancourt²](#)

Abstract

Background: The prevalence of household violence in low- and middle-income countries (LMICs) is high, and exposure to violence has significant adverse effects on both mental health and child development across generations. Evidence-based services to improve parenting practices and reduce household violence in LMICs are scarce, particularly across rural regions of West Africa. This study explored the feasibility, acceptability, and potential benefits of an evidence-based home-visiting intervention to promote early childhood development and reduce household violence-the Family Strengthening Intervention for Early Childhood Development and Violence-Prevention (FSI-ECD + VP)-among vulnerable families in rural regions of Sierra Leone.

Methods: Eighty dual-caregiver households in the Makeni region of Sierra Leone were included in the study (N = 160 caregivers; 73% female). Eligibility criteria included having at least one child aged 6-36 months and elevated scores (> 62.5) on the Difficulties in Emotion Regulation Scale (DERS). Community Health Workers (CHWs) employed in the Makeni region completed a 3-week FSI-ECD + VP training. Families were randomized to receive either the FSI-ECD + VP or treatment as usual (TAU). Research assistants blinded to treatment assignment assessed caregiver mental health, caregiver-child interactions, and household violence at baseline, post-intervention, and 3-month follow-up time points.

Results: Triangulation of quantitative and qualitative data showed that caregivers, CHWs, and supervisors generally perceived the intervention as beneficial, feasible, and acceptable. Mixed effects models showed that caregivers who received the FSI-ECD + VP had significantly improved caregiver-child relationship outcomes compared to TAU as assessed by the Home Observation for Measurement of the Environment and the Observation of Caregiver-Child Interactions at post-intervention. Preliminary data also suggests that caregivers receiving the FSI-ECD + VP were less likely to have experienced intimate partner physical violence during the post-intervention period, and had lower symptoms of anxiety and depression at 3-month follow-up.

Conclusions: FSI-ECD + VP delivery by CHWs in Sierra Leone may be feasible and acceptable; it may also help improve caregiver-child interactions and reduce the likelihood of household violence among vulnerable families with young children. Task-sharing approaches may help increase acceptability and access to evidence-based behavioral interventions that promote

early childhood development and violence prevention among families in rural regions of Sierra Leone and other similar settings.

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Effectiveness of couple-based violence prevention education in reducing intimate partner violence during pregnancy in rural Ethiopia: A cluster randomized controlled trial

[Zelege Dutamo Agde^{1,2}](#), [Jeanette H Magnus³](#), [Nega Assefa⁴](#), [Muluemebet Abera Wordofa¹](#)

Abstract

Background: Pregnancy is often seen as a joyful and fulfilling time for many women. However, a significant number of women in Ethiopia experience intimate partner violence (IPV) during this period. Despite this, there is limited evidence on interventions aimed at preventing violence during pregnancy. The purpose of this trial was to examine the effectiveness of Couple-Based Violence Prevention Education (CBVPE) in reducing IPV during pregnancy in rural Ethiopia.

Method: A cluster randomized controlled trial was conducted using a two-arm parallel group design. The 16 clusters were randomly allocated into 8 intervention groups and 8 control groups. A total of 432 pregnant women (216 in the intervention group and 216 in the control group) participated in the trial. Couple-based violence prevention education was provided to the participants in the intervention group, while the control group received routine or standard care. We used difference-in-difference analysis and the Generalized Estimating Equation (GEE) model to assess the effectiveness of the intervention.

Result: At the endline, 94.9% of women in the intervention group and 95.3% of women in the control group were available for intention-to-treat analysis. There was a substantial drop in the proportion of any IPV during pregnancy from 39.4% at baseline to 13.0% at endline ($p < 0.001$). Women in the intervention group were 74.1% less likely to report any IPV during pregnancy compared to the control group (AOR = 0.259; 95% CI 0.161-0.417). Specifically, the intervention also reduced psychological, physical, and sexual violence during pregnancy.

Conclusion: The study found that CBVPE is effective in reducing IPV during pregnancy in the study setting. Scale-up and adaptation to similar settings are recommended.

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Evaluating the spillover effects of the Sugira Muryango home-visiting intervention on temperament of children aged (0.3-3years) exposed to domestic violence: A cluster randomized controlled trial

[Theodat Siboyintore¹](#), [Jeanne Marie Ntete¹](#), [Jean Mutabaruka¹](#), [Theresa Betancourt²](#), [Sarah Jensen²](#), [Vincent Sezibera^{1,3}](#)

Abstract

Background: Domestic violence, intimate partner violence, and violence against children and women adversely affect children's well-being. The Sugira Muryango Program (SM) in Rwanda, a home-visiting intervention, aimed to improve caregiving practices and family dynamics, may also have potential indirect effects on children's temperament.

Objectives: This study assesses the impact of SM on the temperament of younger children whose families benefited from the intervention, comparing their temperament with those under usual care.

Methods: This study utilized a spillover effect cohort design, focusing on 247 younger siblings of children enrolled in the Sugira Muryango Program (SM) to assess potential spillover effects of the intervention. The temperament of these siblings was measured using the Infant Behavior Questionnaire-Revised Short Form, which was translated into native language of the respondents. Multiple linear regression analysis was performed using SPSS version 29, with the treatment group (SM vs. UC) as the main predictor and temperament as the dependent variable.

Results: The analysis showed no statistically significant differences in key temperament traits such as surgency, negative emotionality, and orienting capacity between the intervention and control groups. The findings indicated that changes in surgency ($B = 1.984$, $t = 1.183$, $p = 0.24$), negative emotionality ($B = -1.657$, $t = -0.915$, $p = 0.36$), and orienting capacity ($B = 0.551$, $t = 0.313$, $p = 0.75$) were not significant.

Conclusion: The results suggest that SM had limited spillover effects on the temperament traits of younger siblings. Given that the intervention was primarily designed to improve broader family dynamics rather than directly impact child temperament, these findings highlight the importance of focusing on direct intervention strategies aimed explicitly at the target child population. Future research should align with the theory of change by examining caregiver-related outcomes, such as parenting practices and mental health, which may influence child temperament. Additionally, considering potential external factors like the COVID-19 pandemic may have influenced the effectiveness of the intervention.

J Adolesc Health. 2025 Mar;76(3):415-428.

doi: 10.1016/j.jadohealth.2024.10.030. Epub 2024 Dec 16.

Pathways From Poverty to Child Mental Health in Burkina Faso: Longitudinal Mediation Analyses in a Cluster-Randomized Clinical Trial

[Leyla Karimli¹](#), [Leyla Ismayilova²](#), [Christine R Wells³](#)

Abstract

Purpose: The study applies the Family Stress Model to examine the impact of an integrated intervention on the mental health of children facing chronic adversity in Burkina Faso. Its primary goal is to enhance understanding of individual and relational factors at the family level as mediators and specific mechanisms through which poverty reduction can impact child well-being.

Methods: Cross-lagged autoregressive longitudinal mediation analyses tested the intervention effect on child mental health, examining maternal depression, maternal anxiety, harsh parenting, and child exposure to abuse as potential mediators. Longitudinal data were collected over the course of 24 months in a cluster-randomized controlled trial conducted among 360 dyads (children aged 10-15 and their female caregivers) in Burkina Faso. Participants were randomized into a control arm, economic intervention using the Graduation approach (Treatment Arm 1), or a combination of economic strengthening and family coaching (Treatment Arm 2).

Results: In Treatment Arm 1, maternal depression fully mediated the intervention effect on child's depression ($B = -0.09$, 95% confidence interval [CI] from -0.26 to -0.003) and child's self-esteem ($B = 0.05$, 95% CI from 0.001-0.18). In Treatment Arm 2, violent parenting practices partially mediated the intervention effect on child's depression ($B = -0.08$, 95% CI from -0.29 to -0.01).

Discussion: Our study underscores the importance of multifaceted interventions merging economic empowerment with family-focused child protection strategies. This approach fosters a supportive family environment, reducing children's vulnerability to mental health issues in resource-poor communities. It enriches our understanding of how parental economic and behavioral interventions impact child mental health outcomes.

Child Abuse Negl. 2025 Apr;162(Pt 2):106850.

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The effectiveness of parenting interventions in reducing violence against children in humanitarian settings in low- and middle-income countries: A systematic review and meta-analysis

[Sophia Backhaus¹](#), [Alexandra Blackwell²](#), [Frances Gardner²](#)

Free article

Abstract

Background: Violence against children is a global phenomenon, yet children living in humanitarian settings are at elevated risk of experiencing violent parenting. Parenting interventions are a recommended prevention strategy.

Objective: To conduct a systematic review and meta-analysis on the effectiveness of parenting interventions in preventing violence against children and related parent and child outcomes.

Participants and setting: Primary caregivers in humanitarian settings in low- and middle-income countries (LMICs).

Methods: A highly sensitive multi-language systematic search in electronic and grey-literature database. Studies were appraised for risk of bias, summary effects by certainty of effect, and effect estimates pooled using robust variance estimation.

Results: Twenty-three randomized trials were meta-analyzed finding a small effect on physical and psychological violence ($n = 14$, $k = 21$, $d = -0.36$, 95 % CI [-0.69, -0.04]), positive parenting ($n = 16$, $k = 43$, $d = 0.48$, 95 % CI [0.29, 0.67]), negative parenting ($n = 17$, $k = 37$, $d = -0.42$, 95 % CI [-0.67, -0.16]), parental poor mental health ($n = 9$, $k = 15$, $d = -0.34$, 95 % CI [-0.66, -0.02]), and internalizing behaviors ($n = 11$, $k = 29$, $d = -0.38$, 95 % CI [-0.70, -0.05]); a non-significant effect on externalizing child behaviors ($n = 9$, $k = 17$, $d = -0.12$, 95 % CI [-0.50, 0.27]). Too few studies reported intimate partner violence, sexual violence, and parenting stress outcomes.

Conclusions: Our findings suggest that parenting interventions in humanitarian settings in LMICs may be an effective strategy to reduce physical and psychological violence, and numerous related parent and child outcomes. However, findings need to be interpreted in light of the limited number of available studies and imprecise statistical significance for selected outcomes.

J Res Adolesc. 2024 Sep;34(3):957-968.

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Short-term impact of a combination intervention on family cohesion: Results from a pilot cluster-randomized clinical trial in Northern Ghana

[Ozge Sensoy Bahar¹](#), [William Byansi²](#), [Abdallah Ibrahim³](#), [Alice Boateng⁴](#), [Portia Buernarkie Nartey¹](#), [Proscovia Nabunya¹](#), [Kingsley Kumbelim⁵](#), [Fred M Ssewamala¹](#), [Mary M McKay⁶](#)

Abstract

Child labor remains a concern in sub-Saharan Africa. Yet, evidence-based preventive efforts are limited. We analyzed longitudinal data from Ghanaian adolescent girls in a pilot randomized clinical trial testing the preliminary impact of a combination intervention on family cohesion as a protective factor against child labor and school dropout. While there was no statistical difference between the control and intervention groups at 9 months, the results show that family cohesion scores improved significantly from baseline to 9 months for the ANZANSI intervention group. Qualitative results indicated improved family cohesion in the intervention group. Hence, future studies should further examine this promising social work intervention.

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Ghanaian women's experience of intimate partner violence (IPV) during group antenatal care: a brief report from a cluster randomised controlled trial

[Samia J Abdelnabi¹](#), [Michelle L Munro-Kramer¹](#), [Cheryl A Moyer²](#), [John E O Williams³](#), [Jody R Lori¹](#)

Abstract

Intimate partner violence (IPV) impacts women of reproductive age globally and can lead to significant negative consequences during pregnancy. This study describes an exploratory aim of a cluster randomised controlled trial designed to assess the outcomes of Group Antenatal Care (ANC) in Ghana. The purpose was to understand the effect of a healthy relationship Group ANC module on experiences of IPV and safety planning as well as to explore the relationship between self-efficacy on the experiences of IPV and safety planning. Data were collected at baseline and at 11-14 months postpartum (post). Survey measures captured reported experiences of violence, self-efficacy, and safety. The chi-square test was used to compare baseline and post scores, and a logistic regression was performed to ascertain the effects of self-efficacy on the experiences of IPV in both groups. The sample included 1,751 participants, of whom 27.9% reported IPV at baseline. Between baseline and postpartum, there was a small increase in reported emotional (6.2% vs. 4.6%) and sexual (5.4% vs. 3.2%) violence in the intervention group compared to the control group. Logistic regression demonstrated that an increasing self-efficacy score was associated with an increased likelihood of experiencing IPV. There were no changes in safety knowledge. This study found higher rates of reported sexual and emotional violence post-intervention among the intervention group. Group ANC may be just one part of a portfolio of interventions needed to address IPV at all socio-ecological levels. **Paper Context** **Main findings:** There was no reduction in experiences of intimate partner violence or increases in safety planning among Ghanaian pregnant women participating in a Group Antenatal Care session focused

on healthy relationships and safety planning. **Added knowledge:** Group Antenatal Care has been identified as an effective modality for providing antenatal care and facilitating conversations about sensitive topics such as intimate partner violence and safety. However, this study highlights the importance of developing multifaceted approaches to decrease the risk of intimate partner violence among women, especially during the critical times of pregnancy and postpartum. **Global health impact for policy and action:** Effective global health action and policy must extend beyond educational efforts, incorporating multifaceted strategies that include healthcare provider training, robust community engagement, and legislation aimed at preventing intimate partner violence, with a special focus on safeguarding the well-being of women during pregnancy and the postpartum period.

Climate change

Lancet Planet Health. 2024 Oct;8(10):e734-e743.

doi: 10.1016/S2542-5196(24)00208-0.

[Effect of heat stress in the first 1000 days of life on fetal and infant growth: a secondary analysis of the ENID randomised controlled trial](#)

[Ana Bonell¹](#), [Ana M Vicedo-Cabrera²](#), [Giovenale Moirano³](#), [Bakary Sonko⁴](#), [David Jeffries⁴](#), [Sophie E Moore⁵](#), [Andy Haines⁶](#), [Andrew M Prentice⁴](#), [Kris A Murray⁷](#)

Abstract

Background: The intersecting crises of climate change, food insecurity, and undernutrition disproportionately affect children. Understanding the effect of heat on growth from conception to 2 years of age is important because of mortality and morbidity implications in the near term and over the life course.

Methods: In this secondary analysis, we used longitudinal pregnancy cohort data from the Early Nutrition and Immunity Development (ENID) randomised controlled trial in West Kiang, The Gambia, which occurred between Jan 20, 2010, and Feb 10, 2015. The ENID trial assessed micronutrient supplementation in the first 1000 days of life starting from 20 weeks' gestation, during which anthropometric measurements were collected prospectively. We used multivariable linear regression to assess the effect of heat stress (defined by Universal Thermal Climate Index [UTCI]) on intrauterine growth restriction based on length-for-gestational age Z score (LGAZ), weight-for-gestational age Z score (WGAZ), and head circumference-for-gestational age Z score (HCGAZ) at birth, and assessed for effect modification of supplement intervention on the relationship between heat stress and infant anthropometry. We used multivariable, multilevel linear regression to evaluate the effect of heat stress on infant growth postnatally based on weight-for-height Z score (WHZ), weight-for-age Z score (WAZ), and height-for-age Z score (HAZ) from 0 to 2 years of age.

Findings: Complete data were available for 668 livebirth outcomes (329 [49%] female infants and 339 [51%] male infants). With each 1°C increase in mean daily maximum UTCI exposure, in the first trimester, we observed a reduction in WGAZ (-0.04 [95% CI -0.09 to 0.00]), whereas in the third trimester, we observed an increase in HCGAZ (0.06 [95% CI 0.00 to 0.12]), although 95% CIs included 0. Maternal protein-energy supplementation in the third trimester was associated with reduced WGAZ (-0.16 [-0.30 to -0.02]) with each 1°C increase in mean daily maximum UTCI exposure, while no effect of heat stress on WGAZ was found with either standard care (iron and folate) or multiple micronutrient supplementation. For the postnatal

analysis, complete anthropometric data at 2 years were available for 645 infants (316 [49%] female infants and 329 [51%] male infants). Postnatally, heat stress effect varied by infant age, with infants aged 6-18 months being the most affected. In infants aged 12 months exposed to a mean daily UTCI of 30°C (preceding 90-day period) versus 25°C UTCI, we observed reductions in mean WHZ (-0.43 [95% CI -0.57 to -0.29]) and mean WAZ (-0.35 [95% CI -0.45 to -0.26]). We observed a marginal increase in HAZ with increasing heat stress exposure at age 6 months, but no effect at older ages.

Interpretation: Our results suggest that heat stress impacts prenatal and postnatal growth up to 2 years of age but sensitivity might vary by age. In the context of a rapidly warming planet, these findings could have short-term and long-term health effects for the individual, and immediate and future implications for public child health.

Complimentary medicine

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[Homoeopathy vs. conventional primary care in children during the first 24 months of life-a pragmatic randomised controlled trial](#)

[Menachem Oberbaum](#)^{#1}, [Anupriya Chaudhary](#)^{#2}, [Hima Bindu Ponnamm](#)³, [Reetha Krishnan](#)⁴, [Dinesh V Kumar](#)⁵, [Mohammed Irfan](#)⁶, [Debadatta Nayak](#)², [Swati Pandey](#)², [Akula Archana](#)⁷, [Sai Bhargavi](#)⁸, [Divya Taneja](#)², [Mohua Datta](#)², [Navin Pawaskar](#)⁹, [Ravindra Mohan Pandey](#)^{10 11}, [Anil Khurana](#)^{2 12}, [Shepherd Roee Singer](#)^{#13 14}, [Raj Kumar Manchanda](#)^{#2 15 16}

Abstract

To compare the difference between primary homoeopathic and conventional paediatric care in treating acute illnesses in children in their first 24 months of life. One hundred eight Indian singleton newborns delivered at 37 to 42 weeks gestation were randomised at birth (1:1) to receive either homoeopathic or conventional primary care for any acute illness over the study period. In the homoeopathic group, conventional medical treatment was added when medically indicated. Clinicians and parents were unblinded. Children in the homoeopathic group experienced significantly fewer sick days than those in the conventional group (RR: 0.37, 95% CI: 0.24-0.58; $p < 0.001$), with correspondingly fewer sickness episodes (RR: 0.53, 95% CI: 0.32-0.87; $p = .013$), as well as fewer respiratory illnesses over the 24-month period. They were taller ($F(1, 97) = 8.92$, $p = .004$, partial eta squared = 0.84) but not heavier than their conventionally treated counterparts. They required fewer antibiotics, and their treatment cost was lower.

Conclusion: Homoeopathy, using conventional medicine as a safety backdrop, was more effective than conventional treatment in preventing sick days, sickness episodes, and respiratory illnesses in the first 24 months of life. It necessitated fewer antibiotics and its overall cost was lower. This study supports homoeopathy, using conventional medicine as a safety backdrop, as a safe and cost-effective primary care modality during the first 2 years of life.

Covid-19

BMC Public Health. 2024 Jul 17;24(1):1924.

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[A prospective randomised controlled trial investigating household SARS-CoV-2 transmission in a densely populated community in Cape Town, South Africa - the transmission of COVID-19 in crowded environments \(TRACE\) study](#)

[Philip Smith](#)¹, [Francesca Little](#)², [Sabine Hermans](#)^{3,4}, [Mary-Ann Davies](#)⁵, [Robin Wood](#)⁶, [Catherine Orrell](#)⁶, [Carey Pike](#)⁶, [Fatima Peters](#)⁷, [Audry Dube](#)⁸, [Daniella Georgeu-Pepper](#)⁸, [Robyn Curran](#)⁸, [Lara Fairall](#)⁸, [Linda-Gail Bekker](#)⁹

Abstract

Background: South Africa's first SARS-CoV-2 case was identified 5th March 2020 and national lockdown followed March 26th. Households are an important location for secondary SARS-CoV-2 infection. Physical distancing and sanitation - infection mitigation recommended by the World Health Organization (WHO) at the time - are difficult to implement in limited-resource settings because of overcrowded living conditions.

Methods: This study (ClinicalTrials.gov [NCT05119348](#)) was conducted from August 2020 to September 2021 in two densely populated, low socioeconomic Cape Town community sub-districts. New COVID-19 index cases (ICs) identified at public clinics were randomised to an infection mitigation intervention (STOPCOV) delivered by lay community health workers (CHWs) or standard of care group. STOPCOV mitigation measures included one initial household assessment conducted by a CHW in which face masks, sanitiser, bleach and written information on managing and preventing spread were provided. This was followed by regular telephonic follow-up from CHWs. SARS-CoV-2 PCR and IgM/IgG serology was performed at baseline, weeks 1, 2, 3 and 4 of follow-up.

Results: The study randomised 81 ICs with 245 HHCs. At baseline, no HHCs in the control and 7 (5%) in the intervention group had prevalent SARS-CoV-2. The secondary infection rate (SIR) based on SARS-CoV-2 PCR testing was 1.9% (n = 2) in control and 2.9% (n = 4) in intervention HHCs (p = 0.598). At baseline, SARS-CoV-2 antibodies were present in 15% (16/108) of control and 38% (52/137) of intervention participants. At study end incidence was 8.3% (9/108) and 8.03% (11/137) in the intervention and control groups respectively. Antibodies were present in 23% (25/108) of control HHCs over the course of the study vs. 46% (63/137) in the intervention arm. CHWs made twelve clinic and 47 food parcel referrals for individuals in intervention households in need.

Discussion: Participants had significant exposure to SARS-CoV-2 infections prior to the study. In this setting, household transmission mitigation was ineffective. However, CHWs may have facilitated other important healthcare and social referrals.

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[Comparison of methylprednisolone alone versus intravenous immunoglobulin plus methylprednisolone for multisystem inflammatory syndrome in children \(MIS-C\)](#)

[Phuc Huu Phan](#)¹, [Canh Ngoc Hoang](#)², [Ha Thu T Nguyen](#)³, [Tung Viet Cao](#)⁴, [Chi Quynh Le](#)³, [Dien Minh Tran](#)^{5,6}

Abstract

Background: As a first-line therapeutic option for multisystem inflammatory syndrome in children (MIS-C) with surging demand, intravenous immunoglobulin (IVIG) is associated with escalating costs and supply shortages, particularly in low-income and middle-income countries. This study compares the effectiveness of methylprednisolone alone versus IVIG combined with methylprednisolone for managing MIS-C.

Methods: We conducted a retrospective cohort study from January 2022 to June 2023 at Vietnam National Children's Hospital. We used propensity score matching to compare the short-term outcomes based on immunomodulatory therapy with methylprednisolone alone or IVIG plus methylprednisolone.

Results: We included 391 patients, comprising 255 boys and 136 girls, who fulfilled the MIS-C case definition of the US Centers for Disease Control and Prevention. Most patients (80.8%) received intravenous methylprednisolone monotherapy, and 19.2% were administered IVIG in addition to methylprednisolone. In general, the laboratory values indicative of hyperinflammatory and hyperthrombotic states displayed significant early response within 2-3 days after initial treatment, including white cell count (SE=1.77, $p<0.001$), NEU (SE=0.76, $p=0.03$), C reactive protein (SE=-46.51, $p<0.001$), PLT (SE=38.05, $p=0.002$), fibrinogen (SE=-0.37, $p=0.002$), d-dimer (SE=-849.8, $p=0.02$); while subsequent improvement in cardiac markers was also observed, with pro-B-type natriuretic peptide (SE=-165.2, $p<0.001$) on day 5 and troponin I (SE=-0.05, $p=0.004$) on day 7. After propensity score weighting, there were 41 patients in each treatment group. Notably, there were no significant differences in the incidence of cardiac events between treatment groups regarding left ventricular dysfunction and coronary artery dilation or aneurysms (10.3% vs 20.7%, $p=0.074$ and 63.4% vs 56.1%, $p=0.653$, respectively). While the median paediatric intensive care unit length of stay (LOS) and hospital LOS were slightly lengthier in the IVIG and methylprednisolone group compared with those of the methylprednisolone group, these differences were not statistically significant ((5 vs 4, $p=0.782$) and (9 vs 7, $p=0.725$), respectively).

Conclusions: Initial treatment with methylprednisolone monotherapy appears not inferior in effectiveness to adjunctive IVIG plus methylprednisolone in MIS-C. Further investigations in randomised controlled trials deserve to be undergone to clarify if IVIG-sparing glucocorticoids are a viable option for achieving favourable outcomes in MIS-C, particularly in resource-limited settings with barriers approaching IVIG therapy.

Dengue

(see Vaccines - dengue)

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[Dengue virus genomic surveillance in the applying Wolbachia to eliminate dengue trial reveals genotypic efficacy and disruption of focal transmission](#)

[Kathryn Edenborough](#)¹, [Endah Supriyati](#)², [Suzanne Dufault](#)³, [Eggi Arguni](#)^{2,4}, [Citra Indriani](#)^{2,5}, [Jai Denton](#)⁶, [R Tedjo Sasmono](#)⁷, [Riris Andono Ahmad](#)^{2,5}, [Katherine L Anders](#)^{6,8}, [Cameron P Simmons](#)^{9,10}

Abstract

Release of *Aedes aegypti* mosquitoes infected with *Wolbachia pipientis* (wMel strain) is a biocontrol approach against *Ae. aegypti*-transmitted arboviruses. The Applying *Wolbachia* to Eliminate Dengue (AWED) cluster-randomised trial was conducted in Yogyakarta, Indonesia in 2018-2020 and provided pivotal evidence for the efficacy of wMel-*Ae. aegypti* mosquito population replacement in significantly reducing the incidence of virologically-confirmed dengue (VCD) across all four dengue virus (DENV) serotypes. Here, we sequenced the DENV genomes from 318 dengue cases detected in the AWED trial, with the aim of characterising DENV genetic diversity, measuring genotype-specific intervention effects, and inferring DENV transmission dynamics in wMel-treated and untreated areas of Yogyakarta. Phylogenomic analysis of all DENV sequences revealed the co-circulation of five endemic DENV genotypes: DENV-1 genotype I (12.5%) and IV (4.7%), DENV-2 Cosmopolitan (47%), DENV-3 genotype I (8.5%), and DENV-4 genotype II (25.7%), and one recently imported genotype, DENV-4 genotype I (1.6%). The diversity of genotypes detected among AWED trial participants enabled estimation of the genotype-specific protective efficacies of wMel, which were similar ($\pm 10\%$) to the point estimates of the respective serotype-specific efficacies reported previously. This indicates that wMel afforded protection to all of the six genotypes detected in Yogyakarta. We show that within this substantial overall viral diversity, there was a strong spatial and temporal structure to the DENV genomic relationships, consistent with highly focal DENV transmission around the home in wMel-untreated areas and a near-total disruption of transmission by wMel. These findings can inform long-term monitoring of DENV transmission dynamics in *Wolbachia*-treated areas including Yogyakarta.

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The influence of fluid resuscitation strategy on outcomes from dengue shock syndrome: a review of the management of 691 children in 7 Southeast Asian hospitals

[Huynh Trung Trieu^{1,2}](#), [Nguyen Lam Vuong^{3,4}](#), [Nguyen Thanh Hung⁵](#), [Tuan Nguyen Minh⁶](#), [Vinh Chau Nguyen Van⁷](#), [Tu Qui Phan⁷](#), [Truong An Nguyen⁸](#), [Su Nguyen Thi Minh²](#), [An Nguyen Thi Truong²](#), [Em Jun Min⁹](#), [Heng Kai Voon⁹](#), [Shirley Chan Huey Ling⁹](#), [Hue Yuen Ling⁹](#), [Lim Eng Seng⁹](#), [Lucy Lum Chai See⁹](#), [Sharifah Faridah Syed Omar⁹](#), [Amnasewary Ramakrishnan¹⁰](#), [Aiu Jer Ling¹¹](#), [Alia Zubaidah Bahtar¹¹](#), [Nachal Nachiappan¹²](#), [Kyaw Zin Wai¹³](#), [Kyi San Thi¹³](#), [Yee Mon Lwin¹³](#), [Nick Ward¹⁴](#), [Anushka Ward¹⁴](#), [Sophie Yacoub²](#), [Hung Trinh²](#), [Phung Khanh Lam²](#), [Bridget Wills^{15,2}](#)

Abstract

Introduction: The pathognomonic feature of dengue shock syndrome (DSS) is a transient capillary leak syndrome resulting in profound intravascular volume depletion. WHO management guidelines recommend particular parenteral fluid regimens during the critical leakage phase, including synthetic colloid solutions in certain circumstances. We set out to describe the actual fluid management strategies employed in different settings and to investigate relationships with clinical outcomes.

Methods: We performed a retrospective review of paediatric DSS cases managed at seven hospitals across Malaysia, Myanmar and Vietnam. We explored the effects of both initial resuscitation (crystalloid alone or mixed crystalloid/colloid in the first 2 hours) and general management: group 1 (conservative-colloid, crystalloid only), group 2 (intermediate-colloid, colloid for 1-4 hours) or group 3 (liberal-colloid, continuous colloid for more than 4 hours)

categorised according to the fluid given over the first 6 hours in clinically stable patients. We incorporated an inverse probability weighting score to adjust for potential differences in baseline severity.

Results: Among all 691 patients, respiratory compromise (HR 2.08, $p=0.022$), requirement for nasal continuous positive airway pressure (NCPAP)/ventilation (OR 2.34, $p<0.045$) and days in hospital after DSS onset (risk ratio, RR 1.33, $p=0.032$) were significantly worse for mixed crystalloid/colloid versus crystalloid-only initial resuscitation regimens, after adjusting for baseline severity. Among the 547/691 children who stabilised within 2 hours, although a liberal-colloid general management strategy (group 3) was associated with a reduction in recurrent shock episodes (RR 0.13, $p=0.043$) when compared with a conservative-colloid strategy (group 1), the risks for respiratory compromise (OR 8.84, $p<0.001$) and requirement for NCPAP/ventilation (OR 8.16, $p<0.001$) were markedly increased. Additionally, the respective costs for group 3 vs group 1 were significantly higher.

Conclusions: The study highlights the potential benefits and risks of using colloid solutions in children with DSS. Formal randomised trials could help determine the most effective and safe parenteral fluid regimens for paediatric DSS. In the meantime, prolonged use of colloid solutions may be inappropriate, especially in settings without access to respiratory support.

Diarrhoea

(See also: Vaccines and immunization - Rotavirus vaccine, Hygiene and Environmental health, Malnutrition, Dengue, Nutrition - Environmental enteric dysfunction)

Treatment of diarrhoea

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[Antibiotics for acute watery or persistent with or without bloody diarrhoea in children: A systematic review and meta-analysis](#)

[Syeda Kanza Naqvi¹](#), [Mustafa Bin Ali Zubairi¹](#), [Ayesha Arshad Ali¹](#), [Ashraf Sharif²](#), [Rehana Abdus Salam³](#), [Zain Hasnain¹](#), [Sajid Soofi^{4,5}](#), [Shabina Ariff⁵](#), [Yasir Bin Nisar⁶](#), [Jai K Das^{1,7}](#)

Abstract

Background: The use of antibiotics in the treatment of acute and persistent watery diarrhoea has long been a subject of contention. While the advantages of using antimicrobials are acknowledged, concerns remain regarding potential adverse effects and antibiotic resistance. Therefore, we conducted a systematic review and meta-analysis to assess the efficacy of antibiotics compared to placebos for the treatment of diarrhoea.

Methods: We searched PubMed, CINAHL, the Cochrane Library, ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform, and Scopus from inception until 20 July 2023 for studies published after the year 2000 assessing antibiotics vs placebo in acute and persistent diarrhoea and/or blood in stools in children less than 10 years of age. We conducted a meta-analysis for the included studies, assessed them using the Risk of Bias 2 tool, and evaluated their quality of evidence through the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework. This

review was commissioned by WHO for revision of their guidelines for childhood diarrhoea management.

Results: We included five randomised controlled trials (RCTs) for acute watery diarrhoea and no study for bloody diarrhoea. Our findings suggest that there is a significant increase in clinical cure (risk ratio (RR) = 2.28; 95% confidence interval (CI) = 1.52, 3.41; low certainty evidence) and parasitological cure (RR = 2.86; 95% CI = 1.72 to 4.74; low certainty evidence) among children with acute watery diarrhoea in the antibiotic group when compared to the placebo group. The duration of diarrhoea (in hours) was significantly reduced (mean difference = -24.90; 95% CI = -34.09, -15.71; low certainty evidence) in the intervention group, while the effect on all-cause mortality (RR = 0.71; 95% CI = 0.40, 1.27; moderate certainty evidence) and the need for intravenous fluid infusion (RR = 0.50; 95% CI = 0.05, 5.17; very low certainty evidence) were comparable between the two groups.

Conclusions: In children under 10 years of age suffering from acute watery or persistent diarrhoea, antibiotics led to an apparent increase in cure rates. However, considering the low certainty of evidence, low number of studies with small sample sizes, and the fact that most studies were conducted in a single country, further investigation and cautious interpretation are warranted, as is a large multi-country RCT that would allow for firmer conclusions.

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Consequences of post-discharge hospitalisation on the growth of young Bangladeshi children hospitalised with diarrhoea: a secondary case-control analysis of Antibiotics for Children with Diarrhea (ABCD) trial

[Md Farhad Kabir¹](#), [Irin Parvin¹](#), [Abu Sadat Mohammad Sayeem Bin Shahid¹](#), [Rina Das^{1,2}](#), [Mst Mahmuda Ackhter¹](#), [Tahmina Alam¹](#), [Sharmin Khanam¹](#), [Jannat Sultana¹](#), [Shajeda Nasrin¹](#), [Rumana Sharmin¹](#), [Mohammad Tashfiq Ahmed³](#), [Mehnaz Kamal¹](#), [Md Tanveer Faruk¹](#), [Sharika Nuzhat¹](#), [Farzana Afroze¹](#), [Tahmeed Ahmed¹](#), [Mohammad Jobayer Chisti¹](#)

Abstract

Background: Due to the scarcity of published data on growth among children with severe diarrhoea requiring readmission during post-discharge follow-up, we aimed to investigate the potential impact of post-discharge readmission at day-90 follow-up on growth in diarrheal children aged 2-23 months.

Methods: We performed a secondary analysis using Bangladesh site data from the Antibiotic for Children with Diarrhea (ABCD) trial, a multi-country, randomised, double-blind, placebo-controlled study conducted from July 2017 to July 2019. Children aged 2-23 months who had severe diarrhoea defined as having acute diarrhoea with some/severe dehydration, or severe stunting, or moderate wasting, were admitted to the facility. In this analysis, we classified children who were re-hospitalised within a 90-day post-discharge follow-up period as cases and randomly selected controls who did not require re-hospitalisation, matching them by similar ages and sexes in a 1:3 ratio. We gathered anthropometric data on enrolment and day 90 follow-up. The outcome variables were changes in nutritional indicators height-for-age (Δ HAZ), weight-for-age (Δ WAZ), weight-for-height (Δ WHZ), and mid-upper arm circumference (Δ MUAC). We assessed for growth changes at day 90 post-discharge follow-up using multivariate linear regression.

Results: Among 1431 diarrhoeal children enrolled, we identified 145 cases and 435 controls. In terms of the baseline admission characteristics, the cases were less likely to be immunised (81% vs. 72%; $P = 0.031$), vomit (11% vs. 22%; $P = 0.001$), and have dehydrating diarrhoea (26% vs. 36%; $P = 0.026$) than the controls. After adjusting for potential covariates, the cases had a significant reduction in growth than the controls at 90 days of post-discharge follow-up, according to anthropometric indices: Δ HAZ ($\beta = -0.11$; 95% confidence interval (CI) = -0.21, -0.01; $P = 0.029$), Δ WAZ ($\beta = -0.24$; 95% CI = -0.35, -0.14; $P < 0.001$), Δ WHZ ($\beta = -0.25$; 95% CI = -0.39, -0.12; $P < 0.001$), and Δ MUAC (for children 6-23 months, $\beta = -0.17$; 95% CI = -0.29, -0.04; $P = 0.011$).

Conclusions: Diarrhoeal children aged 2-23 months requiring readmission during the 90-day post-discharge follow-up period had a significant deterioration of ponderal and linear growth, compared with those who did not require readmission. This finding underscores the importance of early identification of children with risks of post-discharge readmission and designing a package of post-discharge trials, including social and nutritional interventions that may help to reduce post-discharge readmissions as well as subsequent growth faltering.

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Efficacy of probiotics for treatment of acute or persistent diarrhoea in children from birth till 10 years: Systematic review and meta-analysis

[Anmol Minaz^{#1}](#), [Ridwa Alam^{#1}](#), [Uswa Jiواني¹](#), [Khadija Vadsaria¹](#), [Ahmad Khan¹](#), [Aqsa Ishaq¹](#), [Samar Sultan¹](#), [Mariam Mohsin¹](#), [Ashraf Sharif²](#), [Yasir Bin Nisar³](#), [Jai K Das⁴](#), [Sajid Soofi¹](#), [Shabina Ariff⁵](#)

Abstract

Background: Numerous studies have investigated the efficacy of probiotics in treating acute and persistent diarrhoea. However, probiotics have not been established as a recommended management option for diarrhoeal illness by the World Health Organization (WHO). Therefore, we conducted a systematic review of randomised controlled trials to assess the efficacy of probiotics for the management of acute and persistent diarrhoea in children.

Methods: A systematic search on PubMed, CINAHL, Wiley Cochrane Library, Scopus, Clinicaltrials.gov, and WHO International Clinical Trials Registry Platform (ICTRP) was performed. All studies published in the year 2000 and onwards that assessed the use of probiotics in the management of acute and persistent diarrhoea in children aged 0-10 years were included. The risk of bias was assessed using the Cochrane Risk of Bias II (RoB-2) tool and the quality of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach. This review was commissioned by WHO for revision of their guidelines for childhood diarrhoea management.

Results: The review included 98 studies with a total of 17 236 participants. Studies were categorised based on the WHO definition of diarrhoea or author-specified definition. In studies considering the WHO definition of diarrhoea, the probiotics group was more likely to achieve clinical cure (risk ratio = 1.12 (95% confidence interval (CI) = 1.01, 1.24, studies = 14)) and reduce the duration of diarrhoea (mean difference = -13.27 hours (95% CI = -16.72, -9.83, studies = 33)) than the control group in children with acute diarrhoea. However, the effect size was small, and statistical heterogeneity was very high, leading to low certainty of evidence. In children with persistent diarrhoea, probiotics reduced the duration of diarrhoea

by 95 hours (mean difference = -96.45 (95% CI = -110.53, -82.37, studies = 2)), but the certainty of the evidence was very low.

Conclusions: The results from this systematic review suggest low certainty of evidence for the effect of probiotics on clinical cure and duration of diarrhoea in children. There was significant diversity in the genus, species, dosages, and duration of treatment in the trial and administration. High levels of heterogeneity reduced the certainty of evidence. Large-scale randomised clinical trials are needed to evaluate specific probiotic strains and doses. In addition, cost-effective analysis studies are needed to be explored in future research.

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Determinants of post-discharge stunting among diarrhoeal children aged 2-23 months in Bangladesh: findings from Antibiotics for Children with Severe Diarrhea (ABCD) trial

Sharika Nuzhat^{#12}, Rina Das^{#34}, Md Farhad Kabir³, Md Ahshanul Haque³, Abu Sadat Mohammad Sayeem Bin Shahid³, Mehnaz Kamal⁵, Md Tanveer Faruk³, Tahmeed Ahmed³⁵⁶, Mohammad Jobayer Chisti³

Abstract

Background: Despite the global burden of stunting, data regarding the determinants of stunting observed on follow-up after discharge from health care facilities among children treated for severe diarrhoea are limited. We investigated factors influencing stunting during post-discharge follow-up among under-2 children treated for severe diarrhoea. We developed a predictive model to estimate stunting prevalence and identify risk factors without post-discharge anthropometry.

Methods: We analysed data from two sites in Bangladesh participating in the multi-country, double-blind, randomised clinical trial on Antibiotics for Children with Severe Diarrhoea among children aged 2-23 months, from 2017 to 2019. Severe diarrhoea was defined as a child who had acute diarrhoea with severe/some dehydration, or moderate wasting, or severe stunting on admission. Multiple linear regression was constructed to predict the independent factors associated with stunting among the enrolled children who were followed for 180 days after hospital discharge. We developed a predictive model for stunting using 75% of the available data for training, with the remaining 25% reserved as a test set to evaluate model performance. We then applied this predictive model to the children not enrolled in the trial but admitted to the hospital for diarrhoea to estimate the predictive prevalence and determinants of post-discharge stunting at 180 days.

Results: Of the 1431 enrolled children, 589 (41.2%) were stunted at enrolment. By day 180, stunting increased to 698 (49.3%). Linear growth of diarrhoeal children over this follow-up period was positively associated with enrolment length-for-age z score (LAZ), maternal body mass index (BMI), maternal education, duration of diarrhoea, and breastfeeding. We applied the predictive model developed on the enrolled patients' data to the 33 341 children admitted for diarrhoea but not enrolled in the trial. The model estimated that 6142 children (18.4%) in this non-follow-up group would have been stunted at 180 days. Persistent stunting at 180 days for these not-followed children was predicted to be positively associated with dehydration on admission and a higher number of children in the household, while a negative association was predicted with formal parental education and increased maternal BMI.

Conclusions: Our study highlights the need for targeted interventions to mitigate persistent stunting in this vulnerable group recovering from diarrhoea.

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doi: 10.1007/s13312-025-00049-x. Epub 2025 Apr 2.

Intramuscular Versus Oral Ondansetron for Management of Children with Acute Dehydrating Diarrhea and Vomiting: A Randomized Controlled Trial

[Shubham Satyesh¹](#), [Rajesh Kumar Meena¹](#), [Dheeraj Shah^{2,3}](#), [Rumpa Saha⁴](#), [Piyush Gupta¹](#)

Abstract

Objectives: To compare efficacy and safety of intramuscular (IM) ondansetron with oral ondansetron for improving utilization of Oral Rehydration Therapy (ORT) by controlling vomiting in children with acute diarrhea and some dehydration.

Methods: We enrolled children aged 3 months to 12 years presenting with acute diarrhea (duration < 14 days) with some dehydration, and at least two episodes of vomiting within last 6 h in an open-label randomized controlled trial. Participants were randomized to receive single dose (0.2 mg/kg) of IM or oral ondansetron before starting ORT. Primary outcome was failure of ORT (persistence of some dehydration after 4 h of ORT or need for intravenous fluids). Secondary outcomes included need for unscheduled intravenous fluids, amount of Oral Rehydration Salt Solution (ORS) ingested after 4 h, frequency of vomiting episodes, adverse effects, and caregiver satisfaction.

Results: We randomized 60 children (31 IM, 29 oral); 58 (29 per group) were followed-up for all outcomes. There were no significant differences between IM and oral routes in terms of ORT failure (31% vs. 24.1%; RR (95% CI) 1.3 (0.5, 3.0), $P = 0.557$), need for IV fluids during ORT (24.1% vs. 20.7%; $P = 0.753$), mean (SD) ORS ingested (mL) in 4 h [616.2 (429.7) vs. 645.5 (403.5); $P = 0.79$], mean (SD) frequency of vomiting [1.4 (2.0) vs. 2.3 (2.4); $P = 0.107$] or caregiver satisfaction. No adverse events attributable to the intervention were observed.

Conclusion: Intramuscular ondansetron may not offer any advantage over oral use in management of children with acute diarrhea with vomiting and some dehydration.

J Pediatr Gastroenterol Nutr. 2025 Apr;80(4):598-610.

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Identifying risk factors for vomiting during diarrhea: A secondary analysis of a randomized trial of zinc supplementation

[Jeffrey G Edwards¹](#), [Pratibha Dhingra²](#), [Enju Liu³](#), [Usha Dhingra²](#), [Arup Dutta²](#), [Christopher R Sudfeld^{4,5}](#), [Saikat Deb²](#), [Sarah Somji⁶](#), [Said Aboud⁶](#), [Rodrick Kisenge⁶](#), [Sunil Sazawal²](#), [Per Ashorn⁷](#), [Jonathan Simon⁸](#), [Karim P Manji⁶](#), [Christopher P Duggan^{4,5,9}](#)

Abstract

Objectives: Supplemental zinc during acute diarrhea reduces illness duration but also increases vomiting. In a recent trial, we found that children receiving lower daily doses of zinc (5 mg or 10 mg vs. 20 mg) had lower rates of vomiting with comparable stool output and

duration of diarrhea. We performed a secondary analysis to identify sociodemographic and clinical factors associated with vomiting in children with acute diarrhea.

Methods: We performed a secondary data analysis of 4500 children aged 6-59 months with an acute episode of diarrhea (<72 h before enrollment) in a randomized, double-blind controlled trial in India and Tanzania. To identify clinically important risk factors for overall, regimen-related, and regimen-unrelated vomiting, we created log-binomial models with relative risks (RRs) and 95% confidence intervals (CIs).

Results: The trial enrolled 4500 children, of whom 1203 (26.7%) had any vomiting. After adjusting for multiple demographic and clinical characteristics, the presence of dehydration (RR: 1.45, 95% CI: 1.10-1.92), being underweight (RR: 1.22, 95% CI: 1.05-1.41), receipt of the rotavirus vaccine (RR: 1.89, 95% CI: 1.69-2.12), and household wealth above the median (RR: 1.17, 95% CI: 1.07-1.29) were factors associated with an increased risk of vomiting. Rotavirus vaccine receipt was nearly 100% concordant with the study site of Tanzania. Older age and lower zinc dosing were associated with a lower risk of vomiting.

Conclusions: Young, underweight, or dehydrated children are more likely to have concurrent vomiting with zinc supplementation. Identification of these factors may allow providers to better monitor such children, thus reducing the chances of recurrent dehydration or inadequate dietary intake.

Indian Pediatr. 2025 Apr 2.

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Intramuscular Versus Oral Ondansetron for Management of Children with Acute Dehydrating Diarrhea and Vomiting: A Randomized Controlled Trial

[Shubham Satyesh¹](#), [Rajesh Kumar Meena¹](#), [Dheeraj Shah^{2,3}](#), [Rumpa Saha⁴](#), [Piyush Gupta¹](#)

Abstract

Objectives: To compare efficacy and safety of intramuscular (IM) ondansetron with oral ondansetron for improving utilization of Oral Rehydration Therapy (ORT) by controlling vomiting in children with acute diarrhea and some dehydration.

Methods: We enrolled children aged 3 months to 12 years presenting with acute diarrhea (duration < 14 days) with some dehydration, and at least two episodes of vomiting within last 6 h in an open-label randomized controlled trial. Participants were randomized to receive single dose (0.2 mg/kg) of IM or oral ondansetron before starting ORT. Primary outcome was failure of ORT (persistence of some dehydration after 4 h of ORT or need for intravenous fluids). Secondary outcomes included need for unscheduled intravenous fluids, amount of Oral Rehydration Salt Solution (ORS) ingested after 4 h, frequency of vomiting episodes, adverse effects, and caregiver satisfaction.

Results: We randomized 60 children (31 IM, 29 oral); 58 (29 per group) were followed-up for all outcomes. There were no significant differences between IM and oral routes in terms of ORT failure (31% vs. 24.1%; RR (95% CI) 1.3 (0.5, 3.0), $P = 0.557$), need for IV fluids during ORT (24.1% vs. 20.7%; $P = 0.753$), mean (SD) ORS ingested (mL) in 4 h [616.2 (429.7) vs. 645.5 (403.5); $P = 0.79$], mean (SD) frequency of vomiting [1.4 (2.0) vs. 2.3 (2.4); $P = 0.107$] or caregiver satisfaction. No adverse events attributable to the intervention were observed.

Conclusion: Intramuscular ondansetron may not offer any advantage over oral use in management of children with acute diarrhea with vomiting and some dehydration.

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Randomised feasibility study of an intestinal adsorbent in acute diarrhoea in The Gambia

[Paul Rahden^{1,2}](#), [Abdoulie Fatty¹](#), [Momodou Lamin Jobarteh¹](#), [Abdoulwahab Sallah¹](#), [Ebrahim Jaiteh³](#), [Angela Allen⁴](#), [Doreen Umoh⁴](#), [Fanta Bass⁴](#), [Matthew Dodd⁵](#), [Carol Howell⁶](#), [Elena Markaryan⁶](#), [Radovan Hnatic⁷](#), [Stephen Allen^{8,9}](#)

Abstract

Background: Diarrhoea remains a leading cause of death in children. An intestinal adsorbent may reduce diarrhoea duration and severity.

Methods: Randomised controlled feasibility trial with two phases: phase 1 (0-4 hours and double-blind) and phase 2 (up to 5 days and open-label). 50 children aged 6-59 months with acute diarrhoea presenting with no or some dehydration to the emergency paediatric unit and outpatient clinic at Edward Francis Small Teaching Hospital, Banjul, The Gambia were randomised to either standard treatment (oral rehydration fluid and zinc) or standard treatment with polymethylsiloxane polyhydrate for up to 5 days.

Results: Recruitment was completed in 7 months. All but one child completed the study. There were no major protocol deviations although patient-held diaries did not collect reliable information. Time from randomisation to the last watery stool (primary outcome) was shorter in the intervention than control arm (mean difference -19.3 hours, 95% CI -30.9 to -7.8). Stool frequency was lower in the intervention arm on days 2 (95% CI -0.8 to -1.3 to -0.3) and 3 (95% CI -0.8; -1.3 to -0.3). One serious event (death) occurred in the control arm.

Conclusions: A randomised, controlled trial is feasible. Further clinical trials are warranted to confirm the efficacy of polymethylsiloxane polyhydrate in acute diarrhoea and inform management guidelines.

Sci Rep. 2024 Dec 30;14(1):31965.

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Pharmacokinetics of tebipenem pivoxil used in children suffering from shigellosis: a pilot study in Bangladesh

[Sharika Nuzhat¹](#), [Md Ridwan Islam²](#), [Syed Jayedul Bashir²](#), [Subhasish Das²](#), [Rukaeya Amin²](#), [Firdausi Qadri³](#), [Farhana Khanam³](#), [Dilruba Ahmed⁴](#), [Patricia B Pavlinac⁵](#), [Cindy X Zhang⁶](#), [Samuel L M Arnold⁶](#), [Amy Newlands⁷](#), [Mohammad Jobayer Chisti⁴](#), [Tahmeed Ahmed^{4,2,8}](#)

Abstract

With increasing antibiotic resistance in gram-negative bacteria, including those causing Shigellosis, evidence of safety and pharmacokinetics data on new oral antibiotics is crucial. We aimed to investigate the safety and pharmacokinetic properties of an oral carbapenem, tebipenem pivoxil, along with its ability to produce desired results in childhood shigellosis. This randomized pilot clinical trial was conducted at Dhaka Hospital, icddr,b in 2022 between May and September. Thirty suspected shigellosis cases aged 24-59 months were randomized across two treatment groups equally: tebipenem pivoxil and azithromycin.

Pharmacokinetics of tebipenem was assessed among fifteen children who received tebipenem pivoxil using Noncompartmental analysis (NCA). Clinical (absence of fever, abdominal pain/tenderness, diarrhoea, blood in stool, or death before Day-3) and microbiological (absence of *Shigella* on Day-7 culture) success after the antibiotic interventions were also evaluated. Sociodemographic and clinical characteristics were comparable between the randomization arms. Twelve children, each in the azithromycin arm and tebipenem arm, were positive for *Shigella* by culture on enrolment. C_{max} values of 5053.3, 2546.0, and 3759.2 ng/mL were observed for plasma tebipenem on Day-0, 1, and 2 respectively. Clinical success was observed among seven participants in each arm while two in the azithromycin arm and three in the tebipenem arm failed microbiologically. The tolerability and efficaciousness of tebipenem pivoxil appear to be comparable to azithromycin in treating childhood shigellosis in Bangladesh. We recommend a larger clinical trial to determine non-inferiority of tebipenem in regards to the current treatment guidelines.

BMC Health Serv Res. 2024 Sep 6;24(1):1036.

doi: 10.1186/s12913-024-11507-w.

Mobile phone call reminders to improve oral rehydration salt and zinc adherence for acute diarrhea in children: a single-center, randomized controlled trial

[Titilayo Funmilayo Kayode-Alabi¹](#), [Rasheedat Mobolaji Ibraheem²](#), [Kayode Olusegun Alabi³](#), [Aishat Oluwatoyin Bolakale²](#), [Samuel Kolade Ernest²](#)

Abstract

Background: Low-osmolarity oral rehydration salt (ORS) and zinc therapy effectively manage diarrhea in children under five years of age, offering both short- and long-term benefits. Despite this, caregivers' adherence to ORS and zinc is often unsatisfactory due to factors such as forgetfulness, resolution of symptoms, and underestimation of the disease's severity. This study assessed the effect of mobile call reminders on ORS and zinc tablet adherence among children with acute diarrhea in a secondary-level health facility in Kwara State, Nigeria.

Methods: Using an open-label, randomized controlled trial design, this study compared caregiver-child pairs with acute diarrhea aged 6-59 months who received standard instructions (SI) alone (control group) and an intervention group (IG) who received SI plus phone call reminders on days three and seven of zinc sulfate therapy. All participants used a pictorial diary to track loose/watery stools and ORS and zinc tablet treatments for ten days. The primary outcome measures were independent and combined adherence to ORS and zinc therapy. The secondary outcomes were independent and combined adherence scores, defined as the percentage of times the ORS was given post-diarrhea and the percentage of prescribed zinc tablets administered out of ten.

Results: A total of 364/400 mother-child pairs completed the study. The percentage of mothers with full adherence in the intervention group was 82.5% for ORS, 72.1% for zinc, and 58.5% for combined use, compared to 78.8%, 60.8%, and 43.6%, respectively, in the control group. The odds of full adherence to ORS and zinc were 1.6 and 1.7 times higher among intervention mothers [ORS: OR = 1.561, 95% CI = 0.939-2.598, P = 0.085; zinc: OR = 1.671, 95% CI = 1.076-2.593, P = 0.022], and 1.8 times higher for combined use according to WHO

guidelines [OR = 1.818, 95% CI = 1.200-2.754, P = 0.005]. The mean adherence scores for the intervention group were higher than those for the control group by 4.1% (95% CI = 0.60-7.60) for ORS, 7.3% (95% CI = 3.74-10.86) for zinc, and 5.7% (95% CI = 3.23-8.17) for the combined treatment.

Conclusion: Phone reminders can effectively improve consistency of home treatment administered by caregivers for children under five years old.

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Characteristics and outcomes of children 2-23 months of age with prolonged diarrhoea: A secondary analysis of data from the 'Antibiotics for Children with Diarrhea' trial

Irin Parvin¹, Abu Sadat Mohammad Sayeem Bin Shahid¹, Sharika Nuzhat¹, Mst Mahmuda Ackhter¹, Tahmina Alam¹, Md Farhad Kabir¹, Sharmin Khanam¹, Sunil Sazawal², Usha Dhingra², Judd L Walson^{3,4}, Benson O Singa⁵, Karen L Kotloff⁶, Samba O Sow⁷, Naor Bar-Zeev⁸, Queen Dube⁹, Farah Naz Qamar¹⁰, Mohammad Tahir Yousafzai¹⁰, Karim Manji¹¹, Christopher P Duggan¹², Rajiv Bahl¹³, Ayesha De Costa⁹, Jonathon Simon⁹, Per Ashorn^{14,15}, Tahmeed Ahmed¹, Mohammad Jobayer Chisti¹

Abstract

Background: Approximately 12% of all diarrhoeal episodes last for 7-13 days. As such, they are termed prolonged diarrhoea, and are associated with over two-thirds of all diarrhoeal deaths. Due to a lack of robust data, we aimed to evaluate a comparative background characteristics of young children with acute and prolonged diarrhoea, and their outcomes at day 90 follow-up.

Methods: We performed a secondary analysis of data from the Antibiotics for Children with Diarrhea (ABCD) trial. Children aged 2-23 months were enrolled between July 2017 and July 2019 from seven Asian and sub-Saharan African countries. For this analysis, we divide diarrhoea into two categories: acute diarrhoea (duration <7 days) and prolonged diarrhoea (duration ≥7-13 days). We used logistic regression to observe baseline crude and adjusted associations and linear regression to compare post-discharge outcomes.

Results: We analysed data on 8266 children, of whom 756 (9%) had prolonged diarrhoea and 7510 (91%) had acute diarrhoea. Pakistan had the highest proportion of children with prolonged diarrhoea (n/N = 178/1132, 16%), while Tanzania had the lowest (n/N = 12/1200, 1%). From an analysis that adjusted for sex, breastfeeding, nutritional status, clinical presentation, housing, water supply, sanitation, and country, we observed that presentation at a health facility with prolonged diarrhoea was associated with low age (2-12 months) (adjusted odds ratio (aOR) = 1.25; 95% confidence interval (CI) = 1.02, 1.53; P = 0.028), presence of three or more under-five children in the family (aOR = 1.54; 95% CI = 1.26, 1.87; P < 0.001), maternal illiteracy (aOR = 1.45; 95% CI = 1.21, 1.74, P < 0.001), moderate underweight (aOR = 1.25; 95% CI = 1.01, 1.55; P = 0.042) and pathogen (Campylobacter) (aOR = 1.27; 95% CI = 1.12, 1.44; P < 0.001). At day 90 follow-up, children with prolonged diarrhoea had significantly lower weight-for-age z-score compared to children with acute diarrhoea (-1.62, standard deviation (SD) = 1.11 vs -1.52, SD = 1.20; P = 0.032), as well as significantly higher frequency of hospital admission (6.1% vs 4.5%; P = 0.042).

Conclusions: Prolonged diarrhoea was more common in children of younger age, those who were moderately underweight, those with Campylobacter in stool, those with three or more under-five children in a family, and those with illiterate mothers compared to those who had

acute diarrhoea. Children with prolonged diarrhoea more often required hospitalisation during the three-month follow-up period compared to their counterparts.

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Zinc supplementation for acute and persistent watery diarrhoea in children: A systematic review and meta-analysis

[Ayesha Arshad Ali¹](#), [Syeda Kanza Naqvi¹](#), [Zain Hasnain¹](#), [Mustafa Bin Ali Zubairi¹](#), [Ashraf Sharif²](#), [Rehana Abdus Salam³](#), [Sajid Soofi^{4,5}](#), [Shabina Ariff⁵](#), [Yasir Bin Nisar⁶](#), [Jai K Das^{1,7}](#)

Abstract

Background: Zinc is a micronutrient that plays a role in immune system strengthening and regulation of intestinal epithelial cells, and can reduce the duration and severity of diarrhoea. We conducted a systematic review of randomised controlled trials (RCTs) to assess the effectiveness of zinc compared to no zinc for the management of acute and persistent diarrhoea in children.

Methods: We searched PubMed, the Cochrane Library, Scopus, CINAHL, ClinicalTrials.gov, and World Health Organization (WHO) International Clinical Trials Registry Platform from inception until 31 July 2023 for studies published from year 2000 onwards that assessed the use of zinc in the management of acute and persistent diarrhoea in children aged less than 10 years. We conducted the meta-analysis in Cochrane's RevMan software, determined risk of bias in individual studies using the Risk of Bias 2 (RoB 2) tool, and assessed the quality of evidence through the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. This review was commissioned by the WHO for revision of their guidelines for childhood diarrhoea management.

Results: We included 38 RCTs in this systematic review. Our findings suggest that, in children with acute diarrhoea, zinc supplementation resulted in a greater proportion of children who recovered from diarrhoea at last follow-up (risk ratio (RR) = 1.07; 95% confidence interval (CI) = 1.03, 1.1; moderate certainty of evidence) and a reduction in the duration of diarrhoea (mean difference (MD) = -13.27 hours; 95% CI = -17.66, -8.89; moderate certainty of evidence) when compared to placebo. A significant number of children in the zinc group compared to placebo experienced vomiting (RR = 1.46; 95% CI = 1.22, 1.76; moderate certainty of evidence), however, there were few vomiting episodes in low-dose zinc group compared to high-dose (RR = 0.80; 95% CI = 0.72, 0.89; moderate certainty of evidence). In children with persistent diarrhoea, zinc supplementation led to a greater proportion of children who recovered from diarrhoea (RR = 1.75; 95% CI = 1.34, 2.30; low certainty of evidence). The low certainty of evidence ratings were mostly due to high heterogeneity among the studies.

Conclusions: Zinc should continue to be recommended in children under the age of 10 years with acute or persistent diarrhoea, but moderate certainty of evidence concludes that the dose of zinc should be reduced. However, further multi-country randomised clinical trials are required with a direct comparison to assess the appropriate dosage, duration and adverse effects.

Diarrhoea prevention

(also see Hygiene and Environmental health; Water, Sanitation and Hygiene)

Ear disease and hearing loss

Ebola and viral haemorrhagic fever

Endocrine disorders and bone health

Diabetes

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[Marked improvement in HbA1c following introduction of biosimilar insulin to treatment regimen of children and youth with type 1 diabetes in Mali: A randomised controlled trial](#)

[Stéphane Besançon](#)¹, [Aveni Haynes](#)², [Amagara Domon Togo](#)³, [Jessica Lynn Sandy](#)^{2,4,5}, [Jayanthy Maniam](#)², [Asa Traoré Sidibe](#)³, [Sylla Djéneba](#)³, [Carine de Beaufort](#)^{6,7}, [Montserrat Castellsague Perolini](#)⁸, [Giacomo Gastaldi](#)⁹, [David Beran](#)¹⁰, [Cecile Eigenmann](#)², [Graham David Ogle](#)²

Abstract

Aims: Evidence on outcomes of treating type 1 diabetes (T1D) with long-acting basal insulins in low-resourced settings is lacking. This study aimed to evaluate the impact of switching children and youth with T1D in the low-income country of Mali from human insulin via syringe to long-acting biosimilar insulin glargine delivered by reusable pens combined with short-acting insulin via syringe.

Methods: A two-group parallel design randomised trial was conducted enrolling 260 youth aged <25 years, diagnosed with T1D for ≥12 months without prior use of analogue insulin. Youth were randomised 1:1 to either continue receiving current therapy or switch to analogue insulin. The primary outcome was HbA1c, collected at baseline and 3-monthly for 12 months.

Results: Primary outcome data were available for 130 (100%) youth in the intervention group and 128 (98.5%) in the control group. Over the 12-month study period, mean HbA1c decreased from 103 to 65 mmol/mol (11.6%-8.1%) ($p < 0.001$) in the intervention group and from 101 to 93 mmol/mol (11.4% to 10.7%) in the control group ($p < 0.01$), an absolute difference of 30 mmol/mol (95% CI: -37, -24) ($p < 0.001$). The proportion of participants with HbA1c ≥130 mmol/mol (≥14%) decreased from 38.5% to 0% in the intervention group, versus 40.6% to 21.9% in the control group.

Conclusions: Switching to a basal-bolus insulin regimen including biosimilar glargine resulted in marked improvements in HbA1c and diabetic ketoacidosis episodes. With relevant training, resources, and support, use of long-acting analogue insulin for treating T1D in Mali was feasible and acceptable to participants and healthcare professionals.

Indian J Pediatr. 2024 Dec;91(12):1232-1237.

doi: 10.1007/s12098-023-04850-z. Epub 2023 Oct 3.

Carbohydrate Counting vs. Fixed Meal Plan in Indian Children with Type 1 Diabetes Mellitus: A Randomized Controlled Trial

[Rajni Sharma¹](#), [Babita Upadhyay¹](#), [Nitika Lal¹](#), [Rajesh Sagar²](#), [Vandana Jain³](#)

Abstract

Objectives: To study the impact of carbohydrate counting vs. fixed-meal plan on glycemic control, quality of life (QoL) and diabetes-related emotional distress in children with Type 1 diabetes mellitus (T1DM).

Methods: Children aged 6-18 y with T1DM of duration >1 y were eligible for the study if they were on multiple daily injections of insulin and regularly monitoring blood glucose. Those with celiac disease, hypothyroidism, any underlying chronic renal/liver/systemic disease or HbA1c >13% were excluded. Both groups received education on diabetes management and healthy diet. In the intervention arm, parents were taught to quantify carbohydrate content and modify insulin doses according to insulin-carbohydrate ratio. The control arm had dietary prescription according to recommended dietary allowance and food exchange list. Standard validated questionnaires were used to assess the QoL and emotional distress related to diabetes.

Results: One hundred twenty five patients (61 intervention, 64 controls) were enrolled and 91.8% and 84.3%, respectively, completed 6-mo follow-up. There was a reduction in HbA1c in both the groups, but was not statistically significant within or between groups Intervention: 8.9 (1.4) to 8.6 (1.5) vs. control: 9.1 (1.6) to 8.8 (1.9), [95% CI 8.3-9.3 vs. 8.3-9.0, intention to treat (ITT), $p = 0.63$]. There was a significant reduction in diabetes distress in the intervention group; DAWN Problem Areas in Diabetes Questionnaire (PAID) score with a median (interquartile range) of 21 (11-33) vs. control: 27 (20-40), ($p = 0.04$).

Conclusions: Patients in the carbohydrate-counting group demonstrated lower diabetes distress scores and less emotional burnout compared to fixed-meal plan over a 6 mo period though overall glycemic control was comparable between groups.

Indian J Pediatr. 2025 Mar;92(3):235-242.

doi: 10.1007/s12098-023-04844-x. Epub 2023 Oct 21.

Effect of Postmeal Fast-Acting Insulin Aspart Injection on the Frequency of Hypoglycemia among Pre-School Children with Type 1 Diabetes: An Open-Label, Cross-Over, Randomized Control Trial

[Arti Yadav¹](#), [Rakesh Kumar²](#), [Devi Dayal¹](#), [Jaivinder Yadav¹](#), [Smita Pattanaik³](#), [Amol Patil³](#)

Abstract

Objectives: To study the effect of postmeal Fast-acting insulin Aspart (Fiasp®) on the frequency of hypoglycemia compared to premeal injection among preschool children with type 1 diabetes.

Methods: A single-center trial was conducted among 65 pre-school children (6 mo to 6 y) with Type 1 diabetes for at least 6 mo, on multiple daily insulin injections. Children were randomized to receive their meal bolus postmeal or premeal for the first 3 mo, followed by cross-over at 3 mo. The two groups were compared at the end of 6 mo for the change in frequency of hypoglycemia and hyperglycemia, HbA1c, glycemic variability, and parental satisfaction. Ten children (5 in each group) underwent pharmacokinetic studies. The trial was approved by Institutional Ethics Committee and registered with the Controlled Trial Registry of India vide no CTRI/2020/10/028750.

Results: Fifty-four children completed the study, with 27 children in each group. There were no significant differences in the frequency of clinical ($p = 0.921$), severe ($p = 0.167$) or serious ($p = 0.753$) hypoglycemia in the two groups. There were no differences in secondary outcome parameters and pharmacokinetics.

Conclusions: The premeal or postmeal injection of Fiasp® does not affect the frequency of hypoglycemia or other glycemic control parameters among pre-school children with Type 1 diabetes.

Indian J Pediatr. 2025 Mar;92(3):277-283.

doi: 10.1007/s12098-024-05074-5. Epub 2024 Apr 1.

Supplementation of High-Strength Oral Probiotics Improves Immune Regulation and Preserves Beta Cells among Children with New-Onset Type 1 Diabetes Mellitus: A Randomised, Double-Blind Placebo Control Trial

[M N Lokesh¹](#), [Rakesh Kumar²](#), [Neenu Jacob¹](#), [Naresh Sachdeva³](#), [Amit Rawat¹](#), [Jaivinder Yadav⁴](#), [Devi Dayal⁴](#)

Abstract

Objectives: To investigate the mechanism of glycemic control in children with type 1 diabetes (T1D) following high-strength probiotics supplementation by assessing immune-regulatory markers.

Methods: In this single-centre randomised double-blinded placebo-controlled study, children with new-onset T1D on regular insulin therapy were randomised into probiotic or placebo groups with 30 children each. The probiotics group received oral powder of Vivomixx®, and the placebo group received corn starch for six months. The primary outcome parameters included induced T regulatory cells (iTregs) percentage, insulin autoantibodies (IAA), insulinoma associated 2 autoantibodies (IA2), glutamic acid decarboxylase autoantibodies (GAD 65) and plasma interleukin-10 (IL-10) levels. The secondary outcome variables were changes in plasma C-peptide levels and glycemic control parameters.

Results: Twenty-three children in the placebo group and 27 in the probiotic group completed the study. There was a significant increase in the percentage of iTregs (3.40 in the probiotic vs. 2.46 in the placebo group; $p = 0.034$). Median glycated hemoglobin (HbA1c) levels significantly decreased from 68 mmol/mol (8.35%) in the placebo group to 60 mmol/mol (7.55%) in the probiotic group ($p = 0.017$). Median C-peptide levels were significantly higher in probiotics (0.72 ng/ml) vs. placebo group (0.11 ng/ml) ($p = 0.036$). The plasma IL-10 levels significantly increased in the probiotic group after six months of treatment ($p = 0.002$).

Conclusions: The high-strength probiotics improved the immunoregulatory milieu, thereby preserving the beta-cell function and better glycemic control.

BMJ Open Diabetes Res Care. 2025 Apr 7;13(2):e004623.

doi: 10.1136/bmjdr-2024-004623.

0.9% Saline versus Ringer's lactate as initial fluid in children with diabetic ketoacidosis: a double-blind randomized controlled trial

[Ashish Agarwal¹](#), [Muralidharan Jayashree²](#), [Karthi Nallasamy¹](#), [Devi Dayal¹](#), [Savita Verma Atti¹](#)

Abstract

Introduction: Ringer's lactate (RL), a balanced crystalloid by regenerating bicarbonate ion, may lead to early diabetic ketoacidosis (DKA) resolution and reduced hyperchloremia as compared with 0.9% saline (NS).

Research design and methods: This was a double-blind randomized controlled trial conducted in the pediatric emergency and intensive care units of a teaching hospital. Children with type 1 diabetes mellitus (T1DM) aged 9 months to 12 years who presented in DKA were included. Participants were randomized to receive either NS or RL as initial fluid (used for both resuscitation and replacement). The primary outcome was time to resolution of DKA. Secondary outcomes included change in serum chloride and bicarbonate from baseline, total fluid received and incidence of acute kidney injury.

Results: The study was conducted between December 2020 and December 2021, and 67 children were recruited (34 in the NS group and 33 in the RL group). The mean time to DKA resolution was shorter in the RL group compared with the NS group (12.9±7.9 vs 16.8±9 hours). The mean difference and HR for time to DKA resolution in the RL group compared with the NS group were 3.85 hours (95% CI 0.3 to 8) and 1.39 hours (95% CI 1.25 to 1.56), respectively. The rise in chloride from baseline was higher in the NS group as compared with the RL group at 4 and 8 hours (8.7±5.6 vs 3.9±5.1 mmol/L) and (10.8±7.7 vs 4.4±8.3 mmol/L), respectively. On the contrary, the rise in bicarbonate from baseline to 12 hours was significantly higher in the RL group as compared with the NS group (14.7±1.6 vs 12.9±3.1).

Conclusions: The time to resolution of DKA was shorter in RL group as compared with the NS group. Regeneration of bicarbonate from lactate ion in the RL forms a strong physiological basis for this outcome as compared with hyperchloremia induced by NS. This makes RL a favorable option in children with DKA.

Thyroid disease

Bone health

Epigenetics

Clin Epigenetics. 2024 Jul 8;16(1):90.

doi: 10.1186/s13148-024-01693-z.

Effects of improved on-farm crop storage on DNA methylation of mothers and their infants: evidence from a randomized controlled trial in Kenya

[Heike Eichenauer¹](#), [Susanne Fischer¹](#), [Elena Gardini¹](#), [Simon Onsongo²](#), [Ulrike Ehlert³](#)

Abstract

Background: Stress during pregnancy can lead to adverse maternal and infant health outcomes through epigenetic changes in the hypothalamic-pituitary-adrenal axis. Among farmers in low-income countries, one important stressor is food insecurity, which can be reduced using hermetic storage bags. This study aimed to determine, for the first time, whether a hermetic storage bag intervention during pregnancy positively affects maternal and infant DNA methylation of the hypothalamic-pituitary-adrenal axis-related genes FKBP5 and NR3C1. We further analyzed whether anthropometrics, stress, and mental health were associated with DNA methylation.

Methods: This study was part of a larger matched-pair randomized controlled trial focusing on the impact of improved on-farm storage on food security, poverty, and net income of smallholder farming households. A total of N = 149 mothers were recruited by telephone and invited to attend a study appointment at health facilities in Kakamega County, Western Kenya, with their infants in April or May 2021. During the appointment, anthropometric measurements were taken, questionnaires on stress and mental health were administered, and saliva samples were collected. Logistic and multiple linear regression were used to examine the effect of the intervention and related measures on DNA methylation.

Results: Mothers in the intervention group showed higher mean NR3C1 methylation levels than those in the control group, corrected for multiple testing. Maternal postpartum body mass index was positively associated with infant NR3C1 CpG3 DNA methylation. The more stressful life events a mother had experienced in the previous 12 months (including during pregnancy), the lower her FKBP5 CpG3 methylation levels.

Conclusions: Food insecurity and stressful life events during pregnancy seem to exert significant effects on maternal DNA methylation. While these stressors did not appear to impact infant DNA methylation in the present study, maternal postpartum body mass index was significantly related to infant methylation. These findings suggest that while infants may be protected from excessive maternal glucocorticoids by placental barrier activity, maternal metabolic status is still reflected in their epigenetic make-up. Trial registration This study was part of a larger matched-pair randomized controlled trial on the impact of improved on-farm crop storage on welfare, nutrition, and human health.

Brain Behav. 2024 Sep;14(9):e70029.

doi: 10.1002/brb3.70029.

An epigenome-wide study of a needs-based family intervention for offspring of trauma-exposed mothers in Kosovo

[Joanne Ryan¹](#), [Aung Zaw Zaw Phyo¹](#), [Sebahate Pacolli Krasniqi²](#), [Selvi Izeti Carkaxhiu²](#), [Peter Fransquet³](#), [Sara Helene Kaas-Petersen⁴](#), [Dafina Arifaj Limani²](#), [Vjosa Devaja Xhemaili²](#), [Mimoza Salihu²](#), [Qendresa Prapashtica²](#), [Nebahate Zekaj²](#), [Vesa Turjaka²](#), [Shr-Jie Wang^{#4}](#), [Feride Rushiti^{#2}](#), [Line Hjort^{#5 6}](#)

Abstract

Introduction: Maternal stress and trauma during pregnancy have been shown to influence cortisol levels and epigenetic patterns, including DNA methylation, in the offspring. This study aimed to determine whether a tailor-made family intervention could help reduce cortisol levels in children born to traumatized mothers, and to determine whether it effected offspring DNA methylation. The secondary aim was to determine whether the family intervention influenced DNA methylation aging, a marker of biological aging.

Methods: A needs-based family intervention was designed to help address relational difficulties and family functioning, and included a focus on family strengths and problem-solving patterns. Women survivors of sexual violence during the Kosovar war in 1998-1999, and their families (children with or without partners) were randomly assigned to 10 sessions of a family therapy over a 3-5-month period, or to a waitlist control group. Both mothers and children completed assessments prior to and after the intervention phase. Children's blood samples collected at these two time points were used to measure cortisol and epigenome-wide DNA methylation patterns (Illumina EPIC array). Cortisol levels, and genome-wide DNA methylation changes pre-/postintervention were compared between children in the intervention and the waitlist groups. DNA methylation age and accelerated biological aging were calculated.

Results: Sixty-two women-child dyads completed the study, 30 were assigned first to the intervention group, and 32 to the waitlist control group. In adjusted linear regression, the family intervention was associated with a significant decline in cortisol levels compared to the waitlist control ($\beta = -124.72$, 95% confidence interval [CI]: -197.4 to -52.1, $p = .001$). Children in the intervention group, compared to the waitlist control group, showed >1% differential methylation degree at 5819 CpG (5'-C-phosphate-G-3') sites across the genome ($p < .01$), with the largest methylation difference being 21%. However, none of these differences reached genome-wide significant levels. There was no significant difference in DNA methylation aging between the two groups.

Conclusion: We find evidence that a tailored family-based intervention reduced stress levels in the children (based on cortisol levels), and modified DNA methylation levels at a number of sites across the genome. This study provides some preliminary evidence to suggest the potential for tailored interventions to help break the intergenerational transmission of trauma, however, large studies powered to detect associations at genome-wide significant levels are needed.

Epilepsy and acute seizures

Epilepsy

Naunyn Schmiedeberg's Arch Pharmacol. 2024 Jul;397(7):5233-5240.

doi: 10.1007/s00210-024-02954-7. Epub 2024 Jan 24.

[Safety and efficacy of levetiracetam and carbamazepine monotherapy in the management of pediatric focal epilepsy: a randomized clinical trial](#)

[Hadi Montazerlotfelahi](#)¹, [Arsh Haj Mohamad Ebrahim Ketabforoush](#)², [Marzieh Tavakol](#)³, [Mahmoudreza Ashrafi](#)⁴, [Mahdieh Dehghani](#)⁵, [Keihan Mostafavi](#)⁶, [Shayan Mardi](#)⁷, [Sanaz Tajfirooz](#)⁸

Abstract

Due to the limited number of studies in children with focal epilepsy and the importance of choosing the most suitable drug to control seizures in children, the administration of the most effective medication with the most negligible adverse events is vital. This study aimed to evaluate the effectiveness and adverse events of carbamazepine vs. levetiracetam monotherapy in children with focal seizures. A monocentric, randomized, controlled, double-blind, parallel-group clinical trial was designed. This study was approved by the Iranian Registry of Clinical Trials (registration number: IRCT20170216032603N2) on June 19, 2020, and conducted at the neurology department of Imam Ali Hospital, Karaj, Iran, from February 2020 to March 2021. This study assessed 120 patients with recently diagnosed focal seizures aged 2 to 14. Patients were randomly divided into two groups, who received carbamazepine (CBZ) 15 to 20 mg/kg and levetiracetam (LEV) 20 to 40 mg/kg daily, respectively. Patients were evaluated for improvement and complications at weeks 4, 12, and 24. Out of 120 patients included in the study, six patients were excluded due to various complications of CBZ. The mean number of seizures at the end of the fourth, twelfth, and twenty-fourth weeks were 1.09 ± 0.75 , 0.62 ± 0.27 , and 0.39 ± 0.12 in the carbamazepine group and 1.11 ± 0.63 , 0.52 ± 0.21 , and 0.37 ± 0.11 in the LEV group, respectively ($P > 0.05$). Similarly, the number of seizure-free patients was 34, 44, and 48 in the CBZ group compared to 41, 50, and 54 in the LEV group, respectively ($P > 0.05$). On the other hand, the frequency of somnolence, dermatologic complications, and agitation was considerably higher in the CBZ group ($P < 0.05$). Although both medicines were equally effective in seizure control, CBZ was associated with considerably more adverse events and less patient compliance. Physicians should be aware of this difference to prevent unwanted consequences.

Epilepsy Behav. 2024 Sep;158:109939.

doi: 10.1016/j.yebeh.2024.109939. Epub 2024 Jul 12.

Efficacy of oral sodium chloride in reducing the incidence of hyponatremia in children with epilepsy receiving oxcarbazepine monotherapy: A randomized controlled trial (SCHO Trial)

[K C Neha¹](#), [Prateek Kumar Panda¹](#), [Anissa Atif Mirza²](#), [Puneet Dhamija³](#), [Indar Kumar Sharawat⁴](#)

Abstract

Introduction: Hyponatremia is a well-documented adverse effect of oxcarbazepine treatment, but no clinical trial has yet been conducted to explore any intervention for reducing the incidence of hyponatremia.

Materials and methods: This open-label trial evaluated the efficacy of add-on daily oral sodium chloride supplementation of 1-2 g/day for 12 weeks in reducing the incidence of hyponatremia in children receiving oxcarbazepine monotherapy aged 1-18 years. Apart from comparing the incidence of symptomatic and severe hyponatremia, serum and urine sodium levels, serum and urine osmolality, changes in behavior and cognition, and the number of participants with recurrence of seizures and requiring additional antiseizure medication (ASM) were also compared.

Results: A total of 120 children (60 in each group) were enrolled. The serum sodium level at 12 weeks in the intervention group was higher than that of the control group (136.5 ± 2.6 vs 135.4 ± 2.5 mEq/L, $p = 0.01$). The number of patients with hyponatremia was significantly lower in the intervention group (4/60 vs 14/60, $p = 0.01$). However, the incidence of symptomatic and severe hyponatremia (0/60 vs 1/60, $p = 0.67$ for both), changes in social

quotient and child behavior checklist total score (0.6 ± 0.8 vs 0.7 ± 0.5 , $p = 0.41$ and 0.9 ± 1.2 vs 1.1 ± 0.9 , $p = 0.30$ respectively), the number of patients with breakthrough seizures ($9/60$ vs $10/60$, $p = 0.89$), and the number of patients requiring additional ASMs ($8/60$ vs $10/60$, $p = 0.79$) were comparable in both groups.

Conclusions: Daily oral sodium chloride supplementation is safe and efficacious in reducing the incidence of hyponatremia in children with epilepsy receiving oxcarbazepine monotherapy. However, sodium chloride supplementation does not significantly reduce more clinically meaningful outcome measures like symptomatic and severe hyponatremia.

Epilepsia Open. 2024 Nov 8.

doi: 10.1002/epi4.13086. Online ahead of print.

First-choice hormonal therapies for children with infantile epileptic spasms syndrome in South Asia: A network meta-analysis of randomized controlled trials

Nagita Devi^{1,2}, Priyanka Madaan³, Nidhun Kandoth¹, Parth Lal⁴, Jitendra Kumar Sahu⁴, Dipika Bansal¹

Abstract

Considering the peculiar challenges with infantile epileptic spasms syndrome (IESS) in South Asia and a wide variation in the usage of hormonal therapies, we compared the efficacy and safety of various hormonal therapies for children with IESS in South Asia. We searched PubMed, Embase, Scopus, and Web of Science databases from the inception until April 2024. We included only randomized clinical trials (RCTs) evaluating the efficacy and safety of hormonal therapies for IESS in the South Asian region. Complete cessation of epileptic spasms (ES), electro-clinical response, and time taken to be spasm-free at 2 or 6 weeks of therapy were efficacy outcomes, while the occurrence of adverse events was the safety outcome. Effect estimates were reported as odds ratio (OR) or mean difference (MD) with 95% confidence intervals (CI) and Cochrane risk of bias 2.0 (ROB 2.0) used for quality assessment of each study. The surface under the cumulative ranking curve (SUCRA) was used to rank the different therapies and reported as a p-score ranging from 0 to 1. Of 747 citations, nine RCTs comprising 566 children with IESS were included. After 2-week treatment, dexamethasone (OR: 6.72; 95% CI: 1.47, 30.72), adrenocorticotrophic hormone therapy (ACTH) high dose (HD) (OR: 5.30; 95% CI: 1.05, 26.91), and prednisolone HD (OR: 2.41; 95% CI: 1.07, 5.46) had shown significantly greater efficacy for cessation of ES compared with ACTH low dose (LD). Similarly, for electroclinical response, dexamethasone (OR: 9.63; 95% CI: 1.99, 46.70) and prednisolone HD (OR: 3.46; 95% CI: 1.38, 8.68) had greater efficacy compared with ACTH LD. Safety outcomes revealed that hypertension was significantly less common with ACTH LD and prednisolone HD as compared with ACTH HD. This study provides quality evidence on preferred first-choice hormonal therapy for managing IESS in South Asia. ACTH HD, dexamethasone, and prednisolone HD are the most effective hormonal therapy options with dose-dependent therapeutic efficacy. PLAIN LANGUAGE SUMMARY: This study provides insights into the selection of first-line hormonal therapies among the various treatments for managing infantile epileptic spasms syndrome (IESS) in South Asia. The study findings suggested that the effectiveness of these therapies is dose-dependent, with high doses of ACTH, dexamethasone, and prednisolone being the most effective for achieving cessation of epileptic spasms.

Acute seizures and status epilepticus

Pediatr Neurol. 2024 Sep;158:135-143.

doi: 10.1016/j.pediatrneurol.2024.06.014. Epub 2024 Jul 2.

[Intranasal Versus Buccal Versus Intramuscular Midazolam for the Home and Emergency Treatment of Acute Seizures in Pediatric Patients: A Randomized Controlled Trial](#)

[Maha Z Mohammed¹](#), [Iman Elagouza²](#), [Maha El Gaafary³](#), [Rana El-Garhy⁴](#), [Omnia El-Rashidy²](#)

Abstract

Background: Benzodiazepines are the recommended first-line treatment of acute seizures. We wished to compare the efficacy, side effects, and satisfaction after midazolam administration by the buccal, intranasal, or intramuscular route in the treatment of acute seizures in children at homes and in emergency room (ER).

Methods: A prospective, randomized, controlled trial was performed in children aged one month to 17 years with acute seizures lasting longer than five minutes. The primary end point was seizure cessation within 10 minutes of drug administration and no seizure recurrence within 30 minutes.

Results: In the home group, 67 patients received midazolam via buccal route, 60 via intranasal route, and 69 via intramuscular route, whereas in the ER group, 37 patients received buccal, 34 received intranasal, and 34 received intramuscular midazolam. The primary end point was achieved in 94.2% and 85.3% after intramuscular midazolam in the home and ER groups, respectively. The intranasal midazolam was successful in stopping seizures in 93.3% in the home group and 88.2% in the ER group. The buccal route was effective in 91% in the home group and 78.4% in the ER group. There were no significant differences in efficacy between all groups ($P = 0.763$ and $P = 0.509$) among the home and ER groups, respectively. There were no significant cardiorespiratory events in all groups.

Conclusions: Intramuscular, intranasal, and buccal doses of midazolam resolved most seizures in prehospital and emergency settings. Our results indicate that there is no statistically significant difference detected between different routes of midazolam. Intranasal route showed the highest satisfaction rate among caregivers.

Epilepsy Res. 2024 Aug;204:107395.

doi: 10.1016/j.epilepsyres.2024.107395. Epub 2024 Jun 13.

[Efficacy and tolerability of classical and polyunsaturated fatty acids ketogenic diet in controlling paediatric refractory epilepsy - A randomized study](#)

[Subhasree Ray¹](#), [Janak Nathan²](#), [Meena Godhia³](#)

Abstract

Objectives: To measure and compare the efficacy and tolerability of a classical ketogenic diet (CKD) and a polyunsaturated fatty acids ketogenic diet (PUFAKD) in managing childhood refractory epilepsy. Efficacy was assessed by measuring the change in seizure frequency at 3, 6, 9, and 12 months within and between groups. The percentage reduction in seizures at <50 %, 50-90 %, >90 %, and 100 % was also measured. Tolerability was assessed and compared by recording adverse events - vomiting, nausea, lethargy, and constipation.

Methods: 52 children, aged 2-10 years, were randomized, 25 in the CKD group and 27 in the PUFAKD group. Fat: carbohydrate + protein ratio of 2.2:1-4:1 was maintained in both diets; the PUFAKD group only used unsaturated fats with an omega 3: omega 6 ratio of 1:2.8. Ketone levels were measured using keto-dipsticks, with 4+ and 4++ (80-160 mg/dL) being the most optimal values.

Results: A significant decrease ($p=0.001$) in seizures was observed ($n=52$), with no significant difference ($p=0.537$) between the two groups. The mean seizure reduction was 71.1 %, with no significant difference ($p=0.488$) in both groups. The mean compliance rate was 78.3 % ($n=52$). A statistically significant linear trend existed between a higher compliance rate and a greater reduction in seizures ($p = 0.042$, $Z=4.039$) among all children ($n=52$). Nausea ($p=0.033$) and vomiting ($p=0.014$) occurred more in PUFAKD than in CKD.

Conclusion: No significant difference was seen in seizure reduction between the two groups. Compliance correlates with a greater seizure reduction. Despite similar seizure reduction rates, the novel PUFAKD exhibited poorer compliance and more pronounced adverse effects compared to CKD. CKD remained a superior choice over the novel PUFAKD in the management of paediatric refractory epilepsy. More controlled trials with varying PUFA compositions are recommended for long-term evaluations.

J Family Med Prim Care. 2024 Aug;13(8):3368-3373.

doi: 10.4103/jfmpc.jfmpc_1747_23. Epub 2024 Jul 26.

Intravenous levetiracetam versus intravenous phenytoin as second Line treatment in pediatric convulsive status epilepticus- open label randomized controlled trial

Mamum Kartek¹, Abinaya Kannan², Varun Anand³, Manas R Sahoo²

Abstract

Background: Benzodiazepines (BZDs) are recommended as the initial therapy of choice in status epilepticus (SE). The age-old second-line treatment for BZD refractory convulsive SE is intravenous phenytoin (PHT) based predominantly on nonrandomized clinical trial data. We did this study to compare the efficacy and safety of intravenous levetiracetam (LEV) and PHT as second-line antiseizure medication (ASM) for children with SE.

Methodology: A prospective, randomized controlled, open-label study was conducted in children 3 months to 15 years of age with SE in Pediatric Emergency. A total of 41 children were randomly allocated to either group 1 (Levetiracetam) or group 2 (Phenytoin) on the basis of computer-generated randomization. Children who were already on antiseizure medications, either LEV or PHT, or receiving these drugs outside for SE were excluded. Data analysis was done by SPSS V25.

Results: The most common age group presenting with SE was 12 months to 5 years. Clinical cessation of seizure 5 minutes after the completion of drugs was 85% (17/20) in Levetiracetam group and 90.5% (19/21) in Phenytoin group. Recurrence of seizure within 24 hours was noted in 35% (7/20) in Levetiracetam group and 38.1% (8/21) in Phenytoin group. There was no statistically significant difference noted in both the groups in terms of seizure cessation, adverse events, and recurrence.

Conclusion: The efficacy and safety of LEV were found to be comparable to those of PHT in controlling seizure as second-line ASM in SE.

Economics, equity and poverty alleviation

Health Policy Plan. 2024 Nov 14;39(10):1007-1021.

doi: 10.1093/heapol/czae079.

[The impact of digital interventions on health insurance coverage for reproductive, maternal, newborn and child health services utilization in Kakamega, Kenya: a cluster randomized controlled trial](#)

[Amanuel Abajobir¹](#), [Richard de Groot²](#), [Caroline Wainaina¹](#), [Menno Pradhan^{2,3,4}](#), [Wendy Janssens^{2,3}](#), [Estelle M Sidze¹](#)

Abstract

The National Hospital Insurance Fund (NHIF) of Kenya was upgraded to improve access to healthcare for impoverished households, expand universal health coverage, and boost the uptake of essential reproductive, maternal, newborn and child health (RMNCH) services. However, premiums may be unaffordable for the poorest households. The Innovative Partnership for Universal Sustainable Healthcare (i-PUSH) programme targets low-income women and their households to improve their access to and utilization of quality healthcare, including RMNCH services, by providing subsidized, mobile phone-based NHIF coverage in combination with enhanced, digital training of community health volunteers and upgrading of health facilities. This study evaluated whether expanded NHIF coverage increased the accessibility and utilization of quality basic RMNCH services in areas where i-PUSH was implemented using a longitudinal cluster randomized controlled trial in Kakamega, Kenya. A total of 24 pair-matched villages were randomly assigned either to the treatment or the control group. Within each village, 10 eligible households (i.e. with a woman aged 15-49 years who was either pregnant or with a child <4 years old) were randomly selected. The study applied a difference-in-difference methodology based on a pooled cross-sectional analysis of baseline, midline and endline data, with robustness checks based on balanced panels and Analysis of Covariance methods. The analysis sample included 346 women, of whom 248 had had a live birth in the 3 years prior to any of the surveys, and 424 children aged 0-59 months. Improved NHIF coverage did not have a statistically significant impact on any of the RMNCH outcome indicators at midline nor endline. Uptake of RMNCH services, however, improved substantially in both control and treatment areas at endline compared to baseline. For instance, significant increases were observed in the number of antenatal care visits from baseline to midline (mean = 2.62-2.92, $P < 0.01$) and delivery with a skilled birth attendant from baseline to midline (mean = 0.91-0.97, $P < 0.01$). Expanded NHIF coverage, providing enhanced access to RMNCH services of unlimited duration at both public and private facilities, did not result in an increased uptake of care, in a context where access to basic public RMNCH services was already widespread. However, the positive overall trend in RMNCH utilization indicators, in a period of constrained access due to the COVID-19 pandemic, suggests that the other components of the i-PUSH programme may have been beneficial. Further research is needed to better understand how the provision of insurance, enhanced community health volunteer training and improved healthcare quality interact to ensure pregnant women and young children can make full use of the continuum of care.

Environmental health

Water, sanitation and hygiene

BMC Med. 2024 Sep 2;22(1):348.

doi: 10.1186/s12916-024-03558-x.

[Impact of a school-based water and hygiene intervention on child health and school attendance in Addis Ababa, Ethiopia: a cluster-randomised controlled trial](#)

[Sarah Bick¹](#), [Alem Ezezew²](#), [Charles Opondo³](#), [Baptiste Leurent⁴](#), [Wossen Argaw⁵](#), [Erin C Hunter^{6,7,8}](#), [Oliver Cumming¹](#), [Elizabeth Allen³](#), [Robert Dreibelbis⁹](#)

Abstract

Background: School-based water, sanitation and hygiene (WASH) may improve the health and attendance of schoolchildren, particularly post-menarcheal girls, but existing evidence is mixed. We examined the impact of an urban school-based WASH programme (Project WISE) on child health and attendance.

Methods: The WISE cluster-randomised trial, conducted in 60 public primary schools in Addis Ababa, Ethiopia over one academic year, enrolled 2-4 randomly selected classes per school (~ 100 pupils) from grades 2 to 8 (aged 7-16) in an 'open cohort'. Schools were assigned 1:1 by stratified randomisation to receive the intervention during the 2021/2022 or the 2022/2023 academic year (waitlist control). The intervention included improvements to drinking water storage, filtration and access, handwashing stations and behaviour change promotion. Planned sanitation improvements were not realised. At four unannounced classroom visits post-intervention (March-June 2022), enumerators recorded primary outcomes of roll-call absence, and pupil-reported respiratory illness and diarrhoea in the past 7 days among pupils present. Analysis was by intention-to-treat.

Results: Of 83 eligible schools, 60 were randomly selected and assigned. In total, 6229 eligible pupils were enrolled (median per school 101.5; IQR 94-112), 5987 enrolled at study initiation (23rd November-22nd December 2021) and the remaining 242 during follow-up. Data were available on roll-call absence for 6166 pupils (99.0%), and pupil-reported illness for 6145 pupils (98.6%). We observed a 16% relative reduction in odds of pupil-reported respiratory illness in the past 7 days during follow-up in intervention vs. control schools (aOR 0.84; 95% CI 0.71-1.00; $p = 0.046$). There was no evidence of effect on pupil-reported diarrhoea in the past 7 days (aOR 1.15; 95% CI 0.84-1.59; $p = 0.39$) nor roll-call absence (aOR 1.07; 95% CI 0.83-1.38; $p = 0.59$). There was a small increase in menstrual care self-efficacy (aMD 3.32 on 0-100 scale; 95% CI 0.05-6.59), and no evidence of effects on other secondary outcomes.

Conclusions: This large-scale intervention to improve school WASH conditions city-wide had a borderline impact on pupil-reported respiratory illness but no effect on diarrhoeal disease nor pupil absence. Future research should establish relationships between WASH-related illness, absence and other educational outcomes.

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Effects of a community-driven water, sanitation, and hygiene intervention on diarrhea, child growth, and local institutions: A cluster-randomized controlled trial in rural Democratic Republic of Congo

[John P Quattrochi¹](#), [Kevin Croke²](#), [Caleb Dohou³](#), [Luca Stanus Ghib⁴](#), [Yannick Lokaya³](#), [Aidan Coville⁴](#), [Eric Mvukiyehe⁵](#)

Abstract

Background: Diarrhea and growth faltering in early childhood reduce survival and impair neurodevelopment. We assessed whether a national program combining (i) funds for latrine and water upgrades; (ii) institutional strengthening; and (iii) behavior change campaigns reduced diarrhea and stunting, and strengthened local institutions.

Methods and findings: We collaborated with program implementers to conduct a cluster-randomized controlled trial in four provinces of the Democratic Republic of Congo (DRC). Three hundred thirty-two rural villages were grouped into 121 clusters to minimize geographic spillovers. Between 15 March and 30 June 2018, we randomly assigned, after stratifying by province and cluster size, 50 intervention and 71 control clusters. Masking of participants and interviewers was not possible. Primary outcomes were length-for-age Z-score among children under 5 years of age, caregiver-reported diarrhea in last 7 days among children under 5 years of age, and an index of community WASH institutions. The primary analysis was on an intention-to-treat basis, using a binary variable indicating whether the participant was in an intervention or control cluster. Three thousand two hundred eighty-three households were interviewed between November 2022 and April 2023, median 3.6 years post-intervention. The intervention had no effect on diarrhea (adjusted mean difference -0.01 [95% -0.05 to 0.03]). Diarrhea prevalence was high overall, at 38% in the treatment group and 42% in the control group. The intervention had no effect on length-for-age Z-scores in children (adjusted mean difference -0.01 [95% CI -0.15 to 0.12]). In the control group, the mean length-for-age Z-score was -2.18 (1.60 SD). Villages in the intervention group had a 0.40 higher score on the WASH institutions index (95% CI 0.16-0.65). The percentage of villages in the intervention group with an active water, sanitation, and hygiene (or just water) committee was 21 pp higher than the control group. Households in the intervention group were 24 pp (95% CI 12-36) more likely to report using an improved water source, 18 pp (95% CI 10-25) more likely to report using an improved sanitation facility, and reported more positive perceptions of water governance (adjusted difference 0.19 SD [95% CI 0.04-0.34]). The trial had several limitations, including incomplete (86%) adherence in the implementation group, the absence of baseline measures, and the reliance on self-reported outcomes for some measures.

Conclusions: The DRC's national rural WASH program increased access to improved water and sanitation infrastructure, and created new WASH institutions, all of which persisted for at least 3.6 years. However, these effects were not sufficient to reduce diarrhea or growth faltering.

PLoS Negl Trop Dis. 2024 Jul 3;18(7):e0012265.

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Improved water supply infrastructure to reduce acute diarrhoeal diseases and cholera in Uvira, Democratic Republic of the Congo: Results and lessons learned from a pragmatic trial

[Karin Gallandat¹](#), [Amy Macdougall²](#), [Aur lie Jeandron¹](#), [Jaime Mufitini Saidi³](#), [Baron Bashige Rumedeka³](#), [Espoir Bwenge Malembaka^{4,5}](#), [Andrew S Azman^{4,6,7}](#), [Didier Bompangue⁸](#), [Simon Cousens⁹](#), [Elizabeth Allen²](#), [Oliver Cumming¹](#)

Abstract

Background: Safely managed drinking water is critical to prevent diarrhoeal diseases, including cholera, but evidence on the effectiveness of piped water supply in reducing these diseases in low-income and complex emergency settings remains scarce.

Methods: We conducted a trial of water supply infrastructure improvements in Uvira (DRC). Our primary objective was to estimate the relationship between a composite index of water service quality and the monthly number of suspected cholera cases admitted to treatment facilities and, as a secondary analysis, the number of cases confirmed by rapid diagnostic tests. Other exposures included the quantity of supplied water and service continuity. We used Poisson generalised linear models with generalised estimating equations to estimate incidence rate ratios.

Findings: Associations between suspected cholera incidence and water service quality (RR 0.86, 95% CI 0.73-1.01), quantity (RR 0.80, 95% CI 0.62-1.02) and continuity (RR 0.81, 95% CI 0.77-0.86) were estimated. The magnitudes of the associations were similar between confirmed cholera incidence and water service quality (RR 0.84, 95% CI 0.73-0.97), quantity (RR 0.76, 95% CI 0.61-0.94) and continuity (RR 0.75, 95% CI 0.69-0.81). These results suggest that an additional 5 L/user/day or 1.2 hour per day of water production could reduce confirmed cholera by 24% (95% CI 6-39%) and 25% (95% CI 19-31%), respectively.

Interpretation: Ensuring a sufficient and continuous piped water supply may substantially reduce the burden of endemic cholera and diarrhoeal diseases but evaluating this rigorously is challenging. Pragmatic strategies are needed for public health research on complex interventions in protracted emergency settings.

J Epidemiol Glob Health. 2024 Sep;14(3):765-778.

doi: 10.1007/s44197-024-00210-y. Epub 2024 Mar 20.

Improved Child Feces Management Mediates Reductions in Childhood Diarrhea from an On-Site Sanitation Intervention: Causal Mediation Analysis of a Cluster-Randomized Trial in Rural Bangladesh

[Jesse D Contreras¹](#), [Mahfuza Islam²](#), [Andrew Mertens³](#), [Amy J Pickering^{4,5}](#), [Benjamin F Arnold⁶](#), [Jade Benjamin-Chung^{5,7}](#), [Alan E Hubbard³](#), [Mahbubur Rahman⁸](#), [Leanne Unicomb⁸](#), [Stephen P Luby⁹](#), [John M Colford Jr³](#), [Ayse Ercumen^{10,11}](#)

Abstract

Background: The WASH benefits Bangladesh trial multi-component sanitation intervention reduced diarrheal disease among children < 5 years. Intervention components included latrine upgrades, child feces management tools, and behavioral promotion. It remains unclear which components most impacted diarrhea.

Methods: We conducted mediation analysis within a subset of households (n = 720) from the sanitation and control arms. Potential mediators were categorized into indicators of latrine quality, latrine use practices, and feces management practices. We estimated average causal mediation effects (ACME) as prevalence differences (PD), defined as the intervention's effect on diarrhea through its effect on the mediator.

Results: The intervention improved all indicators compared to controls. We found significant mediation through multiple latrine use and feces management practice indicators. The

strongest mediators during monsoon seasons were reduced open defecation among children aged < 3 and 3-8 years, and increased disposal of child feces into latrines. The strongest mediators during dry seasons were access to a flush/pour-flush latrine, reduced open defecation among children aged 3-8 years, and increased disposal of child feces into latrines. Individual mediation effects were small (PD = 0.5-2 percentage points) compared to the overall intervention effect but collectively describe significant mediation pathways.

Discussion: The effect of the WASH Benefits Bangladesh sanitation intervention on diarrheal disease was mediated through improved child feces management and reduced child open defecation. Although the intervention significantly improved latrine quality, relatively high latrine quality at baseline may have limited benefits from additional improvements. Targeting safe child feces management may increase the health benefits of rural sanitation interventions.

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Addressing information and credit barriers to making India open defecation free and improving child health: Evidence from a cluster randomized trial in rural India

Payal Seth¹, Prabhu Pingali¹

Abstract

Background: Open defecation (OD) remains a significant public health challenge in India, contributing to adverse child health outcomes. Eliminating OD and improving child health necessitates both universal access and adoption of toilets. Despite the success of removing credit constraints and enhancing access to subsidized toilets through national sanitation campaigns, the adoption of these toilets is still lagging in India. This is because households might also be lacking information about the benefits of using toilets (information constraint).

Methods: In this paper, we test for the joint efficacy of the removal of information and credit constraints versus solely addressing the credit constraint at eliminating OD, based on a cluster randomized control trial in rural India. We implemented two interventions: a universal community-led behavior change campaign along with subsidized construction of individual household toilets for every household that opted for subsidy (cluster A) and only subsidized construction of individual household toilet construction for every household that opted for the subsidy (cluster B). No behavior change was provided in cluster B. The control group did not receive any intervention.

Results: We find that the removal of information and credit constraints at a near-universal level in cluster A resulted in improved toilet access and adoption, eliminating OD at the community level, with a significant gain in child weight-for-age z-scores (WAZ scores). There was an increase in the percentage of households that owned individual household toilets from 2% to 98% and a decline in female respondents practicing OD from 98% to 4% in cluster A. In cluster B, ownership of individual household toilets improved by 78 percentage points (from 6% to 84%), but OD decreased by only 45 percentage points (from 95% to 50%) for the respondents. The control group saw no significant changes. For children under five, there was a statistically significant increase in WAZ scores by 0.68-0.69 standard deviations in cluster A, while cluster B showed insignificant changes when compared to the control group.

Conclusions: The study implies that supplementing universal financial support with community-level information intervention enhances sustainable adoption of improved

sanitation facilities, aiding India's progress towards an open defecation-free nation and improving child health outcomes.

Parasit Vectors. 2025 Mar 14;18(1):106.

doi: 10.1186/s13071-025-06722-1.

Effect of a novel house (Star home) and toilet design on domestic fly densities in rural Tanzania

[Arnold S Mmbando](#)^{1,2}, [Amos J Ngonzi](#)¹, [Salum Mshamu](#)^{3,4}, [John Bradley](#)⁵, [Thomas Chevalier Bøjstrup](#)⁶, [Halfan S Ngowo](#)¹, [Jakob Knudsen](#)⁶, [Lorenz von Seidlein](#)⁷, [Fredros O Okumu](#)^{1,8,9}, [Steve W Lindsay](#)¹⁰

Abstract

Background: Diarrhoeal disease is the third leading cause of death in children under 5 years old with domestic flies acting as important mechanical vectors of diarrhoeal pathogens. To assess the effectiveness of a novel house design, "Star home", and improved toilets in reducing the abundance of domestic flies, potential carriers of diarrhoeal pathogens, a randomized controlled trial was carried out in rural Tanzania.

Methods: Domestic fly populations were monitored in 28 randomly selected Star homes and 28 traditional thatched roofs and mud-walled houses over 2 years from January 2022 to December 2023. Flies were sampled in kitchens and toilets using baited-fly traps from 07.00 h to 17.30 h every 7 weeks. To assess the production of flies from toilets, traps were placed over drop holes to collect emerging flies. Duration of external door openings to the kitchens was recorded with data loggers.

Findings: Of the 1527 flies collected, 76% were *Chrysomya putoria*, 16% *Musca domestica* and 8% *Sarcophaga* spp. In kitchen collections, there were 46% fewer *C. putoria* flies [adjusted mean rate ratio (RR) = 0.54] and 69% fewer *Sarcophaga* spp. (RR = 0.31) in Star homes compared to traditional houses. There was no difference in the abundance of *M. domestica* in the two study groups. In toilets, there was 49% fewer *C. putoria* (RR = 0.51), but no difference was observed for other domestic fly species. No flies emerged from Star home toilets compared with a mean of 4.2 flies/trap/day in traditional toilets. During the day, the external doors of Star homes were open for an average of 13.0 min/h less than in traditional houses.

Conclusions: Star homes reduced the abundance of domestic flies, apart from houseflies, in the kitchen and there were fewer *C. putoria*, a putative vector of diarrhoeal diseases, in Star home toilets compared to traditional houses. Changing the design of buildings can contribute to a decline in domestic flies and may lead to a reduction in diarrhoeal diseases.

Nat Commun. 2025 Jan 9;16(1):556.

doi: 10.1038/s41467-024-55801-x.

Water, sanitation, handwashing, and nutritional interventions can reduce child antibiotic use: evidence from Bangladesh and Kenya

[Ayse Ercumen](#)¹, [Andrew N Mertens](#)², [Zachary Butzin-Dozier](#)², [Da Kyung Jung](#)², [Shahjahan Ali](#)³, [Beryl S Achando](#)⁴, [Gouthami Rao](#)⁵, [Caitlin Hemlock](#)², [Amy J Pickering](#)^{6,7}, [Christine P Stewart](#)⁸, [Sophia T Tan](#)⁹, [Jessica A Grembi](#)⁹, [Jade Benjamin-Chung](#)^{7,10}, [Marlene Wolfe](#)¹¹, [Gene G Ho](#)², [Md Ziaur Rahman](#)³, [Charles D Arnold](#)⁸, [Holly N Dentz](#)⁸, [Sammy M Njenga](#)¹², [Theodora](#)

[Meerkerk⁴](#), [Belinda Chen²](#), [Maya Nadimpalli¹¹](#), [Mohammad Aminul Islam¹³](#), [Alan E Hubbard²](#), [Clair Null¹⁴](#), [Leanne Unicomb³](#), [Mahbubur Rahman^{3,15}](#), [John M Colford Jr²](#), [Stephen P Luby⁹](#), [Benjamin F Arnold¹⁶](#), [Audrie Lin¹⁷](#)

Abstract

Antibiotics can trigger antimicrobial resistance and microbiome alterations. Reducing pathogen exposure and undernutrition can reduce infections and antibiotic use. We assess effects of water, sanitation, handwashing (WSH) and nutrition interventions on caregiver-reported antibiotic use in Bangladesh and Kenya, longitudinally measured at three timepoints among birth cohorts (ages 3-28 months) in a cluster-randomized trial. Over 50% of children used antibiotics at least once in the 90 days preceding data collection. In Bangladesh, the prevalence of antibiotic use was 10-14% lower in groups receiving WSH (prevalence ratio [PR] = 0.90 (0.82-0.99)), nutrition (PR = 0.86 (0.78-0.94)), and nutrition+WSH (PR = 0.86 (0.79-0.93)) interventions. The prevalence of using antibiotics multiple times was 26-35% lower in intervention arms. Reductions were largest when the birth cohort was younger. In Kenya, interventions did not affect antibiotic use. In this work, we show that improving WSH and nutrition can reduce antibiotic use. Studies should assess whether such reductions translate to reduced antimicrobial resistance.

EClinicalMedicine. 2025 Mar 6;82:103147.

doi: 10.1016/j.eclim.2025.103147. eCollection 2025 Apr.

[Pathways through which water, sanitation, hygiene, and nutrition interventions reduce antibiotic use in young children: a mediation analysis of a cohort nested within a cluster-randomized trial](#)

[Anna T Nguyen¹](#), [Gabby Barratt Heitmann¹](#), [Andrew Mertens²](#), [Sania Ashraf³](#), [Md Ziaur Rahman⁴](#), [Shahjahan Ali⁵](#), [Mahbub Rahman⁵](#), [Benjamin F Arnold⁶](#), [Jessica A Grembi⁷](#), [Audrie Lin⁴](#), [Ayse Ercumen⁸](#), [Jade Benjamin-Chung^{1,9}](#)

Abstract

Background: Low-cost, household-level water, sanitation, and hygiene (WASH) and nutrition interventions can reduce pediatric antibiotic use, but the mechanism through which interventions reduce antibiotic use has not been investigated.

Methods: We conducted a causal mediation analysis using data collected between September 2013 and October 2015 from a cohort nested within the WASH Benefits Bangladesh cluster-randomized trial ([NCT01590095](#)). Among a subsample of children within the WASH, nutrition, nutrition + WASH, and control arms (N = 1409 children; 267 clusters), we recorded caregiver-reported antibiotic use at ages 14 and 28 months and collected stool at age 14 months. Our primary outcome was any caregiver-reported antibiotic use by index children within the past 30 or 90 days measured at age 14 and 28 months. Mediators included caregiver-reported child diarrhea, acute respiratory infection (ARI), and fever; and enteric pathogen carriage in stool measured by qPCR. Both intervention-mediator and mediator-outcome models were controlled for mediator-outcome confounders.

Findings: The receipt of any WASH or nutrition intervention reduced caregiver-reported antibiotic use through all pathways in the past month by 5.5 percentage points (95% CI 1.2, 9.9), from 49.5% (95% CI 45.9%, 53.0%) in the control group to 45.0% (95% CI 42.7%, 47.2%) in the pooled intervention group. When separating this effect into different pathways, we found that interventions reduced antibiotic use by 0.6 percentage points (95% CI 0.1, 1.3)

through reduced diarrhea, 0.7 percentage points (95% CI 0.1, 1.5) through reduced ARI with fever, and 1.5 percentage points (95% CI 0.4, 3.0) through reduced prevalence of enteric viruses. Interventions reduced antibiotic use through any of these measured mediators by 2.1 percentage points (95% CI -0.3, 4.5).

Interpretation: WASH and nutrition interventions reduced pediatric antibiotic use through the prevention of enteric and respiratory infections in a rural, low-income population. Given that many of these infections are caused by viruses or parasites, WASH and nutrition interventions may help reduce inappropriate antibiotic use in similar settings.

Pollutants

Indoor air pollution

Environ Int. 2024 Dec 24;195:109211.

doi: 10.1016/j.envint.2024.109211. Online ahead of print.

Effects of a liquefied petroleum gas stove and fuel intervention on head circumference and length at birth: A multi-country household air pollution intervention network (HAPIN) trial

[Hina Raheel¹](#), [Sheela Sinharoy²](#), [Anaité Diaz-Artiga³](#), [Sarada S Garg⁴](#), [Ajay Pillarisetti⁵](#), [Kalpana Balakrishnan⁴](#), [Marilu Chiang⁶](#), [Amy Lovvorn⁷](#), [Miles Kirby⁸](#), [Usha Ramakrishnan²](#), [Shirin Jabbarzadeh⁹](#), [Alexie Mukeshimana¹⁰](#), [Michael Johnson¹¹](#), [John P McCracken¹²](#), [Luke P Naeher¹²](#), [Ghislaine Rosa¹³](#), [Jiantong Wang⁹](#), [Joshua Rosenthal¹⁴](#), [William Checkley¹⁵](#), [Thomas F Clasen⁷](#), [Jennifer L Peel¹⁶](#), [Lisa M Thompson¹⁷](#); [Household Air Pollution Intervention Network \(HAPIN\) investigators](#)

Abstract

Background: Air pollution may impair child growth and cognitive development, with potential markers including birth length and head circumference.

Methods: The Household Air Pollution Intervention Network (HAPIN) trial was an open label multi-country-randomized controlled trial, with 3200 pregnant women aged 18-34 years (9-19 weeks of gestation) randomly assigned in a 1:1 ratio to receive liquefied petroleum gas (LPG) stove intervention compared to women continuing to cook with solid fuels for 18 months. Particulate matter $\leq 2.5 \mu\text{m}$ (PM_{2.5}), black carbon (BC) and carbon monoxide (CO) 24-hour personal exposures were measured three times during pregnancy. Head circumference and length were measured < 24 h of birth. We conducted intention-to-treat and exposure-response analyses to determine the intervention effects and associations between household air pollution (HAP) exposure during pregnancy and head circumference, head circumference-for-gestational age Z-score, length, and length-for-gestational age Z-scores at birth.

Results: Between May 2018, and Feb 2020, 3200 pregnant women were randomly assigned to intervention (n = 1593) and control groups (n = 1607) with 3060 births included in the analysis. There was a 71.9 % reduction in PM_{2.5} in the intervention group with similar reductions for BC and CO. Intention-to-treat analysis showed that the intervention did not

affect head circumference ($\beta = -0.01$ cm, 95 %CI -0.11, 0.09), head circumference-for-gestational age Z-score ($\beta = -0.01$, 95 %CI -0.08, 0.07), or birth length ($\beta = 0.14$ cm, 95 %CI -0.01, 0.29) but did increase birth length-for-gestational age Z-score ($\beta = 0.09$, 95 %CI 0.01, 0.16). After covariate adjustment, exposure-response analysis revealed that each log-unit increase in BC was associated with a decrease in birth length-for-gestational age Z-score ($\beta = -0.07$, 95 %CI -0.13, -0.005). There was no evidence of hypothesized associations with PM_{2.5} or CO.

Conclusion: An LPG intervention reduced HAP exposure during pregnancy but had minor effects on birth length-for-gestational age Z-score. Birth length-for-gestational age was only associated with BC.

Environ Health Perspect. 2025 Jun;133(6):67004.

doi: 10.1289/EHP15500. Epub 2025 Jun 5.

Effects of Cooking with Liquefied Petroleum Gas or Biomass Fuels on Neurodevelopmental Outcomes in Preschool-Age Children Living in Puno, Peru
[Carolyn J Reuland](#)^{1,2}, [Laura Nicolaou](#)^{1,2,3}, [Maureen M Black](#)^{4,5}, [Mingling Yang](#)^{1,2}, [Ryan McCord](#)⁶, [Milagros Alvarado](#)⁷, [Fiorela Arana](#)⁷, [Paola S Sanchez](#)⁷, [Kendra N Williams](#)^{2,8}, [Shakir Hossen](#)^{1,2}, [Marilú Chiang](#)⁹, [Stella M Hartinger](#)⁷, [William Checkley](#)^{1,2,8}

Abstract

Background: Burning biomass fuels for cooking is a widespread environmental exposure that may adversely affect child health. We conducted an 18-month randomized field trial comparing a liquefied petroleum gas (LPG) stove, continuous fuel delivery, and behavioral messaging intervention starting in pregnancy through infancy with usual cooking practices using biomass fuels in Puno, Peru. A total of 800 pregnant women were enrolled. The intervention successfully lowered personal exposures to fine particulate matter with aerodynamic diameter $\leq 2.5\mu\text{m}$ (PM_{2.5}) during pregnancy and infancy.

Objective: We sought to evaluate the effects of the intervention on neurodevelopment among preschool-age offspring.

Methods: We conducted a longitudinal follow-up study in a subset of Peruvian children born during the trial and assessed neurodevelopment between 24 and 36 months of age. Trained staff measured neurodevelopment using the Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III). The Bayley-III neurodevelopmental assessment test yields separate cognition, language, and motor scores. We measured personal exposures to PM_{2.5} three times during pregnancy and three times in infancy. We conducted modified intention-to-treat analyses of the intervention on Bayley-III scores and exposure-response analyses between prenatal and postnatal PM_{2.5} exposures and Bayley-III scores.

Results: A total of 301 children (mean age 29.0 ± 3.5 months, 47.8% girls, and 54.8% in intervention) were visited. Mean cognitive, language, and motor scores were 90.8 ± 11.0 , 90.8 ± 11.0 , 89.0 ± 10.8 , and 95.3 ± 12.9 , respectively. On intention-to-treat, the adjusted differences between intervention and control arms were -1.9 [98.3% confidence interval (CI): -4.94 – 1.15], -2.94 (-5.98 – 0.1), and -1.35 (-4.99 – 2.29) for the composite cognitive, language, and motor scores, respectively. We did not identify associations between PM_{2.5} exposures during the 18-month intervention and any of the Bayley-III scores or when the personal exposures to PM_{2.5} were separated as either prenatal or postnatal.

Discussion: The LPG intervention did not improve neurodevelopment in Peruvian children. We also did not find an association between prenatal or postnatal PM_{2.5} exposures and neurodevelopment. <https://doi.org/10.1289/EHP15500>.

Exercise and physical activity

Cereb Cortex. 2024 Jul 3;34(7):bhae275.

doi: 10.1093/cercor/bhae275.

[Volleyball training improves working memory in children aged 7 to 12 years old: an fNIRS study](#)

[Xiaohe Zhong](#)^{1,2}, [Yuanfu Dai](#)¹, [Mingchao Xu](#)¹, [Changhao Jiang](#)³

Abstract

This study aimed to investigate the effect of a 12-wk extracurricular volleyball training on working memory from both behavioral and cerebral aspects. A total of 80 children were randomized assigned to (i) the experimental group, who engaged in extracurricular volleyball training for 60 min, thrice a week for 12 wk, and (ii) the control group, who maintained their regular daily routine. Working memory was evaluated in both groups using the N-back task before and after the intervention. Furthermore, functional near-infrared spectroscopy was employed to monitor the level of oxygenated hemoglobin in the prefrontal cortex. The experimental group performed better in the behavioral task than the control group, as evidenced by a shorter response time and a higher correct rate. The functional near-infrared spectroscopy results suggested that the activation of the left dorsolateral prefrontal cortex was significantly higher in the experimental group than in the control group. In addition, correlation analyses showed that the enhancement of left dorsolateral prefrontal cortex activation was significantly correlated with decreasing response time and improving response accuracy in the N-back task. These findings suggest that the left dorsolateral prefrontal cortex is likely the neural substrate for improved working memory performance elicited by 12-wk open skill exercise.

Psych J. 2024 Dec;13(6):954-965.

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[Recreational gymnastics exercise of moderate intensity enhances executive function in Chinese preschoolers: A randomized controlled trial](#)

[Jianhua Zhang](#)^{1,2}, [Jiacheng Lu](#)³, [Youbin Sun](#)⁴, [Ji Li](#)⁴

Abstract

The current study aimed to investigate the impact of recreational gymnastics on executive function in Chinese preschoolers, with a focus on gymnastics potential to enhance core components of executive function. A total of 63 preschool children who received full-time education were randomly assigned to either an intervention group (N = 31, mean age = 66.27 months, SD = 3.12 months) or a control group (N = 32, mean age = 66.79 months, SD = 3.34 months). The intervention group engaged in recreational gymnastics for 60 min, three times

a week for 12 weeks. Meanwhile, the control group continued with their typical outdoor activities at kindergarten and did not participate in any organized sports. The intervention program was primarily conducted through group play and was facilitated by teachers who underwent standardized training. Various simple and complex tasks were utilized to evaluate delay gratification (Snack delay and Wrapped gift), inhibitory control (Stop signal task and Circle drawing task), working memory (Letter memory task and Keep track task), and cognitive flexibility (Go/No-Go task and Dots task). The analysis of covariance revealed that the children who participated in the intervention outperformed the control group on most simple and complex executive function tasks. Specifically, these children demonstrated an enhanced ability to regulate persistent responses, process and update information, and manage high cognitive conflict. The findings of this investigation lend support to the hypothesis that moderate-intensity recreational gymnastics is an efficacious means of enhancing executive function in early childhood. Future research should employ a larger sample size, incorporate a long-term follow-up design, and utilize a multi-method approach to further substantiate the impact of moderate-intensity gymnastics on the executive function of young children, as well as to investigate its underlying mechanism and generalizability.

Worldviews Evid Based Nurs. 2024 Sep 28.

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Effects of exercise interventions on cancer-related fatigue in children with cancer: A meta-analysis

Siyu Wang¹, Mengqiao Li¹, Yuchen Wu¹, Qianlin Guan¹, Ruixing Zhang¹

Abstract

Background: Cancer-related fatigue (CRF) emerges as a common symptom in pediatric cancer patients during treatment. Exercise interventions are increasingly being used as CRF interventions to improve CRF in children with cancer.

Aim: The objective of this meta-analysis was to synthesize the best available evidence concerning the effectiveness of exercise interventions for cancer-related fatigue in children with cancer.

Methods: Six databases were extensively searched from inception to December 2023 to identify relevant randomized controlled trials. The risk of bias and methodological quality were assessed using the Cochrane appraisal tool. Pooled effects were calculated using a random-effects model. Heterogeneity was assessed using the I^2 test.

Results: Eight trials ($n = 465$) were finally included. Exercise was statistically more effective than conventional care in improving CRF in children with cancer ($SMD = -0.62$, 95% CI $[-1.21, -0.03]$) with high statistical heterogeneity ($p = .004$; $I^2 = 86\%$). The results of the subgroup analysis showed that intervention duration <12 weeks ($p < .05$), exercise frequency ≥ 3 times/week ($p < .05$), and exercise duration <45 min/time ($p < .05$) were more effective in improving CRF in children with cancer.

Linking evidence to action: Our results suggest that exercise interventions are effective in reducing CRF in children with cancer. We recommend exercise frequency ≥ 3 times/week, exercise duration <45 min/time, and intervention duration <12 weeks.

J Exp Child Psychol. 2024 Dec;248:106058.

doi: 10.1016/j.jecp.2024.106058. Epub 2024 Sep 4.

Karate Kata training: A promising intervention for behavioral problems in elementary school children

Farzaneh Parsamajd¹, Saeid Teymori²

Abstract

Behavioral issues frequently arise in primary school children, affecting their academic performance, social interactions, and general welfare. These concerns encompass challenges related to attention, concentration, aggression, oppositional behavior, and social maladaptation. The purpose of the current study was to examine the impacts of karate Kata training on extrinsic behavioral problems of elementary school students. The Achenbach Child Behavior Checklist (CBCL) questionnaire was given to all fourth- to sixth-grade students from a male elementary school, totaling 241 students, in Mashhad, Iran. A total of 76 eligible school-aged children with a total score of 65 and above in attention, aggression, oppositional defiance, and social maladaptation issues were selected and randomly assigned to an exercise group (n = 38) or a no-exercise control group (n = 38). Participants in the exercise group were instructed to engage in Kata training, which consists of a series of choreographed movements designed to enhance physical and mental discipline, for a duration of 12 60-min sessions, whereas the participants in the control group followed their daily activities. The CBCL from the Achenbach System of Empirically Based Assessment was used to assess dependent variables such as attention and concentration, aggression, oppositional defiance, and social maladaptation at baseline and post-intervention. The repeated-measures analysis of variance indicated that Kata training results in significant improvements in attention and concentration and significant reductions in aggression, oppositional defiance, and social maladaptation among elementary school students (all ps < .001). These results highlight the potential benefits of incorporating Kata training into interventions aimed at improving the behavioral outcomes of children.

Family planning

Demography. 2024 Oct 1;61(5):1667-1698.

doi: 10.1215/00703370-11581796.

Family Planning and Children's Human Capital: Experimental Evidence From Urban Malawi

Daniel Maggio¹, Mahesh Karra², David Canning³

Abstract

We conduct a randomized controlled trial that provides pregnant and immediate postpartum women with improved access to family planning through counseling, free transportation to a clinic, and financial reimbursement for family planning services over two years. We study the effects of our intervention on child growth and development outcomes among 1,034 children born to participating women directly before the intervention rollout. We find that children born to mothers assigned to the family planning intervention arm were 0.28-0.34 standard deviations taller for their age and 10.7-12.0 percentage points less likely

to be stunted within a year of exposure to the intervention. Children born to mothers assigned to the intervention arm also scored 0.17-0.20 standard deviations higher on a caregiver-reported measure of cognitive development after two years of intervention exposure. Although the non-measurement of children is a challenge in our study, our estimates are robust to multiple methods of correcting for potential attrition bias. Our results are consistent with models of fertility that link couples' fertility decisions to child health and human capital. Our results also suggest that improved access to family planning might have positive downstream effects on child health beyond contraceptive use and fertility outcomes.

PLoS One. 2024 Nov 14;19(11):e0310124.

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Effectiveness of an Interactive Mobile Health Intervention (IMHI) to enhance the adoption of modern contraceptive methods during the early postpartum period among women in Northeast Ethiopia: A cluster Randomized Controlled Trial (RCT)

Nigus Cherie^{1,2}, Muluemebet Abera Wordofa¹, Gurmesa Tura Debelew¹

Abstract

Background: Women in the early postpartum period face substantial unmet needs in contraception to encourage birth intervals and reduce unintended pregnancies. The widespread ownership of mobile devices offers an opportunity to employ mobile health strategies for enhancing communication between healthcare providers and clients. However, little is known about the effectiveness of mobile health interventions to improve early adoption of contraceptive methods after childbirth in Ethiopia.

Objective: This study aimed to evaluate the effectiveness of a mobile health intervention in enhancing the uptake of modern contraceptive methods in the early postpartum period in Dessie and Kombolcha cities, northeast Ethiopia.

Methods: The research was conducted in Dessie and Kombolcha cities zones located in the Amhara region of Northeast Ethiopia from 15th January to 15th June, 2023. Pregnant women with a confirmed gestation of 30 weeks were enrolled and followed up to the 45-day postpartum period. The study employed a cluster randomized control trial involving 764 participants (381 controls and 383 in the intervention group). The intervention group received a new mobile health intervention in addition to the existing healthcare practices, while the control group solely adhered to the current healthcare practices. Data were collected using the Open Data Kit (ODK) and exported to STATA 17 for analysis. The marginal model Generalized Estimating Equations (GEE) through the application of an exchangeable working correlation was applied. The effect of the intervention on the outcome was measured using the odds ratio with a 95% confidence interval at a p-value less than 0.05 significant level.

Results: The study found that 78.7% of participants in the control group and 77.3% in the intervention group had sexual practice after childbirth. The proportion of early postpartum contraceptive uptake in the intervention group (51.6%) was significantly higher than in the control group (38%). The odds of adopting modern contraceptive methods during the early postpartum period were 1.6 times higher among mothers who received the mHealth intervention compared to those in the control group (AOR: 1.6, 95% CI: 1.249-2.123). The study identified significant predictors for the uptake of contraceptive methods during the early postpartum period, including having a live newborn (AOR: 3.7, 95% CI: 1.034-13.353),

parity (AOR: 1.7, 95% CI: 1.069-2.695), and previous experience with contraceptive initiation (AOR: 0.5, 95% CI: 0.358-0.912).

Conclusion: This study findings demonstrated that the potential effectiveness of mobile health interventions in promoting timely contraceptive adoption during early postpartum period. The mobile health intervention, combined with factors such as timing of previous contraceptive initiation, newborn status, and maternal parity, significantly enhances the likelihood of early contraceptive adoption. These nuanced insights provide a strong foundation for developing targeted health interventions and policies aimed at improving early postpartum contraception.

PLoS One. 2025 Feb 5;20(2):e0315029.

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Assessing the application of adapted theory of planned behaviour in predicting postpartum family planning intentions in a pragmatic randomized control trial in Western Kenya

[Morris Senghor Shisanya¹](#), [Mary Kipmerewo²](#), [Everlyne Morema²](#), [Collins Ouma³](#)

Abstract

Introduction: In developing countries like Kenya, addressing the high population growth rate necessitates a focus on early Postpartum Family Planning (PPFP) use. Despite the critical need for PPFP, few researchers explore the application of health behaviour change theories to enhance FP use among postpartum women. This study assesses the application of adapted Theory of Planned Behaviour (TPB) in predicting intention for early PPFP in postpartum women in Western Kenya.

Methods: This randomized control trial included pregnant women aged 15 to 49 attending Antenatal Care (ANC) clinics, randomly assigned to the "Nurses' arm," "Community arm," or "Control arm." The intervention provided family planning (FP) counseling. Trained nurses and Community Health Workers (CHW) delivered counseling in their respective arms, while the control arm received routine care. Adapted TPB was integrated into client exit interviews to identify constructs influencing early PPFP intentions. Structural equation modeling (SEM) was used to predict the intention for early PPFP in the adapted TPB.

Results: The SEM was optimized with the removal of client knowledge on early PPFP. The final model retained satisfaction with PPFP counseling, perceived normative beliefs, attitude towards PPFP, behaviour control of PPFP choice, and perceived risk of early postpartum pregnancy. Only satisfaction with counseling ($P = 0.001$), perceived normative beliefs ($P < 0.0001$), attitude towards PPFP ($P < 0.0001$), and behaviour control of PPFP choice ($P = 0.018$) significantly influenced early PPFP intention.

Conclusion: The study demonstrates a viable application of the adapted TPB model in predicting early PPFP intention in an interventional study.

Dialogues Health. 2025 Apr 19;6:100218.

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Four-year follow-up of CHARM2, an effective family planning intervention, on number and sex of births: Findings from an RCT in rural India

[Anita Raj^{1,2}](#), [Nicole Johns³](#), [Florin Vaida⁴](#), [Mohan Ghule^{1,3}](#), [Namratha Rao¹](#), [Jay G Silverman²](#)

Abstract

Background: Effective family planning interventions may have inadvertent effects on births of girls given son preference in India. We conducted 36 and 48-month follow-ups to our CHARM2 family planning study to determine long-term intervention effects on births and sex of children.

Methods: Our non-blinded two-armed cluster RCT randomized young married couples ($N = 1201$ couples) from 20 geographic clusters (60-61 couples per cluster) into either the CHARM2 intervention or control (referral to local care) condition. CHARM2 offers 5-session gender-synchronized family planning and gender equity counseling delivered by trained local medical providers. Data were collected at baseline in September 2018-June 2019 and then follow-ups at 9, 18, 36 and 48 months, up to September 2023. We retained 88 %-91 % of women across follow-ups with no difference in retention by treatment group. We used adjusted mixed-effects logistic regression models examining sex composition of births at each follow-up and over the total 48-month follow-up to assess differences in all births of boys and girls by treatment group. We adjusted for treatment condition, cluster, and relevant demographics in adjusted models.

Results: We saw no treatment effects on total births or boy births, but lower likelihood of a girl birth was seen at 9-month follow-up and for the total 48-month follow-up period. We found at 9-month follow-up a girl birth was less likely for intervention compared with control participants (7.1 % vs. 10.3 %, respectively, $p = 0.06$), and the male to female sex ratio of births born between baseline and 9-month follow-up was also significantly higher for intervention vs. comparison participants (1.50 [95 % CI 1.00-2.26] vs. 0.83 [95 % CI 0.56-1.21], $p = 0.04$). We conducted a sensitivity analysis to determine treatment effects on boy births and girl births over the 48-month follow-up and again found no effects on boy births, but a significantly lower likelihood of a girl birth for the intervention group (22 % vs 29 %, $p = 0.03$).

Conclusion: The CHARM2 family planning intervention, previously demonstrating significant effects on contraceptive use and women's reproductive agency in rural India, resulted in lower likelihood of girl births over time, suggesting that family planning programs can contribute to sex ratio imbalances if broader social changes eliminating son preference and improving value of a girl child do not occur.

Fever

JAMA Neurol. 2024 Aug 1;81(8):857-865.

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[Acetaminophen and Ibuprofen in Pediatric Central Nervous System Malaria: A Randomized Clinical Trial](#)

[Gretchen L Birbeck^{1,2,3}](#), [Karl B Seydel^{4,5}](#), [Suzanna Mwanza⁶](#), [Derby Tembo^{2,6,3}](#), [Moses Chilombe⁴](#), [Arthur Watts⁷](#), [Ifunanya Ume-Ezeoke¹](#), [Manoj Mathews³](#), [Archana A Patel⁸](#), [Musaku Mwenechanya³](#), [Paul Pensulo⁴](#), [Michael P McDermott⁷](#)

Abstract

Importance: A third of children who survive malaria with neurological involvement (central nervous system [CNS] malaria) develop sequelae. A higher maximum temperature (Tmax) and seizures are risk factors for sequelae.

Objective: To compare aggressive antipyretic therapy using scheduled acetaminophen and ibuprofen vs usual care with acetaminophen alone given only for a temperature of 38.5 °C or higher.

Design, setting, and participants: This randomized clinical trial was conducted at inpatient pediatric services of 1 tertiary care and 1 district hospital in Zambia and a tertiary care center in Malawi. Included were children aged 2 to 11 years with CNS malaria (excluding those with creatinine >1.2 mg/dL), who were enrolled from 2019 to 2022. Data analysis took place from December 2022 to April 2023.

Intervention: The aggressive antipyretic group received acetaminophen (30 mg/kg load, then 15 mg/kg) plus ibuprofen, 10 mg/kg, every 6 hours, regardless of clinical temperature for 72 hours. The usual care group received 15 mg/kg of acetaminophen as needed every 6 hours for a temperature of 38.5 °C or higher.

Main outcomes and measures: The primary outcome variable was Tmax over 72 hours, the total duration of follow-up. Secondary outcomes included seizures and parasite clearance.

Results: Five hundred fifty-three patients were screened, 226 (40.9%) were ineligible, and 57 (10.3%) declined. A total 256 participants (n = 128/group) had a mean (SD) age of 4.3 (2.1) years; 115 (45%) were female, and 141 (55%) were male. The aggressive antipyretic group had a lower Tmax, 38.6 vs 39.2 °C (difference, -0.62 °C; 95% CI, -0.82 to -0.42; P < .001) and lower odds of experiencing multiple or prolonged seizures, 10 (8%) vs 34 children (27%) in the usual care group (odds ratio [OR], 0.26; 95% CI, 0.12 to 0.56). No group difference in parasite clearance time was detected. Severe adverse events occurred in 40 children (15%), 25 (20%) in the usual care group and 15 (12%) in the aggressive antipyretic group, including 13 deaths (10 [8%] and 3 [2%], respectively). Increased creatinine resulted in study drug discontinuation in 8 children (6%) in the usual care group and 13 children (10%) in the aggressive antipyretic group (OR, 1.74; 95% CI, 0.63 to 5.07).

Conclusions and relevance: This study found that aggressive antipyretic therapy reduced mean Tmax to temperature levels comparable with the Tmax among children without neurological impairments in prior observational studies and improved acute seizure outcomes with no prolongation of parasitemia.

Fluid management

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Balanced Salt Solution Versus Normal Saline as Resuscitation Fluid in Pediatric Septic Shock: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

[Sudha Chandel¹](#), [Suresh Kumar Angurana¹](#), [Shankar Prasad¹](#), [Mithlesh Kumar Tiwari¹](#), [Muralidharan Jayashree¹](#), [Karthi Nallasamy¹](#), [Arun Bansal¹](#)

Abstract

Objective. Fluid resuscitation is an important intervention in children with septic shock. The composition of resuscitation fluid is a matter of debate. Our aim was to study the effects of balanced salt solution (BSS) versus normal saline (NS) for resuscitation in pediatric septic shock. **Data sources.** We searched MEDLINE, Embase, LILAC, Cochrane Collaboration, ClinicalTrials.gov, and World Health Organization International Clinical Trials Registry Platform. **Study selection.** Two independent authors screened title and abstracts and then full papers of included studies. **Data extraction:** Two authors extracted data from full papers independently. **Random-effects model** was used for analysis of RCTs. We used Cochrane's risk of bias tool for assessing the quality of studies. **Primary outcome** was mortality and **secondary outcomes** were rates of acute kidney injury (AKI), need for renal replacement therapy (RRT), and adverse effects (hyperchloremia, metabolic acidosis, and fluid overload); and duration of PICU and hospital stay. **Data synthesis:** Five RCTs with 992 children were included. Resuscitation with BSS versus NS was not associated with reduction in mortality (RR 0.82, 95% CI 0.45-1.50, $p = 0.52$; RCTs = 5); with similar results on sensitivity analysis (RR 0.76, 95% CI 0.41-1.41, $p = 0.52$; 4 RCTs = 4). However, resuscitation with BSS was associated with lower rates of AKI (sensitivity analysis RR 0.64, 95% CI 0.50-0.82, $p = 0.0004$; RCTs = 3); lesser need for RRT (RR 0.52, 95% CI 0.35-0.76, $p = 0.0008$; RCTs = 2); and lower rate of hyperchloremia (RR 0.74, 95% CI 0.62-0.87, $p = 0.0002$; RCTs = 3). The data is scant for other secondary outcomes (metabolic acidosis, fluid overload, and duration of PICU and hospital stay) to make any suggestions. The overall 'risk of bias' was low and unclear in most domains. **Conclusion.** Use of BSS as resuscitation fluid in pediatric septic shock was not associated with reduction in mortality. However, BSS was associated with decreased risk of AKI, need of RRT and hyperchloremia.

Indian J Pediatr. 2025 Jul;92(7):725-730.

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5% Dextrose in Ringer's Lactate versus 5% Dextrose Normal Saline as Maintenance Intravenous Fluid Therapy in Children - A Randomised Controlled Trial

[Hemanth Kaviti¹](#), [Joseph John²](#), [Krishna Mohan Gulla¹](#), [Suchanda Sahu³](#)

Abstract

Objectives: To estimate the difference in serum chloride levels between children receiving 5% Dextrose in Ringer's Lactate (RLD5) vs. 5% Dextrose Normal Saline (DNS) and to estimate the incidence of dyselectrolytemia, hyperchloremic metabolic acidosis (HCMA), acute kidney injury (AKI) and all-cause mortality in both groups.

Methods: A randomised controlled trial was conducted in non-critically ill children aged 6 mo to 14 y, admitted between August 2021 and July 2022, requiring intravenous fluids. A sample size of 140 was estimated and randomised, with controls receiving 5% DNS and the intervention group receiving RLD5. Kidney function tests and blood gas analysis were done at admission, 24 h and 48 h after starting the maintenance IV fluid, and outcomes were analysed at 24 h and 48 h. Data was collected using a pre-designed data collection form that included demographic and clinical profile details, and outcomes were analysed using SPSS Version 20 software.

Results: Seventy-one children per group were enrolled. The mean chloride difference between the two groups at 24 and 48 h were 1.67 (p -value 0.03) and 2.78 (p -value 0.01), respectively. The incidence of AKI at 24 h and 48 h was 1.4% and 2.8% in the RLD5 group and

0% and 1.4% in the DNS group, respectively. At 24 h and 48 h, 2.8% and 2.8% of children had HCMA in the RLD5 group, and 14% and 4.2% had HCMA in the DNS group, respectively. There was no mortality in either group.

Conclusions: Though clinically insignificant, there was a statistically significant difference in the serum chloride levels between the groups.

Indian J Pediatr. 2025 Mar;92(3):268-276.

doi: 10.1007/s12098-023-04925-x. Epub 2023 Dec 29.

Additional Bicarbonate Infusion Complements WHO Rehydration Therapy in Children with Acute Diarrhea and Severe Dehydration Presenting with Severe Non-anion Gap Metabolic Acidemia: An Open Label Randomized Trial

[Lalit Takia¹](#), [Arun K Baranwal²](#), [Pramod K Gupta³](#), [Muralidharan Jayashree⁴](#), [Suresh Kumar Angurana⁴](#)

Abstract

Objectives: To assess the efficacy and safety of bicarbonate infusion in children with Acute Diarrhea and Severe Dehydration (ADSD) having severe Non-Anion Gap Metabolic Acidemia (sNAGMA).

Methods: Children (aged 1-144 mo) with ADSD and sNAGMA (pH $\leq$ 7.2 and/or serum bicarbonate $\leq$ 15 mEq/L) were enrolled in an open-label randomized design. Controls (n = 25) received WHO-recommended rehydration therapy with Ringer Lactate, while intervention group (n = 25) received additional bicarbonate deficit correction. Primary outcome was time taken to resolve metabolic acidemia (pH $>$ 7.30 and/or bicarbonate $>$ 15 mEq/L). Secondary outcome measures were adverse outcome [composite of pediatric intensive care unit (PICU) transfer and deaths], acute care area free days in 5 d (ACAFD₅), hospital stay, and adverse effects.

Results: Time taken to resolve metabolic acidemia was significantly lesser with intervention [median (IQR); 8 h (4, 12) vs. 12 h (8, 24); p = 0.0067]. Intervention led to acidemia resolution in significantly more children by 8 h and 16 h (17/25 vs. 9/25, p = 0.035 and 23/25 vs. 17/24, p = 0.018, respectively). Patients with fluid refractory shock needed lesser inotropes in intervention group [median Vasoactive Inotrope Score (VIS), 10.5 vs. 34]. Intervention led to significantly lesser adverse outcome (0/25 vs. 5/25, p = 0.049), and noticeably more ACAFD₅ [median (IQR); 2 (1, 2) vs. 1 (1, 2); p = 0.12]. Two patients died in the control group while none in the intervention group. No adverse effect was documented.

Conclusions: Additional calculated dose of bicarbonate infusion led to significantly early resolution of metabolic acidemia, lesser utilization of critical care facilities, and lesser adverse outcome in children with ADSD and sNAGMA, compared to standard therapy, with no adverse effect.

Indian J Pediatr. 2024 Sep 20.

doi: 10.1007/s12098-024-05240-9. Online ahead of print.

Normal Saline Versus Ringer's Lactate for Intravenous Fluid Therapy in Children with Diabetic Ketoacidosis: A Randomized Controlled Trial

[Devanshi Singhal¹](#), [Shalu Gupta²](#), [Virendra Kumar¹](#)

Abstract

Objectives: To compare normal saline (NS) and ringer's lactate (RL) as intravenous fluid therapy in children with diabetic ketoacidosis (DKA).

Methods: This was a triple blinded randomized controlled trial conducted in the Pediatric Intensive Care Unit (PICU) of a tertiary care hospital in New Delhi from November 2018 to March 2020. The study compared intravenous fluid therapy with ringer's lactate and normal saline in children aged 6 mo to 18 y with DKA as defined by The International Society for Pediatric and Adolescent Diabetes (ISPAD). The primary objective was comparing the time taken to achieve resolution of acidosis ($\text{pH} \geq 7.3$) in both groups. Secondary objectives included comparing the proportion of patients that develop acute kidney injury; comparing the time taken for normalization of anion gap and blood glucose; time taken to change the type of fluid; total amount of fluid and insulin administered; and total length of PICU and hospital stay.

Results: Fifty patients were enrolled, with 25 in each arm and all but one achieved the primary outcome. The median age of the patients was 9 (5, 12) y. The time taken for resolution of acidosis in patients treated with NS was 12 (4, 18) h and with RL was 8 (4, 10) h ($p = 0.16$). The NS group had a significantly higher incidence of hyperchloremia ($p < 0.05$) and longer PICU stay ($p < 0.05$). The metabolic profile and incidence of complications were comparable in both groups.

Conclusions: Ringer's lactate can safely be considered for the management of pediatric DKA and may be preferred in patients that are at a risk of complications due to hyperchloremia.

Indian J Pediatr. 2025 Jan;92(1):7-14.

doi: 10.1007/s12098-023-04867-4. Epub 2023 Oct 18.

[Restricted versus Usual/Liberal Maintenance Fluid Strategy in Mechanically Ventilated Children: An Open-Label Randomized Trial \(ReLiSch Trial\)](#)

[Shubham Charaya¹](#), [Suresh Kumar Angurana²](#), [Karthi Nallasamy³](#), [Muralidharan Jayashree³](#)

Abstract

Objectives: To assess the impact of restricted vs. usual/liberal maintenance fluid strategy on fluid overload (FO) among mechanically ventilated children.

Methods: This open-label randomized controlled trial was conducted over a period of 1 y (October 2020-September 2021) in a Pediatric intensive care unit (PICU) in North India. Hemodynamically stable mechanically ventilated children were randomized to 40% (restricted group, $n = 50$) and 70-80% (usual/liberal group, $n = 50$) of maintenance fluids. The primary outcome was cumulative fluid overload percentage (FO%) on day 7. Secondary outcomes were FO% $>10\%$; vasoactive inotropic score, sequential organ failure assessment score, pediatric logistic organ dysfunction score and oxygenation index from day 1-7; ventilation free days (VFDs) and PICU free days (PFDs) through day 28; and mortality.

Results: The restricted group had statistically non-significant trend towards lower cumulative FO% at day 7 [7.6 vs. 9.5, $p = 0.40$]; and proportion of children with FO% $>10\%$ (12% vs. 26%, $p = 0.21$) as compared to usual/liberal group. The increase in FO% from day 1-7 was significant in usual/liberal group as compared to restricted group ($p < 0.001$ and $p = 0.134$, respectively). Restricted group received significantly lower amount of fluid in the first

5 d; had significantly higher VFDs (23 vs. 17 d, $p = 0.008$) and PFDs (19 vs. 15 d, $p = 0.007$); and trend towards lower mortality (8% vs. 16%, $p = 0.21$).

Conclusions: Restricted as compared to usual/liberal maintenance fluid strategy among mechanically ventilated children was associated with a trend towards lower rate and severity of FO and mortality; and significantly lower fluid volume received, and higher VFDs and PFDs.

Indian J Pediatr. 2025 Jun;92(6):618-624.

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Pattern of Fluid Overload and its Impact on Mortality Among Mechanically Ventilated Children: Secondary Analysis of the ReLiSch Trial

[Shubham Charaya¹](#), [Suresh Kumar Angurana²](#), [Karthi Nallasamy¹](#), [Arun Bansal¹](#), [Jayashree Muralidharan¹](#)

Abstract

Objectives: To assess the pattern of fluid overload (FO) and its impact on mortality among mechanically ventilated children.

Methods: In this secondary analysis of an open-label randomized controlled trial (ReLiSch trial, October 2020-September 2021), hemodynamically stable mechanically ventilated children ($n = 100$) admitted to a tertiary level pediatric intensive care unit (PICU) in North India were enrolled. The primary outcome was pattern of FO (FO% >10% and cumulative FO% from day 1-7); and secondary outcomes were pattern of FO among survivors and non-survivors, and prescription practices of maintenance fluid.

Results: The median (IQR) age was 3.5 (0.85-7.5) y and 57% were males. Common diagnoses were pneumonia (27%), scrub typhus (14%), Landry-Guillain-Barré syndrome (9%), dengue (8%), central nervous system infections (7%) and staphylococcal sepsis (6%). Common organ dysfunction included acute respiratory distress syndrome (ARDS) (41%), shock (38%), and acute kidney injury (AKI) (9%). The duration PICU stay was 11 (7-17) d and mortality was 12%. The FO% >10% was noted in 19% children; and there was significant increase in cumulative FO% from day 1-7 [1.2 (0.2-2.6)% to 8.5 (1.7-14.3)%, ($p = 0.000$)]. Among non-survivors, higher proportion had FO% >10% (66.7% vs. 12.5%, $p = 0.0001$); and trend towards higher cumulative FO% on first seven days. From day 1-7, the percentage of maintenance fluid received increased from 60 (50-71)% to 70 (60-77)% ($p = 0.691$).

Conclusions: One-fifth of mechanically ventilated children had FO% >10% and there was significant increase in cumulative FO% from day 1-7. Non-survivors had significantly higher degree of FO.

Health promotion

Health services

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The impact of digital interventions on health insurance coverage for reproductive, maternal, newborn and child health services in Kakamega, Kenya: a cluster randomized controlled trial

[Amanuel Abajobir¹](#), [Richard de Groot²](#), [Caroline Wainaina¹](#), [Menno Pradhan^{2,3,4}](#), [Wendy Janssens^{2,3}](#), [Estelle M Sidze¹](#)

Abstract

The National Hospital Insurance Fund (NHIF) of Kenya was upgraded to improve access to healthcare for impoverished households, expand universal health coverage (UHC), and boost the uptake of essential reproductive, maternal, newborn and child health (RMNCH) services. However, premiums may be unaffordable for the poorest households. The Innovative Partnership for Universal Sustainable Healthcare (i-PUSH) program targets low-income women and their households to improve their access to and utilization of quality healthcare, including RMNCH services, by providing subsidized, mobile phone-based NHIF coverage in combination with enhanced, digital training of community health volunteers (CHVs) and upgrading of health facilities. This study evaluated whether expanded NHIF coverage increased the accessibility and utilization of quality basic RMNCH services in areas where i-PUSH was implemented using a longitudinal cluster randomized controlled trial in Kakamega, Kenya. A total of 24 pair-matched villages were randomly assigned either to the treatment or the control group. Within each village, 10 eligible households (i.e., with a woman aged 15-49 years who was either pregnant or with a child below 4 years) were randomly selected. The study applied a Difference-in-Difference methodology based on a pooled cross-sectional analysis of baseline, midline and endline data, with robustness checks based on balanced panels and ANCOVA methods. The analysis sample included 346 women, of whom 248 had had a live birth in the 3 years prior to any of the surveys, and 424 children aged 0-59 months. Improved NHIF coverage did not have a statistically significant impact on any of the RMNCH outcome indicators at midline nor endline. Uptake of RMNCH services, however, improved substantially in both control and treatment areas at endline compared to baseline. For instance, significant increases were observed in the number of antenatal care visits from baseline to midline (mean = 2.62 to 2.92) $p < 0.01$ and delivery with a skilled birth attendant from baseline to midline (mean = 0.91 to 0.97 ($p < 0.01$)). Expanded NHIF coverage, providing enhanced access to RMNCH services of unlimited duration at both public and private facilities, did not result in an increased uptake of care, in a context where access to basic public RMNCH services was already widespread. However, the positive overall trend in RMNCH utilization indicators, in a period of constrained access due to the COVID-19 pandemic, suggests that the other components of the i-PUSH program may have been beneficial. Further research is needed to better understand how the provision of insurance, enhanced CHV training and improved healthcare quality interact to ensure pregnant women and young children can make full use of the continuum of care.

Health worker education

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An evaluation of the effectiveness of an updated pre-service midwifery curriculum integrated with emergency obstetric and newborn care in Kenya: a cluster randomised controlled trial

[Duncan N Shikuku^{1,2}](#), [Catherine Mwaura³](#), [Peter Nandikove⁴](#), [Alphonse Uyara⁵](#), [Helen Allott⁶](#), [Lucy Waweru³](#), [Lucy Nyaga⁷](#), [Edna Tallam⁸](#), [Issak Bashir⁹](#), [Eunice Ndirangu¹⁰](#), [Carol Bedwell⁶](#), [Sarah Bar-Zeev¹¹](#), [Charles Ameh^{6,12,13}](#)

Abstract

Introduction: Quality midwifery education is central to improving midwifery service delivery and maternal and newborn health outcomes. In many settings, midwifery educators insufficiently prepared for their teaching role and deficient curriculum compared to international standards affect the quality of healthcare provided by the midwifery graduates. This study assessed the effectiveness of an EmONC enhanced midwifery curriculum delivered by trained and mentored midwifery educators on the quality of education and student performance in Kenya.

Methods: A cluster randomised controlled trial in 20 midwifery colleges (12 intervention, 8 control colleges). Educators in both arms received training in teaching/EmONC skills to deliver the updated national midwifery curriculum. The intervention arm received additional 3-monthly post-training mentoring for 12 months. Educators' knowledge and confidence in EmONC/teaching skills was assessed before and after training and at 3, 6, 9 and 12 months. Teaching skills observations at baseline and endline in both study arms were also assessed. Knowledge, self-rated confidence and three OSCE in EmONC practical skills among final year midwifery students were assessed. Linear mixed effects models were used to evaluate the effect of intervention on educators and students.

Results: Seventy four educators and 146 students participated. Training significantly improved educators' mean knowledge (61.3%-73.3%) and confidence to teach EmONC (3.1-4.2 out of 5). Observed teaching skills mean scores of educators in the intervention arm were significantly higher compared to those of controls at endline (89.4%-vs-72.2%, mean difference 17.2 [95%CI, 3.2-29.8]). Mean scores for students in the intervention arm were significantly higher than those in controls for knowledge (59.6%-vs-51.3%, mean difference 8.3 [95%CI, 1.6-15.0]) and the three skills assessed (means; mean difference (95%CI): shoulder dystocia (64.5%-vs-42.7%; 21.8 (10.8-33.9); newborn resuscitation (43.9% vs 26.1%; 17.8 (2.0-33.9); and maternal shock resuscitation (56.5%-vs-39.2%; 17.3 (8.0-26.0) and combined average skills scores (55.0%-vs-36.0; 19.0 (8.7-29.5)).

Conclusion: Training and supportive mentoring improved the quality of educators' teaching pedagogy and EmONC skills and enhanced students' learning. Overall performance in EmONC knowledge and skills was significantly higher for students who were taught by trained and mentored educators compared to those who received training alone. Thus, a local mentoring system is effective to enhance learning and effectiveness of an EmONC-updated midwifery curriculum.

Haematological disorders

(See also Anaemia and iron deficiency, Malaria: treatment of uncomplicated malaria for study in sickle-cell disease patients)

Sickle cell disease

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[Hydroxyurea for Children and Adults with Hemoglobin SC Disease](#)

[Yvonne A Dei-Adomakoh^{1,2}](#), [Catherine I Segbefia^{3,4}](#), [Teresa S Latham^{5,6}](#), [Adam C Lane^{5,7}](#), [Klenam Dzefi-Tettey^{8,9}](#), [Kwesi Amissah-Arthur^{10,11}](#), [Oksana Corquaye¹²](#), [Lyudmyla Korang¹²](#), [Enoch Mensah¹](#), [Priscilla Ekpale¹](#), [William Ghunney²](#), [Lily G Tagoe⁴](#), [Alpha Oteng²](#), [Emmanuella Amoako⁴](#), [Ernestina Schandorf⁴](#), [Enam Bankas²](#), [Nana A Awuku²](#), [Doreen Seedah⁴](#), [Susan E Stuber^{5,6}](#), [Luke R Smart^{5,6,7}](#), [Russell E Ware^{5,6,7}](#)

Abstract

Background: Hemoglobin SC (HbSC) is a common sickle hemoglobinopathy that causes acute complications, chronic organ damage, and early death with no established disease-modifying treatment. In this trial, we examined the safety and efficacy of hydroxyurea treatment in patients with HbSC.

Methods: Prospective Identification of Variables as Outcomes for Treatment (PIVOT) was a double-blind, randomized, placebo-controlled, non-inferiority phase 2 trial in which we assigned children and adults with HbSC in Ghana to 12 months of hydroxyurea or placebo. The primary end point was hematologic dose-limiting toxicities (DLTs), including cytopenias or elevated hemoglobin levels during 12 months of blinded treatment. Clinical end points included vaso-occlusive pain events, acute chest syndrome, hospitalizations, transfusions, and malaria. Quality-of-life measures, organ function assessments, and rheological measurements were also collected.

Results: Of the 243 enrolled patients (118 female), 212 eligible participants initiated blinded treatment at 20.0±5.0 mg/kg/day. DLTs occurred in more participants on hydroxyurea (33%) than the placebo (11%), with a difference of 22 percentage points (95% confidence interval [CI], 11 to 34 percentage points), which exceeded the predefined 15 percentage point noninferiority margin. Elevated levels of hemoglobin occurred in 12 participants on hydroxyurea and 10 on the placebo. Hydroxyurea treatment was associated with 57.0 versus 149.6 vaso-occlusive pain events per 100 person-years (incidence rate ratio [IRR] 0.38; 95% CI, 0.28 to 0.52), and 12.9 versus 30.6 hospitalizations per 100 person-years (IRR 0.42; 95% CI, 0.22 to 0.81). A composite of acute sickle-related events occurred in 37 participants on hydroxyurea versus 69 participants on placebo (IRR 0.39; (95% CI, 0.26 to 0.59), a difference observed in both children and adults.

Conclusions: The PIVOT trial did not meet its primary end point. Hydroxyurea at 20 mg/kg in patients with HbSC was associated with more hematologic DLTs than placebo, but most were mild and transient. Hydroxyurea was associated with less vaso-occlusive pain and fewer sickle-related events in both children and adults; a new trial will need to be done to establish the efficacy of this approach.

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Safety and efficacy of L-Glutamine in reducing the frequency of acute complications among patients with sickle cell disease: A randomized controlled study

[Fatma Soliman Elsayed Ebeid^{1,2}](#), [Nihal Hussien Aly³](#), [Naglaa Mohammed Shaheen⁴](#), [Samah Mohammed Ahmed Abdellatif⁴](#), [Ahmed Ashraf Mahmoud Okba⁵](#), [Nada Ayman Gad⁶](#), [Sara Mostafa Makkeyah³](#)

Abstract

To evaluate the safety and efficacy of L-glutamine in reducing vaso-occlusive crisis (VOC) and improving cerebral arterial blood flow in children with sickle cell disease (SCD). This is an interventional randomized controlled trial that recruited sixty SCD patients, aged 9.2 ± 3.7 years, who had at least two VOCs during the last 12 months and on a stable dose of hydroxyurea. They were randomly assigned in a 1:1 ratio to receive glutamine (0.3 gm/kg/dose/12h) orally for 24 weeks or the standard of care (SOC). All patients had VOCs in the last year > 3, those on glutamine had a higher number of VOCs and hospitalization for VOC in the last year. There was a decreasing trend in the number, severity, and hospitalization of VOC and a significantly lower cumulative number of VOCs and hospitalizations in the glutamine group than in SOC ($p = 0.008$, $p < 0.001$ respectively). Time-averaged mean maximum velocity for the glutamine group had a marginal increase in both middle cerebral arteries, all values remained normal within a normal range, and in both internal carotid arteries, values increased from abnormally low to normal ranges at week 24. Glutamine reduced the number of VOCs and severity and may have a potentially favorable impact on the cerebral arterial flow velocities.

Indian Pediatr. 2025 Jan 15;62(1):15-19.

doi: 10.1007/s13312-025-3351-0.

Ketorolac vs Morphine for Severe Vaso-Occlusive Crisis in Sickle Cell Disease: An Open-Label Randomized Controlled Trial (KISS Study)

[Sai Pratap Reddy¹](#), [Sunil Natha Jondhale¹](#), [Santosh Kumar Rathia¹](#), [Samreen Yusuf¹](#), [Seema Shah¹](#), [Anil Kumar Goel²](#)

Abstract

Objectives: To compare the efficacy and safety of intravenous (IV) ketorolac and IV morphine in the management of severe vaso-occlusive crisis (VOC) in children with sickle cell disease (SCD).

Method: An open-label, randomized controlled trial was conducted from January 2021 to July 2022 wherein children with SCD aged 3 to 15 years, presenting with severe VOC (score > 6 on the Wong-Baker Faces Pain scale) were included. Block randomization with minimization was done and participants received either IV ketorolac (intervention) or IV morphine infusion (standard). The pain score was reassessed three hourly and if the pain score exceeded 6, the drug dose was escalated every 3 hours, upto a maximum of three escalating doses. A pain score of ≤ 6 were regarded as response.

Results: The mean (SD) pain scores at admission in the ketorolac and morphine groups were 9.28 (0.89) and 9.12 (1.01), respectively ($P = 0.636$). At 3, 6, 9, and 12 hours of infusion, the mean pain scores in the ketorolac and morphine groups were 8.04 (1.24) vs 8.28 (1.24), $P = 0.313$; 7.04 (1.210) vs 7.28 (1.28), $P = 0.331$; 6.40 (1.26) vs 6.28 (1.17), $P = 0.860$; and 5.56 (1.00) vs 5.60 (1.04), $P = 0.817$, respectively. Five and eleven children developed minor side effects

in the ketorolac and morphine groups, respectively ($P = 0.069$). Overall, one child in the ketorolac group and two in the morphine persisted to have severe pain even after 12 hours of therapy ($P = 0.55$).

Conclusion: Intravenous ketorolac may be considered as a good alternative to IV morphine in the management of severe VOC in SCD.

Am J Hematol. 2025 Jul;100(7):1119-1131.

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Arginine Therapy for Pain in Sick Cell Disease: A Phase-2 Randomized, Placebo-Controlled Trial

[Claudia R Morris^{1,2,3}](#), [Dunia Hatabah¹](#), [Rawan Korman¹](#), [Scott Gillespie¹](#), [Nitya Bakshi⁴](#), [Lou Ann Brown¹](#), [Frank Harris¹](#), [Deborah Leake³](#), [Chris A Rees^{1,2,3}](#), [Kirshma Khemani^{1,3}](#), [Elliott P Vichinsky⁵](#), [Alexus Locke³](#), [Bridget Wynn¹](#), [Mark A Griffiths^{1,2,3}](#), [Hagar Wilkinson³](#), [Polly Kumari¹](#), [Lisa Sudmeier⁶](#), [Sruti Shiva⁷](#), [Carlton D Dampier^{1,3}](#)

Abstract

We present a prospective randomized, placebo-controlled trial of intravenous arginine in patients 3-21 years hospitalized with sickle cell disease vaso-occlusive pain episodes (SCD-VOE) at two tertiary-care children's hospitals. Participants were randomized into 1 of 3 arms: Standard-dose (SD; 100 mg/kg/dose) every 8 h, Loading-dose (200 mg/kg followed by SD), or Placebo. The primary outcome was total parenteral opioid use (TPO). Secondary outcomes included time-to-crisis-resolution, pain scores, patient-reported outcomes (PROs), arginine bioavailability, and biomarkers of oxidative stress/mitochondrial function. Of 1548 patients screened, 108 were randomized (36 per study-arm; mean 12.6 ± 3.8 years, 52% female, and 65% hemoglobin-SS). This study did not meet its primary endpoint. TPO, time-to-crisis-resolution, pain scores, and PROs at discharge were similar across arms. Post hoc sensitivity analyses of children 5-16 years old demonstrated nearly double TPO utilization in those receiving placebo versus arginine ($n = 87$, $p = 0.056$), achieving significance in patients with plasma arginine $< 60 \mu\text{M}$. Arginine was low at presentation in 79% of patients (mean $50 \pm 28 \mu\text{M}$), and increased with arginine therapy ($p < 0.001$). Arginine bioavailability at VOE presentation inversely correlated with time-to-crisis-resolution ($r = -0.39$, $p = 0.01$) after placebo, an association eliminated by arginine supplementation ($r = -0.04$, $p = 0.70$). A dose-dependent increase in platelet-mitochondrial activity occurred after arginine versus no change after placebo ($p < 0.001$); plasma protein-carbonyl levels, a measure of oxidative stress, decreased after arginine therapy ($p < 0.001$) but increased in the placebo group ($p = 0.02$). SCD-VOE is associated with an acquired arginine deficiency that correlates with worse clinical outcomes. Arginine improved mitochondrial function and decreased oxidative stress compared to placebo, with clinically relevant opioid-sparing becoming significant in children with the lowest arginine concentration.

Clin Nutr. 2025 Feb 17;47:157-168.

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The effects of nutritional supplementation for children and adolescents with sickle cell disease: A systematic review and meta-analyses

[Bruna C Orsi¹](#), [Daniela Gorski²](#), [Naila E Krul³](#), [Astrid Wiens⁴](#), [Miguel Brito⁵](#), [Fernanda S Tonin⁶](#), [Roberto Pontarolo⁷](#)

Abstract

Background & aims: Sickle cell disease (SCD), a neglected chronic genetic blood disorder that severely impacts the pediatric population, often leading to premature death, is associated with compromised nutritional status. This study aimed to evaluate the effect of nutritional supplementation in SCD-related complications.

Methods: A systematic review with searches in PubMed, Scopus and Web of Science was performed. Randomized controlled trials (RCT) assessing diet or supplements as complementary therapy for children and adolescents with SCD were included (PROSPERO:CRD42024532369). The data for outcomes of interest (efficacy, safety) were pooled by means of pairwise and network meta-analyses with ranking (p-score) analysis. The results were presented as odds ratio or mean differences with 95 % confidence intervals (NMAstudio2.0).

Results: Twenty RCTs were included (2002-2023) (n = 2058), analyzing 9 dietary supplements on different regimens. All patients were in use of hydroxyurea as active treatment. Supplementation with fatty acids (n = 3 studies) and l-arginine (n = 4) presented higher efficacy and safety, significantly improving pain intensity, vaso-occlusive crises (VOC) and inflammation when compared to usual care/placebo (p < 0.05). Vitamin D3 (n = 6) at different dosages may reduce respiratory complications and length of hospital stay, yet further studies are needed to confirm its significant effects. Evidence is limited and of poor quality regarding the effects of add-on vitamin A (n = 2), magnesium sulfate (n = 2) and zinc (n = 4) for this population.

Conclusions: The complementary use of certain supplements (fatty acids, l-arginine, vitamin D3) can enhance the management of VOC and improve patients' physiological functions. These supplements are often affordable and can contribute towards the reduction of opioid use and shorten patients' hospital stays - especially in low/middle-income countries where resources are scarce. Although further studies are needed to refine these findings (e.g., appropriate doses/regimens), practical guidelines and decision-makers may benefit from updated evidence.

Pediatr Blood Cancer. 2025 Jun;72(6):e31637.

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Impact of Food Insecurity on Malnutrition Treatment Response in Nigerian Children With Sickle Cell Anemia and Severe Acute Malnutrition

[Gabriela Ramirez-Cuebas¹](#), [Shehu Umar Abdullahi²](#), [Safiya Gambo³](#), [Hassan Adam Murtala³](#), [Halima Kabir²](#), [Khadija A Shamsu²](#), [Garba Gwarzo²](#), [Sari A Acra⁴](#), [Virginia A Stallings⁵](#), [Mark Rodeghier⁶](#), [Michael R DeBaun^{7,8}](#), [Lauren J Klein^{4,7}](#)

Abstract

Background: In this planned ancillary analysis of our completed clinical trial, we hypothesized that among older children with sickle cell anemia (SCA) and severe acute malnutrition, those with higher levels of food insecurity would have lower end-of-trial body mass index (BMI) z-scores compared to their peers with SCA and lower levels of food insecurity.

Procedure: Data from 108 children who completed the feasibility trial for managing severe acute malnutrition in older children with SCA in Nigeria were analyzed. Children aged 5-12

years old with severe acute malnutrition (BMI z-score of <-3.0) were randomly allocated to receive either supplemental ready-to-use therapeutic food (RUTF) alone or RUTF with moderate-dose hydroxyurea (20 mg/kg/day). Caregivers completed the United States Household Food Security Survey Module to measure food security. We focused on the childhood section for its accuracy in assessing food security in older children. Higher scores (0-8) indicate greater food insecurity. We constructed multivariable linear regression models to estimate the association between childhood food insecurity and BMI z-scores at baseline and endpoint.

Results: Most participants were food insecure, with 55% ($n = 59$) and 34% ($n = 37$) having low and very low food security, respectively. Higher scores on the continuous food security measure, indicating lower food security, were associated with lower BMI z-scores at both study entry ($\beta = -0.05$, $p = 0.047$) and after malnutrition treatment ($\beta = -0.07$, $p = 0.016$).

Conclusions: Among severely malnourished children with SCA, lower childhood food security scores are associated with an adverse treatment response, reflected by a lower BMI z-score at the trial's end.

Lancet Infect Dis. 2025 Jun;25(6):643-655.

doi: 10.1016/S1473-3099(24)00737-0. Epub 2024 Dec 20.

Weekly dihydroartemisinin-piperaquine versus monthly sulfadoxine-pyrimethamine for malaria chemoprevention in children with sickle cell anaemia in Uganda and Malawi (CHEMCHA): a randomised, double-blind, placebo-controlled trial

[Richard Idro¹](#), [Thandile Nkosi-Gondwe²](#), [Robert Opoka³](#), [John M Ssenkusu⁴](#), [Kalibbala Dennis³](#), [Lufina Tsirizani⁵](#), [Pamela Akun⁶](#), [Joseph Rujumba⁶](#), [Winnie Nambatya⁶](#), [Carol Kamya⁷](#), [Nomsa Phiri²](#), [Kirikumwino Joanita⁶](#), [Ronald Komata⁶](#), [Mailosi Innussa²](#), [Emmanuel Tenywa⁸](#), [Chandy C John⁹](#), [Joel Tarning¹⁰](#), [Paolo Denti⁵](#), [Roeland E Wasmann⁵](#), [Feiko O Ter Kuile¹¹](#), [Bjarne Robberstad⁷](#), [Kamija S Phiri¹²](#)

Abstract

Background: In many sub-Saharan African countries, it is recommended that children with sickle cell anaemia receive malaria chemoprevention with monthly sulfadoxine-pyrimethamine or daily proguanil as the standard of care. However, the efficacy of these interventions is compromised by high-grade antifolate resistance of *Plasmodium falciparum* and poor adherence. We aimed to compare the efficacy of weekly dihydroartemisinin-piperaquine and monthly sulfadoxine-pyrimethamine for the prevention of clinical malaria in children with sickle cell anaemia in areas with high-grade sulfadoxine-pyrimethamine resistance of *P falciparum* in Uganda and Malawi.

Methods: We did an individually randomised, parallel group, double-blind, placebo-controlled trial at two hospitals in Uganda and two hospitals in Malawi. Children (aged 6 months to 15 years) with sickle cell anaemia with a bodyweight of at least 5kg were randomly assigned (1:1) by computer-generated block randomisation, stratified by site and weight category, to receive either weekly dihydroartemisinin-piperaquine (approximately 2.5 mg per kg bodyweight dihydroartemisinin and 20 mg per kg bodyweight per day piperaquine) or monthly sulfadoxine-pyrimethamine (approximately 25 mg per kg bodyweight sulfadoxine and 1.25 mg per kg bodyweight). Placebos matching the alternative treatment were used in each treatment group to maintain masking of the different dosing schedules from the participants and caregivers, study staff, investigators, and data analysts. All children younger

than 5 years received penicillin twice daily as standard of care. The primary endpoint was the incidence of clinical malaria, defined as a history of fever in the preceding 48 h or documented axillary temperature of 37.5°C or higher plus the detection of *P falciparum* parasites on microscopy (any parasite density). Secondary efficacy outcomes were any malaria parasitaemia (on either microscopy or malaria rapid diagnostic test), all-cause unscheduled clinic visits, all-cause and malaria-specific hospitalisation, sickle cell anaemia-related events (including vaso-occlusive crises, acute chest syndrome, stroke), need for blood transfusion, and death. All primary and secondary outcomes were assessed in the modified intention-to-treat population, which included all participants who were randomly assigned for whom endpoint data were available. Safety was assessed in all children who received at least one dose of the study drug. Complete case analysis was conducted using negative-binomial regression. This study was registered with Clinicaltrials.gov, [NCT04844099](https://clinicaltrials.gov/ct2/show/study/NCT04844099).

Findings: Between April 17, 2021, and May 30, 2022, 725 participants were randomly assigned; of whom 724 were included in the primary analysis (367 participants in the dihydroartemisinin-piperaquine group and 357 participants in the sulfadoxine-pyrimethamine group). The median follow-up time was 14.7 months (IQR 11.2-18.2). The incidence of clinical malaria was 8.8 cases per 100 person-years in the dihydroartemisinin-piperaquine group and 43.7 events per 100 person-years in the sulfadoxine-pyrimethamine group (incidence rate ratio [IRR] 0.20 [95% CI 0.14-0.30], $p < 0.0001$). The incidence of hospitalisation with any malaria was lower in the dihydroartemisinin-piperaquine group than the sulfadoxine-pyrimethamine group (10.4 vs 37.0 events per 100 person-years; IRR 0.29 [0.20-0.42], $p < 0.0001$) and the number of blood transfusions was also lower in the dihydroartemisinin-piperaquine group than the sulfadoxine-pyrimethamine group (52.1 vs 72.5 events per 100 person-years; IRR 0.70 [0.54-0.90], $p = 0.006$). The incidence of all-cause unscheduled clinic visits and all-cause hospitalisations were similar between the two groups, however, participants in the dihydroartemisinin-piperaquine group had more clinic visits unrelated to malaria (IRR 1.12 [1.00-1.24], $p = 0.042$) and more hospitalisations with lower respiratory tract events (16.5 vs 8.5 events per 100 person-years; IRR 1.99 [1.25-3.16], $p = 0.0036$) than participants in the sulfadoxine-pyrimethamine group. The number of serious adverse events in the dihydroartemisinin-piperaquine group was similar to that in the sulfadoxine-pyrimethamine group (vaso-occlusive crisis [154 of 367 participants dihydroartemisinin-piperaquine group vs 132 of 357 participants in the sulfadoxine-pyrimethamine group] and suspected sepsis [115 participants vs 92 participants]), with the exception of acute chest syndrome or pneumonia (51 participants vs 32 participants). The number of deaths were similar between groups (six [2%] of 367 participants in the dihydroartemisinin-piperaquine group and eight (2%) of 357 participants in the sulfadoxine-pyrimethamine group).

Interpretation: Malaria chemoprophylaxis with weekly dihydroartemisinin-piperaquine in children with sickle cell anaemia is safe and considerably more efficacious than monthly sulfadoxine-pyrimethamine. However, monthly sulfadoxine-pyrimethamine was associated with fewer episodes of non-malaria-related illnesses, especially in children 5 years or older not receiving penicillin prophylaxis, which might reflect its antimicrobial effects. In areas with high *P falciparum* antifolate resistance, dihydroartemisinin-piperaquine should be considered as an alternative to sulfadoxine-pyrimethamine for malaria chemoprevention in children younger than 5 years with sickle cell anaemia receiving penicillin-V prophylaxis. However, there is need for further studies in children older than 5 years.

Thalassaemia

Hearing loss

PLoS One. 2025 Feb 6;20(2):e0318655.

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[Postnatal cytomegalovirus infection and its effect on hearing and neurodevelopmental outcomes among infants aged 3-10 months: A cohort study in Eastern Uganda](#)

[Noela Regina Akwi Okalany¹](#), [David Mukunya²](#), [Peter Olupot-Olupot^{2,3}](#), [Martin Chebet^{1,4}](#), [Francis Okello^{1,2}](#), [Andrew D Weeks⁵](#), [Fred Bisso⁶](#), [Thorkild Tylleskär¹](#), [Kathy Burgoine^{1,3,6}](#), [Ingunn Marie Stadskleiv Engebretsen¹](#)

Abstract

Background: Hearing impairment and neurodevelopmental disorders pose a significant global health burden in children. The link between postnatal cytomegalovirus (CMV) infection and these outcomes remains unclear. This study explored the association of postnatal CMV infection with hearing and neurodevelopmental outcomes in term infants aged 3 to 10 months.

Methods: This was a cohort sub-study within the BabyGel cluster randomised trial in Eastern Uganda. From 1265 term infants screened for CMV, 219 were negative at birth but positive at 3 months, and were age-matched with 219 CMV-negative controls. CMV status was determined by PCR screening of saliva samples, with positive results confirmed using urine samples (Chai Open qPCR, Santa Clara, CA). From the established cohort, 424 infants were successfully followed up between 3 to 10 months of age. Clinical assessments included neurodevelopmental evaluation using the Malawi Developmental Assessment Tool, the Hammersmith Infant Neurological Examination, and hearing screening using Otoacoustic Emission testing (Otoport Lite, Otodynamics Limited). Statistical analyses were performed using descriptive statistics, chi-square tests and log binomial regression models with Stata 18.

Results: Of the 424 infants included in the study, 206 were postnatal CMV-infected and 218 were uninfected. Neurodevelopmental assessments indicated no differences between postnatal CMV-infected infants and uninfected groups (ARR 0.88, 95% CI [0.67, 1.15], $p = 0.346$). Hearing screening revealed a 1.99-fold increased risk of a positive result for postnatal CMV-infected infants compared to uninfected infants (67/106 vs. 39/106, 95% CI [1.27, 3.12], $p = 0.003$).

Conclusion: Postnatal CMV infection was associated with more positive hearing screenings, though no significant differences in neurodevelopmental outcomes were observed in early infancy. Exploration into the feasibility of incorporating hearing and CMV screening into routine care will play a vital role in early identification and intervention, improving the management of both hearing and CMV-related conditions in resource-limited settings.

Heart disease

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Efficacy and Safety of Colchicine in Pediatric Pericarditis: A Systematic Review and Future Directions

[Mohammed Alsabri^{1,2}](#), [Sarah Makram Elsayed³](#), [Ahmed Bostamy Elsnhory⁴](#), [Khaled Abouelmagd⁵](#), [Mohammed Ayyad⁶](#), [Basel F Alqeeq⁷](#), [Abdelmonem Siddiq⁸](#), [Yousef Soliman⁹](#), [Muhammad Azan Shahid¹⁰](#)

Abstract

Pediatric pericarditis presents challenges in its management, necessitating effective therapeutic interventions. Colchicine, known for its efficacy in adults, requires further investigation for its application and safety in pediatric cohorts. A systematic search across renowned databases identified relevant literature on colchicine use in pediatric pericarditis. Twenty-nine articles underwent rigorous screening, with 18 studies meeting inclusion criteria. Data extraction, quality assessment, and synthesis were conducted meticulously. Included studies comprised case reports, case series, and retrospective cohort studies. Colchicine demonstrated efficacy in reducing recurrence rates and symptom burden, with doses ranging from 0.25 mg/day to 2 mg/day. Adverse events were minimal, predominantly gastrointestinal. Notably, nausea was the most common side effect reported. The safety profile of colchicine was favorable, with rare instances of hepatic and hematologic toxicity. Colchicine emerges as a promising therapeutic option for pediatric pericarditis, demonstrating efficacy in reducing recurrence rates and alleviating symptoms. Its favorable safety profile suggests potential as a preferred long-term therapy. However, further research, including randomized controlled trials, is warranted to confirm its efficacy and safety and explore potential combination therapies.

Rheumatic heart disease

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Long-term antibiotic prophylaxis for prevention of rheumatic fever recurrence and progression to rheumatic heart disease

[Jonathan Jh Bray¹](#), [Sophie Thompson²](#), [Samuel Seitler³](#), [Syed Ahsan Ali⁴](#), [Janice Yiu⁵](#), [Mahan Salehi⁶](#), [Mahmood Ahmad⁷](#), [Ferruccio Pelone^{8,9}](#), [Hyeriju Gashau¹⁰](#), [Farhad Shokrane^{9,11,12,13}](#), [Nida Ahmed¹⁴](#), [Miryan Cassandra¹⁵](#), [Eloi Marijon¹⁶](#), [David S Celermajer¹⁷](#), [Rui Providencia¹⁴](#)

Abstract

Background: Rheumatic fever is a non-suppurative, inflammatory sequela of group A Streptococcus pharyngitis that can occur at two to four weeks after infection. Following an episode of rheumatic fever, there is a risk of developing rheumatic heart disease (RHD) later in life that carries significant risk of morbidity and mortality. RHD remains the largest global cause of cardiovascular disease in the young (age < 25 years). The historical literature provides inconclusive evidence that antibiotic prophylaxis is beneficial in reducing the risk of recurrence of rheumatic fever and development of RHD. Antibiotics are thought to work by

reducing the carriage of group A Streptococcus and thus reducing the risk of infection. This review was commissioned by the World Health Organization (WHO) for an upcoming guideline.

Objectives: 1. To assess the effects of long-term antibiotics versus no antibiotics (control) for secondary prevention of rheumatic fever recurrence and associated sequelae in people with previous rheumatic fever or RHD. 2. To assess the effects of long-term intramuscular penicillin versus long-term oral antibiotics for secondary prevention of rheumatic fever recurrence and associated sequelae in people with previous rheumatic fever or RHD.

Search methods: We systematically searched CENTRAL, MEDLINE, Embase, Conference Proceedings Citation Index-Science, clinical trial registers, ISRCTN.com and reference lists without restrictions on language or date up to 10 March 2024.

Selection criteria: We sought randomised controlled trials or quasi-randomised trials, described in any language, including participants with previous rheumatic fever and/or RHD of any age, based in community or hospital settings. Studies were included if they compared firstly antibiotic prophylaxis with no antibiotic prophylaxis, and, secondly, intramuscular penicillin prophylaxis versus oral antibiotic prophylaxis.

Data collection and analysis: We used standardised methodological, Cochrane-endorsed procedures and performed meta-analyses with risk ratios (RR) and Peto odds ratios (Peto OR). Our primary outcomes were recurrence of rheumatic fever, progression or severity of RHD and cardiac complications. Our secondary outcomes were obstetric complications (maternal and foetal events), mortality, treatment adherence, adverse events and acceptability to participants. We performed comprehensive assessments of risk of bias and certainty of evidence, applying the GRADE methodology.

Main results: We included 11 studies (seven RCTs and four quasi-randomised trials) including 3951 participants. The majority of the included studies were conducted in the USA, UK and Canada during the 1950s to 1960s. Most participants with previous rheumatic fever had been diagnosed using the modified Jones criteria (mJC) (four studies), were an average of 12.3 years of age and 50.6% male. We assessed the majority of the included studies to be at high risk of bias, predominantly relating to blinding and attrition bias. Comparison one: antibiotics versus no antibiotics Pooled meta-analysis of six RCTs provides moderate-certainty evidence that antibiotics overall (oral or intramuscular) probably reduce the risk of recurrence of rheumatic fever substantially (0.7% versus 1.7%, respectively) (risk ratio (RR) 0.39, 95% confidence interval (CI) 0.22 to 0.69; 1721 participants). People with early or mild RHD likely have the greatest capacity to benefit from intramuscular antibiotic prophylaxis (8.1%) compared to no antibiotics (0.7%) (RR 0.09, 95% CI 0.03 to 0.29; 1 study, 818 participants; moderate-certainty evidence). Antibiotics may not affect mortality in people with late-stage RHD (RR 1.23, 95% CI 0.78 to 1.94; 1 study, 994 participants; low-certainty evidence). Antibiotics may not affect the risk of anaphylaxis (Peto odds ratio (OR) 7.39, 95% CI 0.15 to 372; 1 study, 818 participants; low-certainty evidence) or sciatic nerve injury (Peto OR 7.39, 95% CI 0.15 to 372; 1 study, 818 participants; low-certainty evidence) compared with no antibiotics, but probably have an increased risk of hypersensitivity reactions (RR 137, 8.51 to 2210; 2 studies, 894 participants; moderate-certainty evidence) and local reactions (RR 29, 1.74 to 485; 1 study, 818 participants; moderate-certainty evidence). Comparison two: intramuscular antibiotics versus oral antibiotics Pooled analysis of two RCTs showed that prophylactic intramuscular benzathine benzylpenicillin likely reduces recurrence of rheumatic fever substantially when compared to oral antibiotics (0.1% versus 1%, respectively) (RR 0.07, 95% CI 0.02 to 0.26; 395 participants; moderate-certainty evidence).

Furthermore, it is unclear whether intramuscular benzyl penicillin is superior to oral antibiotics in reducing the risk of mortality in the context of RHD (Peto OR 0.22, 95% CI 0.01 to 4.12; 1 study, 431 participants; very low-certainty evidence). There were no data available on progression of latent RHD or adverse events including anaphylaxis, sciatic nerve injury, delayed hypersensitivity/allergic reactions and local reactions to injection.

Authors' conclusions: This review provides evidence that antibiotic prophylaxis likely reduces the risk of recurrence of rheumatic fever compared to no antibiotics, and that intramuscular benzathine benzylpenicillin is probably superior to oral antibiotics (approximately 10 times better). Moreover, intramuscular benzathine benzylpenicillin likely reduces the risk of progression of latent RHD. Evidence is scarce, but antibiotics compared with no antibiotics may not affect the risk of anaphylaxis or sciatic nerve injury, but probably carry an increased risk of hypersensitivity reactions and local reactions. Antibiotics may not affect all-cause mortality in late-stage RHD compared to no antibiotics. There is no evidence available to comment on the effect of intramuscular penicillin over oral antibiotics for progression of latent RHD and adverse events, and little evidence for all-cause mortality. It is important to interpret these findings in the context of major limitations, including the following: the vast majority of the included studies were conducted more than 50 years ago, many before contemporary echocardiographic studies; methodology was often at high risk of bias; outdated treatments were used; only one study was in latent RHD; and there are concerns regarding generalisability to low socioeconomic regions. This underlines the need for ongoing research to understand who benefits most from prophylaxis.

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Enhanced support for adherence to rheumatic heart disease prophylaxis for children in the public health system in Uganda (CAMPS): a pragmatic randomised trial

[Sarah de Loizaga¹](#), [Jafesi Pulle²](#), [Okumu Atanas²](#), [Juliet Alepere²](#), [Jane-Liz Nambogo²](#), [Emma Ndagire²](#), [Gloria Kaudha²](#), [Nicholas J Ollberding³](#), [Emmy Okello²](#), [Joselyn Rwebembera²](#), [Andrea Beaton⁴](#)

Abstract

Background: Secondary antibiotic prophylaxis is the only intervention known to prevent rheumatic heart disease progression, yet delivery of prophylaxis at scale in low-resource settings has proven challenging, undermining many global programmes. We sought to assess whether enhanced prophylaxis support for rheumatic heart disease, administered through community health workers in the public health system, was feasible and a scalable model.

Methods: The CAMPS trial was a pragmatic randomised trial of prophylaxis supports integrated into routine care in Eastern Uganda. Children and adolescents with rheumatic heart disease who were aged 5-17 years were randomly assigned (1:1) using permuted block randomisation to either usual care or enhanced support. Enhanced support consisted of case managers and peer groups. Participants and providers were not masked to treatment assignment due to the study design. Children were followed up for 12 months to compare the primary outcome of prophylaxis adherence, measured as a continuous variable of days covered, using a modified intention-to-treat analysis principle. Secondary outcomes were treatment satisfaction, and patient and caregiver health-related quality of life scores. This trial is registered at ClinicalTrials.gov, [NCT05502042](#), and has been completed.

Findings: Between Aug 9, 2022, and Aug 9, 2023, 208 individuals were enrolled in the study and included in the analysis. 104 (50%) individuals were randomly assigned to the usual care group and 105 (50%) to the enhanced support group; one participant in the usual care group was excluded from the primary analysis as they died before the first injection, meaning that 103 participants were analysed in the usual care group. 121 (58%) participants were female and 87 (42%) were male. After 12 months, mean adherence was 80·0% (SD 19·0) for those receiving usual care, compared with 98·2% (7·1) for those receiving enhanced support (estimated mean difference in adherence of 18·2%, 95% CI 14·4-22·1; $p<0\cdot0001$). No significant differences were found between groups in treatment satisfaction (mean between-group difference of 0·1 points [95% CI -1·9 to 2·1] at 12 months) or quality of life (2·3 [-1·1 to 5·8] for patient score; 1·3 [-1·6 to 4·1] for caregiver score).

Interpretation: The integration of community health workers into rheumatic heart disease supports within the public health system provides an effective and likely scalable model to improve outcomes for children with rheumatic heart disease in low-resource settings. Further research should examine scale-up and scale-out of these strategies, formally explore cost, and rigorously partner with diverse groups of patients to shape adaptations to this design and ensure appropriateness for all groups affected by rheumatic heart disease.

Congenital heart disease and cardiac surgery

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[The effect of individualized nutrition training of children with congenital heart disease \(CHD\) on their growth and development a randomized controlled trial](#)

[Emel Yuruk¹](#), [Senay Cetinkaya²](#)

Abstract

Objective: This study investigated the effectiveness of individualized nutrition training for mothers of children who underwent congenital heart disease (CHD) surgery on their children's growth and development.

Methods: The researchers conducted a randomized controlled trial at Çukurova University Medical Faculty Balcalı Hospital in Adana, Turkey, between January 20th, 2021, and June 30th, 2021. They recruited 42 children with CHD and their families. Researchers used a personal information form, growth parameter measurements, and the Ankara Developmental Screening Inventory to assess the children. Participants were randomly divided into three groups. Control group, received standard care. Experimental group 1 (orally fed), received family-centered care and individualized nutrition training focused on age-appropriate food content, preparation methods, and meeting children's caloric needs. Experimental group 2 (orally and nutritionally fed), received the same interventions as group 1. The training programs for the experimental groups included information on strengthening breast milk and additional nutritional nutrition support. The training programs for the experimental groups likely addressed feeding challenges specific to children with CHD.

Results: The study found a statistically significant difference in weight gain between the first and third follow-ups within the training group (children who received individualized nutrition education). This suggests that the training may have positively impacted weight

gain. Additionally, the children in the training groups who were breastfed for longer than 12 months had better growth parameters and developmental scores compared to those with shorter breastfeeding durations.

Conclusion: This study suggests that individualized nutrition training for mothers of children with CHD surgery may support their children's growth and development, particularly when combined with prolonged breastfeeding.

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Population Pharmacokinetics and Target Attainment of Allopurinol and Oxypurinol Before, During, and After Cardiac Surgery with Cardiopulmonary Bypass in Neonates with Critical Congenital Heart Disease

[Wan-Yu Chu^{#12}](#), [Maaïke Nijman^{#345}](#), [Raymond Stegeman³⁴⁶](#), [Johannes M P J Breur⁴](#), [Nicolaas J G Jansen⁶⁷](#), [Joppe Nijman⁷](#), [Kim van Loon⁸](#), [Erik Koomen⁷](#), [Karel Allegaert⁹¹⁰](#), [Manon J N L Benders³](#), [Thomas P C Dorlo¹²](#), [Alwin D R Huitema¹¹¹²¹³](#); [CRUCIAL trial consortium](#)

Abstract

Background: The CRUCIAL trial ([NCT04217421](#)) is investigating the effect of postnatal and perioperative administration of allopurinol on postoperative brain injury in neonates with critical congenital heart disease (CCHD) undergoing cardiac surgery with cardiopulmonary bypass (CPB) shortly after birth.

Objective: This study aimed to characterize the pharmacokinetics (PK) of allopurinol and oxypurinol during the preoperative, intraoperative, and postoperative phases in this population, and to evaluate target attainment of the current dosing strategy.

Methods: Nonlinear mixed-effects modeling was used to develop population PK models in 14 neonates from the CRUCIAL trial who received up to five intravenous allopurinol administrations throughout the postnatal and perioperative periods. Target attainment was defined as achieving an allopurinol concentration >2 mg/L in at least two-thirds of the patients during the first 24 h after birth and between the start and 36 h after cardiac surgery with CPB.

Results: A two-compartment model for allopurinol was connected to a one-compartment model for oxypurinol with an auto-inhibition effect on the conversion, which best described the PK. In a typical neonate weighing 3.5 kg who underwent cardiac surgery at a postnatal age (PNA) of 5.6 days, the clearance (CL) of allopurinol and oxypurinol at birth was 0.95 L/h (95% confidence interval 0.75-1.2) and 0.21 L/h (0.17-0.27), respectively, which subsequently increased with PNA to 2.97 L/h and 0.41 L/h, respectively, before CPB. During CPB, allopurinol and oxypurinol CL decreased to 1.38 L/h (0.9-1.87) and 0.12 L/h (0.05-0.22), respectively. Post-CPB, allopurinol CL increased to 2.21 L/h (1.74-2.83), while oxypurinol CL dropped to 0.05 L/h (0.01-0.1). Target attainment was 100%, 53.8%, and 100% at 24 h postnatally, 24 h after the start of CPB, and 36 h after the end of cardiac surgery, respectively. The combined concentrations of allopurinol and oxypurinol maintained $\geq 90\%$ inhibition of xanthine oxidase (IC_{90xO}) throughout the postnatal and perioperative period.

Conclusions: The minimal target concentration of allopurinol was not achieved at every predefined time interval in the CRUCIAL trial; however, the dosing strategy used was deemed adequate, since it yielded concentrations well exceeding the IC_{90xO}. The decreased CL of both compounds during CPB suggests influence of the hypothermia, hemofiltration, and the

potential sequestration of allopurinol in the circuit. The reduced CL of oxypurinol after CPB is likely attributable to impaired kidney function.

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Optimizing Recovery: Early Versus Delayed Chest Tube Removal in Pediatric Cardiac Surgery Patients: A Randomized Controlled Trial

[Abdulraouf M Z Jijeh^{1,2,3}](#), [Ghassan A Shaath^{1,2,3}](#), [Sameh R Ismail^{1,2,3}](#), [Mohamed S Kabbani^{1,2,3}](#), [Omar M Hijazi^{1,3}](#), [Hayan Altaweel¹](#), [Husam Hamada¹](#), [Ammar Qadi¹](#), [Anis Fatima¹](#), [Abdrabo Abdrabo¹](#), [Wiaam Ahmed¹](#), [Nuha Ahmed¹](#), [Ahmed Elsaoudi¹](#), [Ahmed Yousef¹](#), [Rehana Shafi¹](#), [Husam I Ardah^{3,4}](#), [Ahmad Elwy⁵](#), [Abdullah A Alghamdi^{2,3,5}](#)

Abstract

Objectives: To evaluate the safety and efficacy of an early chest tube removal protocol in reducing tube duration without increasing complications following pediatric cardiac surgery.

Design: A single-center, randomized controlled trial.

Setting: Pediatric cardiac ICU.

Patients: Two hundred fifteen pediatric patients with chest tubes after cardiac surgery.

Interventions: Patients were randomized to early removal (drainage threshold < 6 mL/kg over 8 hr) or late removal (24-hr assessment) groups. Primary outcomes included chest tube duration, whereas secondary outcomes encompassed ICU stay, ventilation time, hospital stay, and complication rates.

Measurements and main results: Median chest tube duration was significantly shorter in the early removal group (3 d) compared with the late removal group (4.9 d; $p < 0.0001$). Rates of fluid reaccumulation and pneumothorax were low and comparable between groups. Notably, no patients in either group required tube reinsertion. ICU and total hospital stay durations were similar across groups.

Conclusions: An early chest tube removal protocol following pediatric cardiac surgery suggests a reduction in chest tube duration without increasing the risk of complications. These findings support the adoption of an evidence-based early removal approach to enhance patient comfort and optimize ICU resource utilization in pediatric cardiac surgery patients.

HIV / AIDS

HIV diagnosis and disclosure

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Impact of point-of-care birth test-and-treat on clinical outcomes among infants with HIV: A cluster randomized trial in Mozambique and Tanzania

[Ilesh V Jani¹](#), [Issa Sabi²](#), [Kira Elsbernd^{3,4}](#), [Bindiya Meggi¹](#), [Arlete Mahumane¹](#), [Anange Fred Lwilla²](#), [Kassia Pereira¹](#), [Siriel Boniface²](#), [Raphael Edom²](#), [Joaquim Lequechane¹](#), [Falume Chale¹](#), [Nhamo Chiwerengo²](#), [Nyanda E Ntinginya²](#), [Chishamiso Mudenyanga⁵](#), [Mariana](#)

[Mueller³](#), [Martina Rauscher⁶](#), [Michael Hoelscher^{3,7,6,8}](#), [Nuno Taveira⁹](#), [W Chris Buck¹⁰](#), [Arne Kroidl^{3,7}](#), [LIFE study consortium](#)

Abstract

Background: We assessed the impact of point-of-care (PoC) test-and-treat at birth on clinical outcomes and viral suppression among HIV-positive infants in Mozambique and Tanzania.

Methods: This cluster-randomized trial allocated health facilities to intervention, providing PoC-testing and antiretroviral treatment (ART) at birth and week 4-8, or control, starting these at week 4-8. The primary outcome was proportions of clinical events (mortality, morbidity, retention, virological failure, toxicity) among HIV-positive infants at month-18. We estimated incidence rate ratios adjusted for timing of HIV-detection (aIRR) and reported viral suppression <1000 copies/mL.

Findings: Among 6602 neonates enrolled October 2019-September 2021, 125 were diagnosed HIV-positive by week 12. In the intervention arm, 38/69 (55.1%) were diagnosed at birth with 35 initiating ART within two days. In the control arm, 27/56 (48.2%) were retrospectively detected HIV-positive at birth, of whom 6/56 (10.7%) died or were lost to follow-up before testing. Median age at ART initiation was 6 (intervention) versus 33 days (control). Birth test-and-treat was not associated with a significant reduction in clinical outcomes up to month-18 [53 (76.8%) versus 48 (85.7%); aIRR 0.857; 95% CI 0.505-1.492], but showed a 68% relative reduction in 6-month mortality. Viral suppression was poor overall, but improved in the intervention group at month 18 (65.7% versus 29.6%; $p=0.005$).

Interpretation: PoC test-and-treat at birth is feasible in resource-poor settings and resulted in clinically-relevant reduction of early infant mortality, though improved clinical outcomes were not sustained to month-18. Poor viral suppression may undermine early survival benefits, calling for better paediatric treatments and tailored adherence interventions.

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[Impact of children's age on parental HIV disclosure: a parental HIV disclosure intervention among parents living with HIV in China](#)

[Wendi Da^{1,2}](#), [Ran Zhang^{1,2}](#), [Yuejiao Zhou³](#), [Zhiyong Shen³](#), [Shan Qiao^{1,2}](#), [Xiaoming Li^{1,2}](#)

Abstract

Parental HIV disclosure, where parents living with HIV (PLH) communicate their diagnosis to their children, is crucial for family communication. This study assessed intervention effects of a parental HIV disclosure intervention on psychosocial factors, focusing on child's age impact. Data from a randomized controlled trial involving 791 PLH in China were analyzed at baseline (W1), 6-month (W2), and 12-month follow-ups (W3). The study measured effects on psychosocial factors (HIV disclosure knowledge, outcome expectancy, action self-efficacy, and action planning) using the proportional latent change score method. Among PLH with children aged 6-9, the intervention yielded significant intervention effects on knowledge ($\Delta = 0.190$, $p = .004$), action self-efficacy ($\Delta = 0.342$, $p = .001$), and action planning ($\Delta = 0.389$, $p < .001$) from W1 to W2. For PLH with children aged 10-12, the intervention significantly enhanced action self-efficacy ($\Delta = 0.162$, $p = .003$) and action planning ($\Delta = 0.367$, $p = .001$) from W1 to W2, but there was a reduction in perceived benefits ($\Delta = -0.175$, $p = 0.024$) from W2 to W3. For PLH with children aged 13-15, significant intervention effects were observed on action planning, both from W1 to W2 ($\Delta = 0.251$, $p = .045$) and from W2 to W3 ($\Delta = 0.321$, $p <$

.001). These findings highlight the importance of tailoring interventions to consider psychosocial factors and children's developmental stages to enhance HIV disclosure practices.

Prevention of mother to child transmission

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Bone Mineral Content, Growth, and Renal Health of Infants With Perinatal Exposure to Maternal Dolutegravir Versus Efavirenz and Tenofovir Disoproxil Fumarate Versus Tenofovir Alafenamide: The Randomized IMPAACT 2010 (VESTED) Trial

[Tapiwa G Mbengeranwa¹](#), [Lauren Ziemba²](#), [Sean S Brummel²](#), [Ben Johnston³](#), [Haseena Cassim⁴](#), [Gerhard Theron⁵](#), [Zukiswa Ngqawana⁶](#), [Deo Wabwire⁷](#), [Katie McCarthy⁸](#), [John Shepherd⁹](#), [Shahin Lockman^{2,10,11}](#), [Lameck Chinula¹²](#), [Lynda Stranix-Chibanda^{1,13}](#); [IMPAACT 2010/VESTED study team and investigators](#)

Abstract

Background: The impact on infant bone, growth, and renal health of in utero and breast milk exposure to contemporary antiretroviral treatment (ART) remains unclear.

Methods: Six hundred forty-three pregnant women with HIV in 9 countries in Africa, Asia, and the Americas were randomized to start ART with dolutegravir (DTG) + emtricitabine (FTC)/tenofovir alafenamide (TAF), DTG + FTC/tenofovir disoproxil fumarate (TDF), or efavirenz (EFV)/FTC/TDF between 14 and 28 weeks' gestation and continued for 50 weeks postpartum. Pairwise comparisons used 2-sample t tests of mean week 26 infant bone mineral content (BMC) assessed by dual-energy X-ray absorptiometry in a subset; mean infant z-scores for length-for-age z-score (LAZ), weight-for-age z-score (WAZ), and weight-for-length (WLZ) at 26 and 50 weeks; and mean infant creatinine and estimated creatinine clearance at birth and 26 weeks.

Results: Five hundred seventy-seven infants were included in the growth analysis, and 169 in the dual-energy X-ray absorptiometry analysis. Week 26 infant spine BMC was significantly lower in the EFV/FTC/TDF arm (133.5 g) than in the DTG + FTC/tenofovir alafenamide [143.4 g; mean difference (95% confidence intervals): 0.22 (0.02, 0.42) g] and DTG + FTC/TDF [137.4; mean difference (95% confidence interval): 0.20 (0.01, 0.40) g] arms. Mean LAZ and WAZ scores through week 50 were also significantly lower in the EFV/FTC/TDF versus DTG arms, but not WLZ. Infant obesity was rare (2%-4%) and similar between arms. There was no apparent by-arm difference in infant creatinine or estimated creatinine clearance through week 50 (P-values ≥ 0.18).

Conclusions: It is reassuring that maternal DTG-based ART during pregnancy and breastfeeding was associated with higher infant spine BMC, better growth, and less stunting than EFV/FTC/TDF.

J Acquir Immune Defic Syndr. 2024 Aug;96(4):385-392.

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Characterizing HIV drug resistance in cases of vertical transmission in the VESTED randomized antiretroviral treatment trial

[Marley D Bishop¹](#), [Violet Korutaro²](#), [Ceejay L Boyce¹](#), [Ingrid A Beck¹](#), [Sheila M Styrchak¹](#), [Kevin Knowles³](#), [Lauren Ziemba⁴](#), [Sean S Brummel⁴](#), [Anne Coletti⁵](#), [Patrick Jean-Philippe⁶](#), [Nahida Chakhtoura⁷](#), [Tichaona Vhembo⁸](#), [Haseena Cassim⁹](#), [Maxensia Owor¹⁰](#), [Lee Fairlie¹¹](#), [Sikhulile Moyo^{12,13}](#), [Lameck Chinula¹⁴](#), [Shahin Lockman^{12,13,15}](#), [Lisa M Frenkel^{1,16}](#)

Abstract

Introduction: VESTED ([NCT03048422](#)) compared the safety and efficacy of three antiretroviral treatment (**ART**) regimens in pregnant and postpartum women:

dolutegravir+emtricitabine/tenofovir alafenamide fumarate;

dolutegravir+emtricitabine/tenofovir disoproxil fumarate (**TDF**);

efavirenz/emtricitabine/TDF. Vertical HIV transmission (**VT**) occurred to 4/617 (0.60%) live-born infants, who were evaluated for HIV drug resistance (**HIVDR**) and other risk factors.

Setting: In 2018-2020, pregnant (weeks-14-28) women living with HIV and ≤14 days of ART were enrolled at 22 international sites and followed with their infants through 50 weeks postpartum.

Methods: HIV sequences derived by single genome amplification (**SGA**) from longitudinally collected specimens were assessed from VT Cases for HIVDR in protease, reverse transcriptase, integrase, and the *nef* 3' polypurine tract (**3'PPT**).

Results: The four Case mothers were prescribed efavirenz-based-ART for 1-7 days prior to randomization to study ART. Their infants received postnatal nevirapine+/-zidovudine prophylaxis and were breastfed. A total of 833 SGA sequences were derived. The "major" (Stanford HIVDR Score ≥60) non-nucleoside reverse transcriptase inhibitor (**NNRTI**) mutation (K103N) was detected persistently in one viremic mother, and likely contributed to VT of HIVDR. Major NNRTI HIVDR mutations were detected in all three surviving infants. No integrase, nor high frequencies of 3'PPT mutations conferring dolutegravir HIVDR were detected. The timing of HIV infant diagnosis, plasma HIV RNA levels and HIVDR suggests one *in utero*, one peripartum, one early, and one late breastfeeding transmission.

Conclusions: VT was rare. New-onset NNRTI HIVDR in Case mothers was likely from efavirenz-ART prescribed prior to study dolutegravir-ART, and in one case appeared transmitted to the infant despite nevirapine prophylaxis.

AIDS. 2024 Jul 15;38(9):1304-1313.

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Effects of preterm birth, maternal ART and breastfeeding on 24-month infant HIV-free survival in a randomized trial

[Sufia Dadabhai^{1,2}](#), [Victoria B Chou³](#), [Mauricio Pinilla⁴](#), [Lameck Chinula^{5,6}](#), [Maxensia Owor⁷](#), [Avy Violari⁸](#), [Dhayendre Moodley⁹](#), [Lynda Stranix-Chibanda^{10,11}](#), [Taguma Allen Matubu¹²](#), [Gift Tafadzwa Chareka¹³](#), [Gerhard Theron¹²](#), [Aarti Avinash Kinikar¹³](#), [Mwangelwa Mubiana-Mbewe¹⁴](#), [Lee Fairlie¹⁵](#), [Raziya Bobat¹⁶](#), [Blandina Theophil Mmbaga¹⁷](#), [Patricia M Flynn¹⁸](#), [Taha E Taha¹](#), [Katie S McCarthy¹⁹](#), [Renee Browning²⁰](#), [Lynne M Mofenson²¹](#), [Sean S Brummel⁴](#), [Mary Glenn Fowler³](#); [IMPAACT PROMISE 1077BF/FF team](#)

Abstract

Background: IMPAACT 1077BF/FF (PROMISE) compared the safety/efficacy of two HIV antiretroviral therapy (ART) regimens to zidovudine (ZDV) alone during pregnancy for HIV prevention. PROMISE found an increased risk of preterm delivery (<37 weeks) with

antepartum triple ART (TDF/FTC/LPV+r or ZDV/3TC/LPV+r) compared with ZDV alone. We assessed the impact of preterm birth, breastfeeding, and antepartum ART regimen on 24-month infant survival.

Methods: We compared HIV-free and overall survival at 24 months for liveborn infants by gestational age, time-varying breastfeeding status, and antepartum ART arm at 14 sites in Africa and India. Kaplan-Meier survival probabilities and Cox proportional hazards ratios were estimated.

Results: Three thousand four hundred and eighty-two live-born infants [568 (16.3%) preterm and 2914 (83.7%) term] were included. Preterm birth was significantly associated with lower HIV-free survival [0.85; 95% confidence interval (CI) 0.82-0.88] and lower overall survival (0.89; 95% CI 0.86-0.91) versus term birth (0.96; 95% CI 0.95-0.96). Very preterm birth (<34 weeks) was associated with low HIV-free survival (0.65; 95% CI 0.54-0.73) and low overall survival (0.66; 95% CI 0.56-0.74). Risk of HIV infection or death at 24 months was higher with TDF-ART than ZDV-ART (adjusted hazard ratio 2.37; 95% CI 1.21-4.64). Breastfeeding initiated near birth decreased risk of infection or death at 24 months (adjusted hazard ratio 0.05; 95% CI 0.03-0.08) compared with not breastfeeding.

Conclusion: Preterm birth and antepartum TDF-ART were associated with lower 24-month HIV-free survival compared with term birth and ZDV-ART. Any breastfeeding strongly promoted HIV-free survival, especially if initiated close to birth. Reducing preterm birth and promoting infant feeding with breastmilk among HIV/antiretroviral drug-exposed infants remain global health priorities.

J Infect Dis. 2024 Nov 15;230(5):1224-1234.

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Dolutegravir- Versus Efavirenz-Based Treatment in Pregnancy: Impact on Red Blood Cell Folate Concentrations in Pregnant Women and Their Infants

[Denise L Jacobson¹](#), [Krista S Crider²](#), [Patricia DeMarrais¹](#), [Sean Brummel¹](#), [Mindy Zhang³](#), [Christine M Pfeiffer³](#), [Cynthia A Moore⁴](#), [Katie McCarthy⁵](#), [Benjamin Johnston⁶](#), [Terence Mohammed⁷](#), [Tichaona Vhembo⁸](#), [Enid Kabugho⁹](#), [Gerald Agaba Muzorah¹⁰](#), [Haseena Cassim¹¹](#), [Lee Fairlie¹²](#), [Elizabeth S Machado¹³](#), [James S Ngocho¹⁴](#), [Roger L Shapiro¹⁵](#), [Lena Serghides¹⁶](#), [Nahida Chakhtoura¹⁷](#), [Lameck Chinula¹⁸](#), [Shahin Lockman^{19,20}](#)

Abstract

Background: In the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) 2010/VESTED study, pregnant women were randomized to initiate dolutegravir (DTG) + emtricitabine (FTC)/tenofovir alafenamide (TAF), DTG + FTC/tenofovir disoproxil fumarate (TDF), or efavirenz (EFV)/FTC/TDF.

Methods: We assessed red blood cell (RBC) folate concentrations at maternal study entry and delivery, and infant birth. RBC folate outcomes were (1) maternal change entry to delivery (trajectory), (2) infant, and (3) ratio of infant-to-maternal delivery. Generalized estimating equation models for each log(folate) outcome were fit to estimate adjusted geometric mean ratio (Adj-GMR)/GMR trajectories (Adj-GMRTs) of each arm comparison in 340 mothers and 310 infants.

Results: Overall, 90% of mothers received folic acid supplements and 78% lived in Africa. At entry, median maternal age was 25 years, gestational age was 22 weeks, CD4 count was 482 cells/ μ L, and log₁₀ HIV RNA was 3 copies/mL. Entry RBC folate was similar across arms. Adj-

GMRT of maternal folate was 3% higher in the DTG + FTC/TAF versus EFV/FTC/TDF arm (1.03 [95% confidence interval {CI}, 1.00-1.06]). The DTG + FTC/TAF arm had an 8% lower infant-maternal folate ratio (0.92 [95% CI, .78-1.09]) versus EFV/FTC/TDF.

Conclusions: Results are consistent, with no clinically meaningful differences between arms for all RBC folate outcomes, and they suggest that cellular uptake of folate and folate transport to the infant do not differ in pregnant women starting DTG- versus EFV-based antiretroviral therapy.

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Lower Insulin Sensitivity Through 36 Months of Life With in Utero HIV and Antiretroviral Exposure in Botswana: Results From the Tshilo Dikotla Study

[Jennifer Jao^{1,2,3}](#), [Lauren B Bonner⁴](#), [Katrina Dobinda⁴](#), [Kathleen M Powis^{3,5,6}](#), [Shan Sun²](#), [Justine Legbedze²](#), [Keolebogile N Mmasa⁷](#), [Joseph Makhema³](#), [Mompoti Mmalane³](#), [Samuel Kgole³](#), [Gosego Masasa³](#), [Sikhulile Moyo³](#), [Mariana Gerschenson⁸](#), [Terence Mohammed³](#), [Elaine J Abrams⁹](#), [Irwin J Kurland¹⁰](#), [Mitchell E Geffner¹¹](#)

Abstract

Background: There are little data on changes in insulin sensitivity during the first few years of life following in utero human immunodeficiency virus (HIV) and antiretroviral (ARV) exposure.

Methods: The Tshilo Dikotla study enrolled pregnant persons with HIV (PWH) (receiving tenofovir/emtricitabine or lamivudine plus dolutegravir or efavirenz) and pregnant individuals without HIV, as well as their liveborn children. Newborns were randomized to receive either zidovudine (AZT) or nevirapine (NVP) postnatal prophylaxis. Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) was assessed at birth and 1, 18, 24, and 36 months of life. We fit linear mixed-effects models to evaluate the association between in utero HIV/ARV exposure and average HOMA-IR from birth through 36 months of life, adjusting for confounders.

Results: A total of 419 children were included (287 with in utero HIV/ARV exposure and uninfected [CHEU] and 132 without in utero HIV/ARV exposure [CHUU]). CHEU were born to older women (29.6 vs 25.3 years of age) with higher gravidity (3 vs 1). HOMA-IR was persistently higher in CHEU versus CHUU in adjusted analyses (mean difference of 0.07 in log₁₀ HOMA-IR, P = .02) from birth through 36 months of life. Among CHEU, no differences in HOMA-IR were observed from birth through 36 months by in utero ARV exposure status or between AZT and NVP infant prophylaxis arms.

Conclusions: In utero HIV/ARV exposure was associated with lower insulin sensitivity throughout the first 36 months of life, indicating persistent early life metabolic disturbances which may raise concern for poorer metabolic health later in life.

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Risk of Congenital Anomalies with Dolutegravir-Based Anti-retroviral Regimens: A Systematic Review and Meta-analysis

[Shuvasree Payra¹](#), [Divya Harsha¹](#), [Keshav Kumar¹](#), [Pramod Kumar Manjhi¹](#), [Shruti Singh¹](#), [Rajesh Kumar¹](#), [Sunil Kumar Singh¹](#), [Alok Kumar¹](#), [Vikas Maharshi²](#)

Abstract

Background and objectives: Dolutegravir has been used as a first-line anti-human immunodeficiency virus drug because of its better efficacy compared with other counterpart medicines. However, making a unanimous decision on its use during pregnancy has become difficult for stakeholders following congenital anomalies reported with its use. The objective of this systematic review and meta-analysis was to study the risk of congenital anomalies in newborns exposed to dolutegravir-based-regimens compared with those exposed to non-dolutegravir-based regimens during the antenatal period.

Methods: An extensive literature search was performed in MEDLINE (through PubMed), EMBASE, Cochrane Database of Systematic Reviews, Google Scholar, and ClinicalTrials.gov until 30 November, 2023. Studies reporting data on congenital anomalies following antenatal use of dolutegravir were included. Risk of bias for randomized controlled trials, non-randomized controlled trials, and observational studies was assessed using RoB2, ROBINS-I, and ROBINS-E tools, respectively. A meta-analysis was performed in 'RevMan 5.4.1' using a random-effects model. Heterogeneity was assessed by the 'Q' statistic and I^2 value. A sensitivity analysis was performed for higher heterogeneity/high-risk studies. The study protocol was registered in PROSPERO [CRD42023446374] a priori.

Results: Of 26 eligible studies, 12 (six randomized controlled trials and six observational studies with a pooled sample of 32,617) were included in a meta-analysis and 14 in a qualitative synthesis only. The meta-analysis does not show a statistically significant difference in the risk of congenital anomalies between newborns exposed antenatally to dolutegravir-based regimen(s) and those exposed to non-dolutegravir-based regimens [risk ratio 1.10; 95% confidence interval 0.79-1.53; $p = 0.59$]. Heterogeneity was moderate ($I^2 = 47\%$). Pooled results for randomized controlled trials and observational studies separately and the sensitivity analysis for heterogeneity provided similar results.

Conclusions: The risk of congenital anomalies was not significantly different between dolutegravir-based regimens and non-dolutegravir-based-regimens in newborns exposed during their antenatal period.

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Inflammation, antiretroviral therapy continuation, and HIV disease progression in postpartum women with HIV

[Rupak Shivakoti¹](#), [Mark J Giganti²](#), [Michael M Lederman³](#), [Rachel Ketchum²](#), [Sean Brummel²](#), [Daniela Moisi³](#), [Allen T Matubu⁴](#), [Sufia Dadabhai^{5,6}](#), [Dhayendre Moodley⁷](#), [Avy Violari⁸](#), [Lameck Chinula⁹](#), [Maxensia Owor¹⁰](#), [Amita Gupta¹¹](#), [Taha E Taha⁵](#), [Patricia M Flynn¹²](#), [Judith S Currier¹³](#), [Mary Glenn Fowler¹⁴](#); [PROMISE study team](#)

Abstract

Background: Higher levels of inflammation are associated with increased HIV disease progression, but data are lacking in postpartum women with HIV (WHIV), who generally have a distinct immune profile. Further, the impact of discontinuation of antiretroviral therapy

(ART) on inflammation is not well understood for postpartum women. We studied the relationship of ART discontinuation, inflammation, and HIV disease progression in postpartum WHIV.

Setting: We conducted a 1:3 case-control study (N=347) nested within a multi-country randomized trial comparing postpartum ART continuation vs. discontinuation in WHIV with WHO clinical stage 1 disease and who did not meet criteria for ART at the time. Median follow-up time was 97.1 weeks.

Methods: Cases were defined as WHIV who progressed to HIV disease stage 2 or greater during follow-up. Controls were selected using a risk set sampling strategy. Plasma levels of inflammatory biomarkers interleukin-6 (IL-6), interferon γ (IFN γ), tumor necrosis factor α (TNF α), intestinal fatty acid-binding protein (I-FABP), soluble CD14(sCD14) and CD163 (sCD163) before (i.e., baseline) and 4 weeks after randomization were measured using immunoassays. Weighted multivariable regression models assessed the association between inflammation with HIV disease progression, by randomization arm (ART continuation vs. discontinuation).

Results: Postpartum WHIV with higher levels of baseline I-FABP and persistently high levels of IFN γ and TNF α had increased hazards of HIV disease progression. Significantly larger increases in I-FABP and sCD14, and smaller increases in TNF α and sCD163 between baseline and week 4 were observed for postpartum participants who continued ART than among those who discontinued ART.

Conclusion: Postpartum WHIV with higher levels of immune biomarkers have increased hazards of HIV disease progression, suggesting an important role for inflammation in HIV treatment outcomes. Our results showed that continuation of ART compared to discontinuation had differential impacts on various immune markers, with the discontinuation results relevant in settings of poor adherence, or treatment interruption.

Antiretroviral therapy (ART)

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[Virological outcomes and genotypic resistance on dolutegravir-based antiretroviral therapy versus standard of care in children and adolescents: a secondary analysis of the ODYSSEY trial](#)

[Ellen White](#)¹, [Cissy Kityo](#)², [Moirra J Spyder](#)³, [Hilda A Mujuru](#)⁴, [Immaculate Nankya](#)⁵, [Adeodata R Kekitiinwa](#)⁶, [Abbas Lugemwa](#)⁷, [Elizabeth Kaudha](#)², [Afaaf Liberty](#)⁸, [Haseena Cassim](#)⁸, [Moherndran Archary](#)⁹, [Mark F Cotton](#)¹⁰, [Grace Miriam Ahimbisibwe](#)¹¹, [Tim R Cressey](#)¹², [Chaiwat Ngampiyaskul](#)¹³, [Ussanee Srirompotong](#)¹⁴, [Osee Behuhuma](#)¹⁵, [Yacine Saidi](#)¹⁶, [Alasdair Bamford](#)¹⁷, [Robin Kobbe](#)¹⁸, [Eleni Nastouli](#)³, [Pablo Rojo](#)¹⁹, [Carlo Giaquinto](#)²⁰, [Diana M Gibb](#)²¹, [Deborah Ford](#)²¹, [Anna Turkova](#)¹⁷; [ODYSSEY trial team](#)

Abstract

Background: ODYSSEY showed superior efficacy for dolutegravir-based antiretroviral therapy (ART) versus standard of care (SOC) in children living with HIV starting first-line or second-line ART aged 4 weeks or older. Here, we aim to compare virological outcomes and

resistance in the dolutegravir group versus SOC for first-line and second-line ART up to 96 weeks.

Methods: ODYSSEY was an open-label, multicentre, randomised, non-inferiority trial done in 29 centres in seven countries (Germany, Spain, South Africa, Thailand, the UK, Uganda, and Zimbabwe). ODYSSEY recruited children living with HIV aged at least 28 days and younger than 18 years, weighing at least 3 kg, starting first-line ART (ODYSSEY A), or switching to second-line therapy after treatment failure (ODYSSEY B). Children were randomly assigned (1:1) to dolutegravir plus two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs; dolutegravir group) versus the SOC group (non-nucleoside reverse transcriptase inhibitor [NNRTI], boosted protease inhibitor, or non-dolutegravir integrase strand-transfer inhibitor, plus two NRTIs). Two randomised cohorts were combined in this exploratory analysis: children weighing at least 14 kg were enrolled between Sept 20, 2016, and June 22, 2018, and children weighing less than 14 kg were enrolled between July 5, 2018, and Aug 26, 2019. Virological failure was defined as an inadequate virological response at week 24 with an ART switch or confirmed HIV-1 RNA viral load of at least 400 copies per mL after week 36. Virological suppression was defined as two consecutive viral loads of less than 400 copies per mL and was compared between groups, including an ART switch and death as competing risks. Children with virological failure were tested for post-failure genotypic resistance, with baseline results used to identify emergent resistance. Development of emergent resistance was a secondary trial outcome and all other outcomes are exploratory. ODYSSEY was registered with ClinicalTrials.gov ([NCT02259127](https://clinicaltrials.gov/ct2/show/study/NCT02259127)), EUDRACT (2014-002632-14), and ISRCTN (ISRCTN91737921).

Findings: In ODYSSEY at enrolment, 381 participants started first-line ART (ODYSSEY A: 189 in the dolutegravir group and 192 in the SOC group) and 407 participants started second-line ART (ODYSSEY B: 202 in the dolutegravir group and 205 in the SOC group). 72 participants in ODYSSEY A and 13 participants in ODYSSEY B weighed less than 14 kg. 401 (51%) of 788 participants were female and 387 (49%) were male. Virological suppression occurred significantly earlier in the dolutegravir group (adjusted [cause-specific] hazard ratio [HR] 1.57 [95% CI 1.35 to 1.83]; $p<0.0001$). Overall, 51 (13%) participants had virological failure by 96 weeks in the dolutegravir group versus 86 (22%) in the SOC group (including 18 [10%] vs 43 [22%] in ODYSSEY A and in 33 [16%] vs 43 [21%] in ODYSSEY B; adjusted HR 0.56 [0.40 to 0.79]; $p=0.0011$). Among ODYSSEY B participants starting dolutegravir, virological failure was higher in children starting zidovudine (HR 2.22 [1.01 to 4.88]; $p=0.048$) and similar in those starting tenofovir disoproxil fumarate (1.19 [0.50 to 2.83]; $p=0.70$) compared with abacavir. Time to virological suppression was marginally faster in participants receiving second-line dolutegravir and abacavir with high-level abacavir resistance at baseline compared with those with no, low-level, intermediate-level resistance (cause-specific HR 1.70 [1.01 to 2.85]; $p=0.046$); and failure rates by week 96 were similar (HR 0.90 [0.23 to 3.61]; $p=0.88$). An estimated 1% (95% CI 0 to 2) of participants in the dolutegravir group versus 20% (14 to 26) in the SOC group in ODYSSEY A had emergent resistance to at least one drug-class within their first-line regimen (risk difference -20% [-25 to -14]; $p<0.0001$); 4% (1 to 6) versus 5% (2 to 8) had resistance to drug within their initial second-line regimen (risk difference -1% [-5 to 3]; $p=0.60$). 3% (0 to 5) of participants in the dolutegravir group had emergent integrase strand-transfer inhibitors resistance compared with 3% (1 to 6) of participants in the SOC group who had emergent resistance to the anchor drug (risk difference 0% [-4 to 3]; $p=0.78$).

Interpretation: Dolutegravir led to faster virological suppression and lower risk of virological failure than NNRTIs and boosted protease inhibitor-based SOC. Participants

starting second-line dolutegravir-based ART with an abacavir or tenofovir backbone were at lower risk of virological failure than those starting zidovudine. During first-line therapy, dolutegravir protected against emergent resistance; starting second-line therapy, the risk of emergent resistance to nucleoside reverse transcriptase inhibitor backbone, and anchor drugs, was similar among participants starting dolutegravir within their second-line regimen and those starting mainly boosted protease inhibitor-based SOC.

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[A prediction model for virologic failure in adolescents living with HIV in Uganda: Findings from the Suubi+Adherence study](#)

[Samuel Kizito](#)¹, [Fred M Ssewamala](#)², [Torsten B Neilands](#)³, [Proscovia Nabunya](#)², [Phionah Namatovu](#)⁴, [Josephine Nabayinda](#)², [Mary M McKay](#)², [Kimberly J Johnson](#)², [Ross Brownson](#)²

Abstract

Objectives: Adolescents living with HIV (ALHIV) have low viral suppression levels, with 1 in 3 ALHIV experiencing virologic failure, calling for more efforts to reverse these trends. We developed and validated a model that predicts the risk of virologic failure (VF) among ALHIV.

Study design: Cross-sectional study.

Methods: We used baseline data from 702 ALHIV enrolled in the Suubi + Adherence cluster-randomized clinical trial. Participants were aged 10-16 years, living with HIV and aware of their HIV status, and are living with a family. We developed a risk-prediction model for VF (viral load of ≥ 200 copies/mL) using sociodemographic, behavioral, psychological, economic, and treatment-related factors. LASSO logistic regression using 10-fold cross-validation with bootstrapping was used to select the predictors for the final model. Model performance was assessed by determining the discrimination using the area under the curve and calibration by drawing a calibration plot.

Results: Using a lambda value of 0.007, the final model had 24 predictors (and interaction terms). The predictors included the participants' age, sex, work status, stigma, depressive symptoms, adherence self-efficacy, HIV knowledge, duration with HIV, time spent on ART, communication with the caregiver, family cohesion, social support, orphanhood status, number of people in the household, HIV disclosure, years spent at the current residence, and household asset ownership. The model predicted VF with AUC of 73.8 (95 % CI: 68.3-78.0) and calibration slope of 0.985.

Conclusions: We developed and validated a model to predict the risk of virologic failure among ALHIV in Uganda, demonstrating its potential utility in identifying individuals at elevated risk for VF. Future models could be refined by incorporating clinical characteristics such as CD4 count to further improve predictive accuracy.

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[Resistance-informed versus empirical management of viraemia in children and adolescents with HIV in Lesotho and Tanzania \(GIVE MOVE trial\): a multisite, open-label randomised controlled trial](#)

[Jennifer Anne Brown¹](#), [Isaac Kaumbuthu Ringera²](#), [Ezekiel Luoga³](#), [Moniek Bresser⁴](#), [Buoang Mothobi⁵](#), [Lorraine Kabundi⁶](#), [Mulume Ilunga⁶](#), [Kuen Mokhele⁵](#), [Andreas Boy Isaac⁶](#), [Ntsepiseng Tsoaeli⁶](#), [Thomas Mbaya⁶](#), [Brenda Simba⁷](#), [Kasasi Mayogu⁷](#), [Elizabeth Mabula⁷](#), [Molisana Cheleboi⁸](#), [Mamello Molatelle⁸](#), [Namvua Kimera⁹](#), [Getrud Joseph Mollel³](#), [David Sando⁷](#), [Nadine Tschumi¹](#), [Alain Amstutz¹⁰](#), [Lineo Thahane¹¹](#), [Mosa Molapo Hlasoa⁶](#), [Buntshi Paulin Kayembe⁶](#), [Josephine Muhairwe⁵](#), [Thomas Klimkait¹²](#), [Tracy Renée Glass⁴](#), [Maja Weisser¹³](#), [Niklaus Daniel Labhardt¹⁴](#)

Abstract

Background: Children and adolescents with HIV taking antiretroviral therapy (ART) have high rates of viraemia. We assessed if genotypic resistance testing (GRT) to inform onward treatment improved treatment outcomes in Lesotho and Tanzania, two countries with little access to GRT.

Methods: The Genotype-Informed Versus Empirical Management of Viremia (GIVE MOVE) open-label, parallel-group randomised controlled trial enrolled children and adolescents with HIV between the ages of 6 months and 19 years, taking ART, and with a viral load at least 400 copies per mL. Participants were recruited from ten clinical centres and hospitals in Lesotho and Tanzania. Participants were electronically randomly allocated 1:1 to receive either GRT with expert recommendation (GRT group) or repeat viral-load testing and empirical onward treatment (usual care group). Participants and study staff were not masked, but the endpoint committee and laboratory staff conducting viral-load testing were. Participants in both groups received at least three sessions of enhanced adherence counselling, and in the GRT group, blood for GRT assessed via Sanger sequencing was drawn at enrolment. The composite primary endpoint was death, hospitalisation, a new WHO HIV clinical stage 4 event, or not having documented viral suppression of less than 50 copies per mL at 36 weeks in the modified intention-to-treat population, which excluded participants who were retrospectively found to be ineligible after randomisation. Serious adverse events were analysed in the modified intention-to-treat population. The trial was registered with ClinicalTrials.gov ([NCT04233242](#)) and the trial status is completed.

Findings: Between March 3, 2020, and July 5, 2022, 286 participants were enrolled and 284 were included in the modified intention-to-treat analysis (144 in the GRT group and 140 in the usual care group). Of these participants, 158 (56%) were female and 126 (44%) were male. Five (3%) in the GRT group and four (3%) in the usual care group did not complete follow-up but were included in the primary analysis. The median age across both groups was 14 years (IQR 9-16). The composite primary endpoint occurred in 67 (47%) participants in the GRT group and 73 (52%) in the usual care group (adjusted odds ratio 0.79 [95% CI 0.49 to 1.27]; adjusted risk difference -0.06 [95% CI -0.17 to 0.06]; $p=0.34$); all participants reaching the composite primary endpoint had no documented viral suppression at 36 weeks. No deaths were recorded, and only one clinical stage 4 event requiring hospitalisation occurred (in the usual care group); this was the only serious adverse event recorded in the study.

Interpretation: GRT-informed management did not significantly improve treatment outcomes for children and adolescents with viraemia while taking ART.

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[Second-Line Antiretroviral Therapy for Children Living with HIV in Africa](#)

[Victor Musiime^{1,2}](#), [Mutsa Bwakura-Dangarembizi^{3,4}](#), [Alexander J Szubert⁵](#), [Vivian Mumbiro⁴](#), [Hilda A Mujuru³](#), [Cissy M Kityo²](#), [Abbas Lugemwa⁶](#), [Katja Doerholt⁵](#), [Chishala Chabala⁷](#), [Shafic Makumbi⁸](#), [Veronica Mulenga⁷](#), [Helen McIlleron⁹](#), [David Burger¹⁰](#), [Eva Natukunda²](#), [Clare Shakeshaft⁵](#), [Kyomuhendo Jovia Linda²](#), [Kusum Nathoo⁴](#), [Lara Monkiewicz⁵](#), [Ibrahim Yawe¹¹](#), [Monica Kapasa¹²](#), [Mary Nyathi¹³](#), [Joyce Lungu⁷](#), [Bwendo Nduna¹⁴](#), [Wedu Ndebele¹⁵](#), [Annabelle South⁵](#), [Mwate Mwamabazi¹⁴](#), [Godfrey Musoro⁴](#), [Anna Griffiths⁵](#), [Khozya Zyambo¹²](#), [Rashidah Nazzinda²](#), [Kevin Zimba¹²](#), [Yingying Zhang¹⁶](#), [Simon Walker¹⁶](#), [Anna Turkova⁵](#), [A Sarah Walker⁵](#), [Alasdair Bamford^{5,17}](#), [Diana M Gibb⁵](#); [CHAPAS-4 Trial Team](#)

Abstract

Background: Children living with human immunodeficiency virus (HIV) have limited options for second-line antiretroviral therapy (ART).

Methods: In this open-label trial with a 2-by-4 factorial design, we randomly assigned children with HIV who had first-line treatment failure to receive second-line therapy with tenofovir alafenamide fumarate (TAF)-emtricitabine or standard care (abacavir or zidovudine, plus lamivudine) as the backbone and dolutegravir or ritonavir-boosted darunavir, atazanavir, or lopinavir as the anchor drug. The primary outcome was a viral load of less than 400 copies per milliliter at 96 weeks. We hypothesized that TAF-emtricitabine would be noninferior to standard care, that dolutegravir and ritonavir-boosted darunavir would each be superior to ritonavir-boosted lopinavir and atazanavir analyzed in combination, and that ritonavir-boosted atazanavir would be noninferior to ritonavir-boosted lopinavir. Safety was also assessed.

Results: A total of 919 children underwent randomization; 458 were assigned to receive TAF-emtricitabine, and 461 to receive standard care. Assigned anchor drugs were dolutegravir (229 participants), ritonavir-boosted darunavir (232), ritonavir-boosted atazanavir (231), and ritonavir-boosted lopinavir (227). The median age of participants was 10 years, and 497 (54.1%) were male. The median viral load at baseline was 17,573 copies per milliliter. At week 96, TAF-emtricitabine was superior to standard care: the adjusted difference in the percentage of participants with a viral load of less than 400 copies per milliliter was 6.3 percentage points (95% confidence interval [CI], 2.0 to 10.6; $P = 0.004$). Dolutegravir was superior to ritonavir-boosted lopinavir and atazanavir analyzed in combination (adjusted difference, 9.7 percentage points; 95% CI, 4.8 to 14.5; $P < 0.001$), but ritonavir-boosted darunavir was not (adjusted difference, 5.6 percentage points; 95% CI, 0.3 to 11.0; $P = 0.04$ [prespecified threshold, $P = 0.03$]). Ritonavir-boosted atazanavir was noninferior to ritonavir-boosted lopinavir. One child died, and 29 (3.2%) had serious adverse events, with no significant between-group differences.

Conclusions: Second-line ART regimens including TAF-emtricitabine and dolutegravir were effective for children, with no evidence of safety concerns. Ritonavir-boosted darunavir was also effective. (Funded by the European and Developing Countries Clinical Trials Partnership and others; CHAPAS-4 ISRCTN Registry number, ISRCTN22964075.).

HIV-exposed infants and children

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Growth, physical, and cognitive function in children who are born HIV-free: School-age follow-up of a cluster-randomised trial in rural Zimbabwe

[Joe D Piper^{1,2,3}](#), [Clever Mazhanga¹](#), [Marian Mwapaura¹](#), [Gloria Mapako¹](#), [Idah Mapurisa¹](#), [Tsitsi Mashedze¹](#), [Eunice Munyama¹](#), [Maria Kuona¹](#), [Thombizodwa Mashiri¹](#), [Kundai Sibanda¹](#), [Dzidzai Matemavi¹](#), [Monica Tichagwa¹](#), [Soneni Nyoni¹](#), [Asinje Saidi¹](#), [Manasa Mangwende¹](#), [Dzivaidzo Chidhanguro¹](#), [Eddington Mpofu¹](#), [Joice Tome¹](#), [Gabriel Mbewe¹](#), [Batsirai Mutasa¹](#), [Bernard Chasekwa¹](#), [Handrea Njovo⁴](#), [Chandiwana Nyachowe⁴](#), [Mary Muchekeza⁴](#), [Kuda Mutasa¹](#), [Virginia Sauramba¹](#), [Ceri Evans^{1,5}](#), [Melissa J Gladstone⁵](#), [Jonathan C Wells⁶](#), [Elizabeth Allen³](#), [Melanie Smuk²](#), [Jean H Humphrey⁷](#), [Lisa F Langhaug¹](#), [Naume V Tavengwa¹](#), [Robert Ntozini¹](#), [Andrew J Prendergast^{1,2}](#)

Abstract

Background: Globally, over 16 million children were exposed to HIV during pregnancy but remain HIV-free at birth and throughout childhood by 2022. Children born HIV-free (CBHF) have higher morbidity and mortality and poorer neurodevelopment in early life compared to children who are HIV-unexposed (CHU), but long-term outcomes remain uncertain. We characterised school-age growth, cognitive and physical function in CBHF and CHU previously enrolled in the Sanitation Hygiene Infant Nutrition Efficacy (SHINE) trial in rural Zimbabwe.

Methods and findings: The SHINE trial enrolled pregnant women between 2012 and 2015 across 2 rural Zimbabwean districts. Co-primary outcomes were height-for-age Z-score and haemoglobin at age 18 months (clinicaltrials.gov [NCT01824940](#)). Children were re-enrolled if they were aged 7 years, resident in Shurugwi district, and had known pregnancy HIV-exposure status. From 5,280 pregnant women originally enrolled, 376 CBHF and 2016 CHU reached the trial endpoint at 18 months in Shurugwi; of these, 264 CBHF and 990 CHU were evaluated at age 7 years using the School-Age Health, Activity, Resilience, Anthropometry and Neurocognitive (SAHARAN) toolbox. Cognitive function was evaluated using the Kaufman Assessment Battery for Children (KABC-II), with additional tools measuring executive function, literacy, numeracy, fine motor skills, and socioemotional function. Physical function was assessed using standing broad jump and handgrip for strength, and the shuttle-run test for cardiovascular fitness. Growth was assessed by anthropometry. Body composition was assessed by bioimpedance analysis and skinfold thicknesses. A caregiver questionnaire measured demographics, socioeconomic status, nurturing, child discipline, food, and water insecurity. We prespecified the primary comparisons and used generalised estimating equations with an exchangeable working correlation structure to account for clustering. Adjusted models used covariates from the trial (study arm, study nurse, exact child age, sex, calendar month measured, and ambient temperature). They also included covariates derived from directed acyclic graphs, with separate models adjusted for contemporary variables (socioeconomic status, household food insecurity, religion, social support, gender norms, caregiver depression, age, caregiver education, adversity score, and number of children's books) and early-life variables (length-for-age-Z-score) at 18 months, birthweight, maternal baseline depression, household diet, maternal schooling and haemoglobin, socioeconomic status, facility birth, and gender norms. We applied a Bonferroni correction for the 27 comparisons (0.05/27) with threshold of $p < 0.00185$ as significant. We found strong evidence that cognitive function was lower in CBHF compared to CHU across multiple domains. The KABC-II mental processing index was 45.2 (standard

deviation (SD) 10.5) in CBHF and 48.3 (11.3) in CHU (mean difference 3.3 points [95% confidence interval (95% CI) 2.0, 4.5]; $p < 0.001$). The school achievement test score was 39.0 (SD 26.0) in CBHF and 45.7 (27.8) in CHU (mean difference 7.3 points [95% CI 3.6, 10.9]; $p < 0.001$); differences remained significant in adjusted analyses. Executive function was reduced but not significantly in adjusted analyses. We found no consistent evidence of differences in growth or physical function outcomes. The main limitation of our study was the restriction to one of two previous study districts, with possible survivor and selection bias.

Conclusions: In this study, we found that CBHF had reductions in cognitive function compared to CHU at 7 years of age across multiple domains. Further research is needed to define the biological and psychosocial mechanisms underlying these differences to inform future interventions that help CBHF thrive across the life-course.

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Growth of children who are HIV-exposed but uninfected: a systematic review and meta-analysis

[Gabriel Loni Ekali¹](#), [Pascal Roland Enok Bonong²](#), [Cyprien Kengne-Nde³](#), [Julie Jesson⁴](#), [Ceri Evans⁵](#), [Andrew J Prendergast⁶](#), [Valérie Leroy⁴](#)

Abstract

Background: Pooled analyses summarising long-term growth outcomes in children who are HIV-exposed uninfected (HEU) compared with children who are HIV-unexposed (HU) are lacking. We aimed to summarise the existing literature on growth outcomes.

Methods: We did a systematic review and meta-analysis of published literature on 60-month growth outcomes (length-for-age Z score [LAZ], weight-for-age Z score [WAZ], weight-for-length Z score [WLZ], head circumference-for-age Z score [HCAZ], stunting [LAZ<-2], wasting [WLZ<-2], underweight [WAZ<-2], and microcephaly [HCAZ<-2]) in children who were HEU compared with children who were HU. Medline, EMBASE, Cochrane Library, WHO Global Index Medicus and Web of Science were searched from Jan 1, 1989 to Dec 31, 2022. Randomised controlled trials and cohort studies comparing growth in children who were HEU versus children who were HU were included. Study-specific estimates were pooled by use of random-effects and fixed-effect meta-analysis. Results were stratified by age (birth; 0-5 months; 6-11 months; 12-17 months; 18-23 months; and 24-60 months) and antiretroviral therapy (ART) period (pre-ART [before 2003]; ART [2003 onwards]). This study is registered with PROSPERO, CRD42018091762.

Findings: 28 studies were included; 25 (90%) were done in Africa and 23 (82%) in the ART period, reporting growth outcomes on 11 794 children who were HEU and 23 826 children who were HU from 15 countries. Across all ages in the pre-ART and ART periods, children who were HEU had significantly lower LAZ compared with children who were HU. In the ART period, children who were HEU were more likely to be stunted at all ages except for 0-5 months. Pre-ART, significantly lower WAZ was found in children who were HEU from 6-11 months to 18-23 months, and at all ages during the ART period. Children who were HEU had significantly higher odds of underweight at birth than children who were HU; this difference persisted to age 2 years. Pre-ART and ART HCAZ were significantly lower for children who were HEU at all ages, except for 24-60 months, even though heterogeneity was high. No differences in WLZ were found between groups. Differences between children who were HEU

and children who were HU tended to be more pronounced during the ART period compared with the pre-ART period, particularly at younger ages.

Interpretation: Children who are HEU have more growth faltering than children who are HU, which is present at birth and persists over the first 24 months. These growth disparities remain evident during the ART period. Interventions to promote healthy growth probably need to start antenatally.

Chronic co-morbidity in paediatric HIV

BMC Pulm Med. 2024 Jul 12;24(1):339.

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[Longitudinal lung function trajectories in response to azithromycin therapy for chronic lung disease in children with HIV infection: a secondary analysis of the BREATHE trial](#)

[Tafadzwa Madanhire^{1,2}](#), [Grace McHugh³](#), [Victoria Simms^{3,4}](#), [Lucky Ngwira⁵](#), [Carmen Gonzalez-Martinez^{5,6}](#), [Robina Semphere⁶](#), [Brewster Moyo⁵](#), [Claire Calderwood^{3,7}](#), [Mark Nicol^{8,9}](#), [Tsitsi Bandason³](#), [Jon O Odland^{10,11}](#), [Andrea M Rehman⁴](#), [Rashida A Ferrand^{3,7}](#)

Abstract

Background: Chronic lung disease (CLD) is common among children with HIV (CWH) including in those taking antiretroviral therapy (ART). Azithromycin has both antimicrobial and anti-inflammatory effects and has been effective in improving lung function in a variety of lung diseases. We investigated lung function trajectories among CWH with CLD on ART enrolled in a randomized controlled trial of adjuvant azithromycin. We also investigated factors that modified the effect of azithromycin on lung function.

Methods: The study used data from a double-blinded placebo-controlled trial conducted in Malawi and Zimbabwe of 48 weeks on azithromycin (BREATHE:

ClinicalTrials.gov [NCT02426112](#)) among CWH aged 6 to 19 years taking ART for at least six months who had a forced expiratory volume in one second (FEV₁) z-score <-1.0. Participants had a further follow-up period of 24 weeks after intervention cessation. FEV₁, forced vital capacity (FVC) and FEV₁/FVC were measured at baseline, 24, 48 and 72-weeks and z-scores values calculated. Generalized estimating equations (GEE) models were used to determine the mean effect of azithromycin on lung-function z-scores at each follow-up time point.

Results: Overall, 347 adolescents (51% male, median age 15 years) were randomized to azithromycin or placebo. The median duration on ART was 6.2 (interquartile range: 3.8-8.6) years and 56.2% had an HIV viral load < 1000copies/ml at baseline. At baseline, the mean FEV₁ z-score was - 2.0 (0.7) with 44.7% (n = 155) having an FEV₁ z-score <-2, and 10.1% had microbiological evidence of azithromycin resistance. In both trial arms, FEV₁ and FVC z-scores improved by 24 weeks but appeared to decline thereafter. The adjusted overall mean difference in FEV₁ z-score between the azithromycin and placebo arms was 0.004 [-0.08, 0.09] suggesting no azithromycin effect and this was similar for other lung function parameters. There was no evidence of interaction between azithromycin effect and baseline age, lung function, azithromycin resistance or HIV viral load.

Conclusion: There was no observed azithromycin effect on lung function z-scores at any time point suggesting no therapeutic effect on lung function.

Nutrition, growth and development in children with HIV

Cotrimoxazole, isoniazid and antimalarial preventative therapy

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[Isoniazid preventive therapy during infancy does not adversely affect growth among HIV-exposed uninfected children: Secondary analysis of data from a randomized controlled trial](#)

[Ashenafi Shumey Cherkos](#)¹, [Sylvia M LaCourse](#)^{2,3,4}, [Daniel A Enquobahrie](#)², [Jaclyn N Escudero](#)⁴, [Jerphason Mecha](#)⁵, [Daniel Matemo](#)⁶, [John Kinuthia](#)^{6,7}, [Sarah J Iribarren](#)⁸, [Grace John-Stewart](#)^{2,3,4,9}

Abstract

Background: Isoniazid preventive therapy (IPT) decreases risk of tuberculosis (TB) disease; impact on long-term infant growth is unknown. In a recent randomized trial (RCT), we assessed IPT effects on infant growth without known TB exposure.

Methods: The infant TB Infection Prevention Study (iTIPS) trial was a non-blinded RCT among HIV-exposed uninfected (HEU) infants in Kenya. Inclusion criteria included age 6-10 weeks, birthweight ≥ 2.5 kg, and gestation ≥ 37 weeks. Infants in the IPT arm received 10 mg/kg isoniazid daily for 12 months, while the control trial received no intervention; post-trial observational follow-up continued through 24 months of age. We used intent-to-treat linear mixed-effects models to compare growth rates (weight-for-age z-score [WAZ] and height-for-age z-score [HAZ]) between trial arms.

Results: Among 298 infants, 150 were randomized to IPT, 47.6% were females, median birthweight was 3.4 kg (interquartile range [IQR] 3.0-3.7), and 98.3% were breastfed. During the 12-month intervention period and 12-month post-RCT follow-up, WAZ and HAZ declined significantly in all children, with more HAZ decline in male infants. There were no growth differences between trial arms, including in sex-stratified analyses. In longitudinal linear analysis, mean WAZ ($\beta = 0.04$ [95% CI: -0.14, 0.22]), HAZ ($\beta = 0.14$ [95% CI: -0.06, 0.34]), and WHZ [$\beta = -0.07$ [95% CI: -0.26, 0.11)] z-scores were similar between arms as were WAZ and HAZ growth trajectories. Infants randomized to IPT had higher monthly WHZ increase (β to 24 months 0.02 [95% CI: 0.01, 0.04]) than the no-IPT arm.

Conclusion: IPT administered to HEU infants did not significantly impact growth outcomes in the first two years of life.

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doi: 10.1002/jcph.6193. Epub 2025 Jan 24.

[Extended Treatment Duration of Artemether-Lumefantrine in Ugandan Children with HIV on Efavirenz-Based Antiretroviral Therapy: A Randomized Controlled Pharmacokinetic and Pharmacodynamic Trial](#)

[Meghan E Whalen](#)¹, [Richard Kajubi](#)², [Justin Goodwin](#)³, [Francis Orukan](#)², [McKenzie Colt](#)³, [Liusheng Huang](#)¹, [Kacey Richards](#)³, [Thomas J Hoffmann](#)⁴, [Francesca T Aweeka](#)¹, [Sunil Parikh](#)³, [Norah Mwebaza](#)^{2,5}

Abstract

Malaria and HIV co-infection are prevalent in sub-Saharan Africa causing significant drug interactions with co-treatment. We previously reported a 30%-70% reduction in exposure to the standard 3-day (6-dose) artemether-lumefantrine (AL) treatment for malaria when given with efavirenz-based HIV therapy, impacting malaria reinfection risk. We conducted a prospective, randomized study comparing the 3-day regimen to an extended 5-day (10-dose) regimen with pharmacokinetic sampling for artemether, dihydroartemisinin, lumefantrine, and desbutyl-lumefantrine (DBL) over 42 days. The primary outcome was comparative pharmacokinetics between regimens compared among children with HIV and among children without HIV receiving a 3-day regimen as controls (median age 5.3 years [range 1.4-13.9]; median weight 17.3 kg [range 8.7-39.1]). Children with HIV (n = 57; median age 10.8 years [range 3.4-17.1]; median weight 26.6 kg [range 14.6-54.5]) contributed 76 malaria episodes, with 71 included in the analysis. Another 97 children without HIV (median age 5.3 years [range 1.4-13.9]; median weight 17.3 kg [range 8.7-39.1]) contributed 114 episodes of malaria, with 109 included in the analysis. In the setting of efavirenz, artemether, dihydroartemisinin, lumefantrine, and DBL cumulative exposure was 2.09, 2.31, 1.90, and 1.65 fold higher with 5-day versus 3-day AL (all $P < .001$), and comparable to 3-day AL in children without HIV. The extended regimen in children with HIV did not result in a statistically significant reduction in recurrence risk at 28 or 42 days. Extending the duration of AL to 5 days compensated for a clinically significant reduction in all components of AL in the context of EFV-based antiretroviral therapy in young children.

HIV-TB coinfection

HIV vaccine

(see Vaccine – HIV vaccine)

Helminth and other gastrointestinal disorders

(See also Anaemia, Diarrhoea, Micronutrients and food fortification, Malaria and HIV)

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doi: 10.1186/s40249-024-01241-0.

Coverage of community-wide mass drug administration platforms for soil-transmitted helminths in Benin, India, and Malawi: findings from the DeWorm3 project

[Arianna Rubin Means](#)^{#12}, [Kristjana Hrönn Ásbjörnsdóttir](#)^{#34}, [Katherine C Sharrock](#)⁵⁴, [Sean R Galagan](#)⁵⁴, [Kumudha Aruldas](#)⁶, [Euripide Avokpaho](#)⁷, [Félicien Chabi](#)⁷, [Katherine E Halliday](#)⁸, [Parfait Houngbegnon](#)⁷, [Gideon John Israel](#)⁶, [Saravanakumar Puthupalayam Kaliappan](#)⁶, [David Kennedy](#)⁸, [Hugo Legge](#)⁸, [William E Oswald](#)⁸⁹, [Gokila Palanisamy](#)⁶, [Elliott Rogers](#)⁸¹⁰, [Joseph Timothy](#)⁸, [Emily Pearman](#)⁴, [Rohan Michael Ramesh](#)⁶, [James Simwanza](#)¹¹, [Jasmine Farzana Sheik-Abdullah](#)⁶, [Mariyam Sheikh](#)⁵⁴, [Comlanvi Innocent Togbevi](#)⁷, [Stefan Witek-McManus](#)⁸¹², [Rachel L Pullan](#)⁸, [Robin Bailey](#)¹³¹¹, [Khumbo Kalua](#)¹¹¹⁴, [Moudachirou Ibikounlé](#)⁷¹⁵, [Adrian J F Luty](#)¹⁶, [Sitara S R Ajampur](#)⁶, [Judd L Walson](#)⁴¹⁷

Abstract

Background: Soil-transmitted helminths (STH) affect approximately 1.5 billion people globally. The current STH control strategy is annual or twice-annual preventive chemotherapy, typically school-based deworming targeting children and women of reproductive age. Mathematical modeling suggests that it may be possible to interrupt STH transmission through high-coverage community-wide mass drug administration (cMDA). DeWorm3 is a cluster randomized trial testing cMDA for prevalence reduction and transmission interruption. The purpose of this study is to describe coverage of cMDA in study clusters over time and correlates of coverage at individual and cluster levels.

Methods: From 2018-2020, DeWorm3 delivered six rounds of cMDA with 400 mg albendazole at sites in Benin, India, and Malawi. We report coverage, treatment uptake, and directly observed therapy across all rounds. Factors associated with coverage at the cluster level were identified using binomial generalized estimating equations, while factors associated with non-treatment at the individual level were identified using binomial mixed-effects models.

Results: Coverage was high across all clusters and rounds, exceeding the WHO target of 75% in all sites and across all rounds (78% to 95%); cluster-level coverage tended to increase over time. Younger, unmarried, and migratory adults were more likely to be untreated at all sites; adult males were more likely to be untreated in Benin and Malawi. Among children, girls were more likely to be untreated, as were non-school-attending and migratory children. Higher adult education was associated with greater odds of non-treatment among adults, but lower odds among children in the household. Belonging to a less wealthy or minority language-speaking household was associated with non-treatment among both adults and children.

Conclusions: It is possible to deliver community-wide MDA with high coverage. Unique individual and community-level factors influence treatment across settings, and these may be addressed through targeted programming.

Lancet. 2024 Aug 17;404(10453):683-691.

doi: 10.1016/S0140-6736(24)01403-X.

[**Efficacy and safety of emodepside compared with albendazole in adolescents and adults with hookworm infection in Pemba Island, Tanzania: a double-blind, superiority, phase 2b, randomised controlled trial**](#)

[Lyndsay Taylor¹, Ahmada Ali Ahmada², Msanif Said Ali², Said Mohammed Ali², Jan Hattendorf¹, Ibrahim Said Mohammed², Jennifer Keiser³](#)

Abstract

Background: Human hookworm is a cause of enormous global morbidity. Current treatments have insufficient efficacy and their extensive and indiscriminate distribution could also result in drug resistance. Therefore, we tested the efficacy and safety of emodepside, a strong anthelmintic candidate that is currently undergoing clinical development for onchocerciasis and soil-transmitted helminth infections.

Methods: We conducted a double-blind, superiority, phase 2b, randomised controlled clinical trial comparing emodepside and albendazole. Participants in the emodepside group received six 5 mg tablets of emodepside (totalling 30 mg) and one placebo; participants in the albendazole group received one 400 mg tablet of albendazole and six placebos.

Participants were recruited from four endemic villages and three secondary schools in Pemba Island, Tanzania. Participants aged 12-60 years were eligible for treatment if they were positive for hookworm infection, and they had 48 or more eggs per gram from four Kato-Katz thick smears and at least two slides had more than one hookworm egg present. Participants' treatment allocation was stratified by infection intensity and efficacy was measured by cure rate: participants who were hookworm positive and became hookworm negative after treatment. Adverse events were reported at 3 h, 24 h, 48 h, and 14-21 days post-treatment. The trial is registered at ClinicalTrials.gov, [NCT05538767](https://clinicaltrials.gov/ct2/show/study/NCT05538767).

Findings: From Sept 15 to Nov 8, 2022, and from Feb 15 to March 15, 2023, 1609 individuals were screened for hookworm. Of these, 293 individuals were treated: 147 with albendazole and 146 with emodepside. Emodepside demonstrated superiority, with an observed cure rate against hookworm of 96.6%, which was significantly higher compared with albendazole (cure rate 81.2%, odds ratio 0.14, 95% CI 0.04-0.35; $p=0.0001$). The most common adverse event in the emodepside treatment group was vision blur at 3 h after treatment (57 [39%] of 146). Other common adverse events were vision blur at 24 h after treatment (55 [38%]), and headache and dizziness at 3 h after treatment (55 [38%] for headache and 43 [30%] for dizziness). In the emodepside treatment group, 298 (93%) of the 319 adverse events were mild. The most commonly reported adverse events in the albendazole treatment group were headache and dizziness at 3 h after treatment (27 [18%] of 147 for headache and 14 [10%] for dizziness). No serious adverse events were reported.

Interpretation: This phase 2b clinical trial confirms the high efficacy of emodepside against hookworm infections, solidifying emodepside as a promising anthelmintic candidate. However, although the observed safety events were generally mild in severity, considerations must be made to balance the strong efficacy outcomes with the increased frequency of adverse events compared with albendazole.

Clin Pharmacol Ther. 2025 Jan;117(1):203-213.

doi: 10.1002/cpt.3424. Epub 2024 Sep 23.

Population Pharmacokinetics and Exposure-Response Analysis of a Fixed-Dose Combination of Ivermectin and Albendazole in Children, Adolescents, and Adults

[Jaime Algorta¹](#), [Stella Kepha²](#), [Alejandro Krolewiecki^{3,4}](#), [Hanbin Li⁵](#), [Justin Giang⁵](#), [Pedro Fleitas⁶](#), [Charles Mwandawiro²](#), [José Muñoz⁶](#); [STOP Consortium](#)

Abstract

Trichuris trichiura is a soil-transmitted helminth causing intestinal disease. Albendazole is the standard treatment despite its moderate efficacy, which is improved when co-administered with ivermectin. A fixed-dose combination adds practical advantages mainly for mass drug administration. The aim of this article is to define the population pharmacokinetic models and exposure-response of an innovative albendazole/ivermectin combination. Data were obtained from a phase I clinical trial in healthy adults and from a phase II trial in children and adolescents infected with *T. trichiura*. Nonlinear mixed-effects models were built for albendazole and ivermectin using NONMEM®. Area under the curve was calculated using the empirical Bayes estimates of the pharmacokinetic parameters of each individual and used for evaluation of exposure-response between cure rate and pharmacokinetic exposure. The pharmacokinetics of albendazole was described using a two-compartmental model with first-order absorption and the pharmacokinetics of ivermectin

was described using a two-compartmental model with zero-order followed by first-order absorption. Clearance and volume of distribution increased with body weight for both albendazole and ivermectin. Day 1 area under the curve of albendazole and ivermectin from the children and adolescents treated with the combination regimens were similar to the healthy adults treated with control drugs. A flat exposure-response relationship was observed between the cure rate and drug exposure. Population pharmacokinetic of a combination of albendazole and ivermectin in children, adolescents, and adults, either healthy or infected by *T. trichiura* was described. The dosage selected in the phase II trial was appropriate for the subsequent phase III.

Lancet Infect Dis. 2025 May;25(5):548-559.

doi: 10.1016/S1473-3099(24)00669-8. Epub 2025 Jan 10.

Albendazole-ivermectin co-formulation for the treatment of *Trichuris trichiura* and other soil-transmitted helminths: a randomised phase 2/3 trial

[Alejandro Krolewiecki¹](#), [Stella Kepha²](#), [Pedro E Fleitas³](#), [Lisette van Lieshout⁴](#), [Woyneshet Gelaye⁵](#), [Augusto Messa Jr⁶](#), [Javier Gandasegui³](#), [Jaime Algorta⁷](#), [Valdemiro Novela⁶](#), [Áuria de Jesus⁶](#), [Martin Rono²](#), [Dawit Degarege⁵](#), [Dereje Bedane⁵](#), [Jusper Mwahanje⁸](#), [Inácio Mandomando⁶](#), [Charles Mwandawiro²](#), [Wendemagegn Enbiale⁵](#), [José Muñoz⁹](#); [Stopping Transmission of Intestinal Parasites \(STOP\) consortium](#)

Abstract

Background: Treatments for soil-transmitted helminthiasis face challenges, especially in addressing *Trichuris trichiura*. Combination regimens, particularly of ivermectin and albendazole, are promising. We aimed to assess the safety, efficacy, and palatability of a combination tablet for the treatment of *T. trichiura*, hookworm, and *Strongyloides stercoralis* infections among school-aged children in Ethiopia, Kenya, and Mozambique.

Methods: We conducted an adaptive phase 2/3, randomised, parallel-group, active-controlled, superiority trial in 15 schools in Ethiopia, Kenya, and Mozambique. Eligible participants for both phases were aged 5-18 years, weighed at least 15 kg, and were infected with *T. trichiura*, hookworms, or *S. stercoralis*. Participants were randomly assigned via a computer-generated sequence to either a single dose of a fixed-dose combination (FDC×1) of albendazole (400 mg) plus ivermectin (9 mg or 18 mg), three consecutive daily doses of an FDC (FDC×3) of albendazole (400 mg) plus ivermectin (9 mg or 18 mg), or a single dose of albendazole alone (400 mg) via block randomisation, stratified by soil-transmitted helminth species. Participants and those administering the treatments were not masked to treatment assignment, but those assessing the outcomes were masked. The primary outcome of phase 2 (conducted in Kenya only) was safety during the first 3 h after the intervention and for 7 days, and the primary outcome of phase 3 was efficacy (ie, the proportion of individuals cured at day 21 out of the total number infected at baseline) for *T. trichiura*; both primary outcomes were analysed in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, [NCT05124691](#), and is terminated.

Findings: Between Jan 20, 2022, and March 24, 2023, 1001 participants were recruited (465 [46%] were female and 536 [54%] were male). 636 (64%) were infected with *T. trichiura*, 360 (36%) with hookworm, and 104 (10%) with *S. stercoralis*; 94 (9%) of 1001 participants had co-infections and were included in the analysis of each infecting species. A total of 243 participants were allocated to the albendazole group, 381 to the FDC×1 group, and 377 to the

FDC×3 group. In both phase 2 and 3, gastrointestinal symptoms were the most common mild-to-moderate adverse events in the FDC groups, but resolved within 48 h without intervention. At least one treatment-related adverse event occurred in 34 (14%) of 243 participants in the albendazole group, 75 (20%) of 381 participants in the FDC×1 group, and 88 (23%) of 377 participants in the FDC×3 group. No serious adverse events occurred. For *T trichiura*, both FDC groups had a higher cure rate (97·2% [95% CI 95·2- 99·3] for FDC×3 and 82·9% [78·2-87·5] for FDC×1) than albendazole (35·9% [27·7-44·1]), with absolute differences of 61·3% (98% CI 50·2-71·2) and 47·0% (34·7-58·1), respectively. For hookworms, FDC×3 had a higher cure rate (95·0% [95% CI 91·1-98·9]) than albendazole (65·1% [56·0-74·2]), with absolute differences of 29·9% (98% CI 17·2-42·4), whereas FDC×1 had a similar cure rate (79·8% [72·8-86·9]) to albendazole. The sample size for efficacy evaluation of *S stercoralis* was not met.

Interpretation: An FDC of albendazole plus ivermectin has a similar safety profile but superior efficacy to albendazole alone against *T trichiura* infection and hookworms. These findings open opportunities for control of all soil-transmitted helminth species of interest, including potentially *S stercoralis*. Evaluation of safety in larger populations and implementation scenarios are the next steps for this innovation to promote its incorporation into programmatic activities.

J Epidemiol Glob Health. 2024 Sep;14(3):884-904.

doi: 10.1007/s44197-024-00231-7. Epub 2024 May 2.

Efficacy of Albendazole and Mebendazole Against Soil Transmitted Infections among Pre-School and School Age Children: A Systematic Review and Meta-Analysis

[Temesgen Bekele](#)¹, [Lata Lachisa](#)¹, [Arega Tsegaye](#)¹, [Ketema Bacha](#)¹, [Tsige Ketema](#)²

Abstract

Background: Soil-transmitted helminthic (STH) infections are the leading cause of stunting among children. To lessen the burden, the World Health Organization (WHO) recommended a periodic deworming program through the use of single-dose therapy in the endemic regions. Therefore, the purpose of this study was to synthesize evidence about the efficacy of anthelmintic drugs against STH infections among preschool and school-age children.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed in this study. Relevant electronic databases, including PubMed, Scopus, Embase, DOAJ, Science Direct, the WHO Clinical Trials.gov library, Google Scholar, and AJOL databases, were searched for relevant publications. Randomized controlled trials (RCTs) and non-randomized interventional studies focused on the efficacy of albendazole and mebendazole against STHs in children were included in the study. Review Manager was used to analyze the data. A random effects model was used to obtain the pooled estimated efficacy. To evaluate heterogeneity, the I^2 test and Cochrane Q (χ^2) were employed. The risk of publication bias was investigated using Egger's test and the funnel plot. The protocol of this review was registered at the PROSPERO international prospective register of systematic reviews (CRD42023401196).

Results: Of the 69 publications selected for the systematic review, 66 with complete data were included in the meta-analysis. Single doses of albendazole and mebendazole have shown satisfactory efficacy [egg reduction rate (ERR)] against *Ascaris lumbricoides* [95.54%

(95% CI: 88.75-102.34%) and 98.69% (95% CI: 97.68-99.65%), respectively. The effectiveness of these two drugs against *Trichuris trichiura* and hookworms was comparatively low (< 80% ERR), except for albendazole, which showed high ERRs [93.44% (95%CI: 92.39-94.49%)] against hookworms. The cure rate (CR) of albendazole against *T. trichiura*, *A. lumbricoides*, and hookworms were 50.8%, 91.3%, and 78.32%, respectively. Likewise, mebendazole showed CRs of 48.15%, 92.8%, and 49.32% against *T. trichiura*, *A. lumbricoides*, and hookworms, respectively. Subgroups such as studies conducted after 2000, diagnostic type (McMaster), and longer follow-up weeks significantly reduced the efficacy of the two drugs against *T. trichura*. While the combination of albendazole or mebendazole with other drugs and RCT showed significantly improved efficacy against *T. trichura*. The count of eggs per gram of stool (EPG) was identified as one of the variables that negatively and significantly influenced the efficacy of albendazole or mebendazole against *A. lumbricoides*.

Conclusion: Despite the wide range of ERRs and CR reported in the different articles included in this review, the pooled estimated efficacy of albendazole and mebendazole against STHs falls in the satisfactory category of WHO recommendations. Further evaluation of the combination of anthelmintic drugs as a preventive chemotherapy option and routine drug efficacy testing are necessary to prevent the emergence and widespread use of drug-resistant STHs.

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Follow up study of symptomatic human cystic echinococcosis treatment with albendazole and praziquantel, in Uruguay

[Daniel Da Rosa¹](#), [Elisa Figueredo²](#), [Michel Rosas²](#), [Fernando Goñi³](#)

Abstract

Background: Cystic echinococcosis (CE) is a chronic disease considered a neglected one. Cystic echinococcosis is endemic in Uruguay and the region. Surgery, using various technical approaches, has the potential to safely remove the cyst(s) and lead to a complete cure in a high number of patients with simple forms of CE. However, surgery may be impractical in patients with multiple cysts in several organs, high surgical risk, or in patients with previous multiple surgeries. In these cases, the pharmacological treatment with the benzimidazolic drug Albendazole (ABZ) alone or combined with Praziquantel (PZQ), has been promising as the best choice to achieve improvement or cure.

Methods: In this study, we analyze the results obtained on the anti-parasitic treatment of 43 patients diagnosed with CE between the years 2003 and 2020. Patients were treated before and/or after surgery with ABZ or the combination ABZ/PZQ. The standardize protocol of the anti-parasitic drug treatment before surgery was 7 days, 15 days or 1 month depending on the urgency and availability of the surgical procedure. All cases that involved confirmed locations on lungs underwent immediate surgery with minimal pre-treatment when possible. After surgery, the standardize protocol of anti-parasitic drug treatment consisted of six cycles of 30 days each and resting intervals of 15 days in between. ABZ was used in all cases, administered orally, twice daily, at a total dosage of 15 mg/kg/day, with food high in fat content for improved absorption. The follow up was carried out according to WHO-IWGE guidelines for 5 years.

Results: Of the 43 patients fourteen were ≤ 15 years of age and had a differentiated pre-surgical treatment. From the ≥ 16 years of age, 36 completed the treatments and the 5 years follow up. Four patients changed geographical locations, without a forwarding contact, after the post-surgery treatment. No patient died during the study. Of the 36 patients that completed the study, 32 were treated only with ABZ; 93.75% achieved treatment success as determined by improvement or cure, and 6.25% treatment failure determined by no change or worsening. The last four patients received the ABZ/PZQ combination therapy and achieved 100% treatment success.

Conclusion: The pharmacological treatment resulted in a good option not only as palliative but also as potentially curative. The main relevance of its use was in cases with previous multiple surgeries or surgeries with potential life-threatening complications due to the number and location of cysts and concurrent comorbidities. A follow-up of at least 5 years would be recommended to assure remission and control of the transmission. More randomized trials are needed to provide clear clinical evidence of different pharmacological treatments for CE.

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Different regimens for eradication of *Helicobacter pylori* infection in children: a randomized controlled trial

[Sana Hosny Barakat¹](#), [Hind M Hanafy¹](#), [Maha Guimei²](#), [Elsaid Hamdy Elsayy³](#), [Ahmed F M Khalil¹](#)

Abstract

Eradication of *Helicobacter pylori* (*H. pylori*) infection in children is challenging due to increased antibiotic resistance and decreased effectiveness of the current therapeutic choices, especially in developing countries. The purpose of this study is to compare the efficacy and safety of triple therapy (TT), sequential therapy (ST), hybrid therapy (HT), concomitant therapy (CT), and ciprofloxacin-based triple therapy (CTT) as an empirical therapy for *H. pylori* eradication in children. In this randomized controlled trial, 200 children (aged between 3 and 16 years) with both positive rapid urease test and histopathology for *H. pylori* infection were included. Patients were randomly assigned to receive either TT, ST, HT, CT, or CTT. The eradication status was evaluated using a stool antigen test (SAT) 4 weeks after stoppage of antibiotic therapy and 2 weeks after stoppage of proton pump inhibitors. SAT was performed using an ELISA monoclonal antibody-based kit. The most common presenting symptom was epigastric pain (79%). The most common endoscopic findings were gastric antral erythema (98%) and antral nodularity (54.5%). All gastric biopsies showed superficial lamina propria infiltration with plasma cells and lymphocytes. Active gastritis with neutrophils infiltration was seen in 75% of the cases. Gastric atrophy and intestinal metaplasia were uncommon histopathological findings (8.5% and 1%, respectively). The eradication rates for TT, ST, HT, CT, and CTT were 70%, 77.5%, 80%, 85%, and 90%, respectively, with the latter achieving a statistically significant difference when compared with TT ($p = 0.025$). The rate of occurrence of adverse effects among different regimens was not statistically different.

Conclusion: As an empirical treatment for children with *H. pylori* infection, CTT is safe and provides the highest eradication rate. HT, ST, and CT might not be superior to TT.

Hepatitis and chronic liver disease

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Expected Eight-Week Prenatal Versus Twelve-Week Perinatal Tenofovir Alafenamide Prophylaxis to Prevent Mother-To-Child Transmission of Hepatitis B Virus: A Multicenter, Prospective, Open-label, Randomized Controlled Trial

[Qing-Lei Zeng¹](#), [Yi-Hua Zhou²](#), [Xiao-Ping Dong³](#), [Ji-Yuan Zhang⁴](#), [Guang-Ming Li⁵](#), [Jiang-Hai Xu⁶](#), [Zhi-Min Chen⁷](#), [Ning Song⁸](#), [Hong-Xu Zhang⁹](#), [Ru-Yue Chen¹](#), [Xue-Yan Lv¹](#), [Shuo Huang¹](#), [Wei-Zhe Li¹](#), [Ya-Jie Pan¹](#), [Ying-Hua Feng¹⁰](#), [Zhi-Qin Li¹](#), [Guo-Fan Zhang¹¹](#), [Wan-Bao Lin¹²](#), [Guo-Qiang Zhang¹³](#), [Guo-Tao Li¹³](#), [Wei Li¹⁴](#), [Yan-Li Zeng¹⁴](#), [Da-Wei Zhang⁴](#), [Guang-Lin Cui¹⁵](#), [Jun Lv¹](#), [Yan-Min Liu¹](#), [Hong-Xia Liang¹](#), [Chang-Yu Sun¹](#), [Fu-Sheng Wang⁴](#), [Zu-Jiang Yu¹](#)

Abstract

Introduction: The course of maternal antiviral prophylaxis to prevent mother-to-child transmission of hepatitis B virus (HBV-MTCT) varies greatly, and it has not been demonstrated in a randomized controlled study.

Methods: In this multicenter, open-label, randomized controlled trial, eligible pregnant women with HBV DNA of 5.3-9.0 log₁₀ IU/mL who received tenofovir alafenamide fumarate (TAF) from the first day of 33 gestational weeks to delivery (expected eight-week) or to four-week postpartum (expected twelve-week) were randomly enrolled at a 1:1 ratio and followed until six-month postpartum. All infants received standard immunoprophylaxis (hepatitis B immunoglobulin and vaccine). The primary endpoint was the safety of mothers and infants. The secondary endpoint was infants' HBV-MTCT rate at seven months of age.

Results: Among 119 and 120 intention-to-treat pregnant women, 115 and 116 women were followed until delivery, and 110 and 112 per-protocol mother-infant dyads in two groups completed the study. Overall, TAF was well tolerated, no one discontinued therapy due to adverse events (0/239, 0%, 95% confidence interval [CI] 0%-1.6%), and no infant had congenital defects or malformations at delivery (0/231, 0%, 95% CI 0%-1.6%). The infants' physical development at birth (n=231) and at seven months (n=222) were normal. Furthermore, 97.0% (224/231, 95% CI 93.9%-98.5%) of women achieved HBV DNA <5.3 log₁₀ IU/mL at delivery. The intention-to-treat and per-protocol infants' HBV-MTCT rates were 7.1% (17/239, 95% CI 4.5%-11.1%) and 0% (0/222, 95% CI 0%-1.7%) at seven months of age. Comparatively, 15.1% (18/119, 95% CI 9.8%-22.7%) versus 18.3% (22/120, 95% CI 12.4%-26.2%) of women in the two groups had mildly elevated alanine aminotransferase levels at three-month and six-month postpartum, respectively (P=0.507); notably, no one experienced alanine aminotransferase flare (0% [0/119, 95% CI 0%-3.1%] versus 0% [0/120, 0%-3.1%]).

Discussion: Maternal TAF prophylaxis to prevent HBV-MTCT is generally safe and effective, and expected eight-week prenatal duration is feasible

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Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate for Preventing Vertical Transmission in Chronic Hepatitis B Mothers: A Systematic Review and Meta-Analysis

Calvin Q Pan^{1,2}, Lin Zhu³, Andy S Yu⁴, Yuchan Zhao⁵, Bo Zhu⁶, Erhei Dai⁵

Abstract

Objective: International guidelines recommend maternal tenofovir disoproxil fumarate (TDF) therapy accompanied by infant immunoprophylaxis to prevent hepatitis B virus (HBV) mother-to-child transmission (MTCT) in highly viremic mothers. However, pooled analyses for tenofovir alafenamide (TAF) effects and comparisons between the 2 regimens are lacking.

Design: In this meta-analysis, pairs of independent reviewers performed multiple database searches from inception to 31 March 2024 and extracted data from cohort studies and randomized controlled trials (RCTs) in highly viremic mothers. The outcomes of interest were the reduction of MTCT and safety in the TDF-treated, TAF-treated, and control groups.

Results: We included 31 studies with 2588 highly viremic mothers receiving TDF, 280 receiving TAF, and 1600 receiving no treatment. Compared to the control, TDF therapy reduced the MTCT rate in infants aged 6-12 months (risk ratio: 0.10, 95% confidence interval [CI] .07-.16). Pairwise meta-analysis between TAF and TDF revealed similar effects on reducing MTCT (risk ratio: 1.09, 95% confidence interval .16-7.61). Network meta-analysis showed equal efficacy of the 2 regimens in reducing MTCT (risk ratio: 1.09, 95% CI .15-7.65). The surface under the cumulative ranking curve revealed TDF as the best regimen compared with TAF (probability ranking: .77 vs .72), while receiving a placebo during pregnancy had the lowest efficacy (probability ranking 0.01). There were no safety concerns for mothers and infants in all regimens.

Conclusions: Compared to placebo or no treatment, maternal TDF and TAF prophylaxis are equally effective and without safety concerns in reducing MTCT in highly viremic mothers.

Injury prevention

Integrated management of Childhood Illness (IMCI)

Iodine deficiency

Kidney disease

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A comparison of health-related quality of life between continuous ambulatory peritoneal dialysis and automated peritoneal dialysis in children with stage 5 chronic kidney disease in Thailand: a randomized controlled trial

[Montarat Thavorncharoensap^{1,2}](#), [Usa Chaikledkaew^{1,2}](#), [Sitaporn Youngkong^{1,2}](#), [Montira Assanatham^{1,3}](#), [Suwannee Wisanuyotin⁴](#), [Thanaporn Chaiyapak⁵](#), [Natthida Pongwilairat⁶](#), [Kongrapun Srisuwan⁷](#), [Parkpoom Bhumichitra⁸](#), [Patamakom Pruangprasert⁹](#), [Pantipa Boonyapapong¹⁰](#), [Nawarat Chongchet¹¹](#), [Uthaiwan Khongkhanin¹²](#), [Prayong Vachvanichsanong¹³](#), [Wattana Chartapisak¹⁴](#), [Anirut Pattaragarn¹⁵](#)

Abstract

Background: Improving health-related quality of life (HRQoL) is one of the main goals in managing stage 5 chronic kidney disease (CKD). However, limited evidence compares HRQoL between continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) in children. This open-label randomized controlled trial (RCT) aimed to compare HRQoL in pediatric patients with stage 5 CKD receiving CAPD vs. APD in Thailand.

Methods: Children with stage 5 CKD were randomized 1:1 to receive APD or CAPD. The primary outcome was HRQoL, measured by EQ-5D-5L, EQ-5D-3L, and PedsQL at baseline, week 16 and week 48. Outcomes were analyzed using linear mixed models.

Results: A total of 60 patients were recruited: 30 with CAPD and 30 with APD. General characteristics, utility scores measured by EQ-5D and HRQoL score measured by PedsQL were comparable between both groups at baseline. During follow-up, no significant differences in terms of utility and HRQoL scores could be identified at week 16 and week 48. Although the children in the APD group seemed to have more favorable changes in some PedsQL domains of PedsQL (school and social domain), as compared to the CAPD group, it was not found that the improvement from baseline was significantly different between both groups.

Conclusions: No significant benefit of APD was found over CAPD in terms of HRQoL improvement. However, larger studies are warranted along with qualitative studies to examine the complete impacts of APD on HRQoL among pediatric patients with stage 5 CKD and their families.

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doi: 10.1007/s00467-024-06619-8. Online ahead of print.

[Single \(375 mg/m²\) vs. double dose of rituximab along with mycophenolate mofetil for children with steroid-dependent/frequently relapsing nephrotic syndrome: a multicentre open-label randomized controlled trial](#)

[Rajiv Sinha¹](#), [Subal Pradhan²](#), [Sumantra Raut³](#), [Sushmita Banerjee⁴](#), [Subhankar Sarkar⁵](#), [Shakil Akhtar⁴](#), [Deblina Dasgupta⁴](#), [Sanjukta Poddar⁴](#), [Mita Mandal⁶](#), [Vineet Kumar Kamal⁷](#), [Arpita Ray Chaudhury³](#), [Yincent Tse⁸](#)

Abstract

Background: Optimal dosing of rituximab when given with mycophenolate mofetil (MMF) for frequently relapsing nephrotic syndrome/steroid-dependent nephrotic syndrome (FRNS/SDNS) remains uncertain.

Methods: This was a prospective, non-inferiority, open-label randomized controlled multicentre study. Children (2-18 years old) with difficult FRNS/SDNS were randomized to group A (rituximab 375 mg/m² once) or group B (rituximab 375 mg/m² twice; 7-14 days apart) followed by continuous MMF and 3 months of tapered steroids. Primary outcome at an 18-month follow-up was time to first relapse. Secondary outcomes included post rituximab time to CD19 repopulation, sustained remission and significant adverse events (SAEs).

Results: Ninety-six children (median age 8.6 years; IQR 6.4 to 11.3 years, 72% male) were randomized, 48 per arm. CD19 depletion (< 1%) was achieved in both groups. Three from single dose and two from double dose arm were lost to follow-up or withdrew. After 18 months, although non-inferiority could not be demonstrated, there was no difference in primary outcome either by intention-to-treat or per-protocol analysis. The restricted mean time to first relapse was 14.5 months (95% CI 13.1-15.9) in group A and 14.8 months (95% CI 13.5-16.1) in group B ($p = 0.69$). Relapse rate was similar between group A (19/45; 42%) and group B (16/46; 35%) ($p = 0.53$, hazard ratio 0.86 (95% CI 0.46-1.6)). Secondary outcomes were also similar between the groups.

Conclusions: Among children with FRNS/SDNS although non-inferiority could not be demonstrated, no statistically significant difference in outcome was found between 375 and 750 mg/m² rituximab when accompanied with MMF.

Leishmaniasis

Lymphatic filariasis

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doi: 10.4269/ajtmh.24-0050. Print 2024 Oct 1.

LEDoxy-SL: A Placebo-Controlled, Double-Blind, Randomized, 24-Month Trial of Six Weeks of Daily Doxycycline Plus Hygiene-Based Essential Care for Reducing Progression of Filarial Lymphedema in Sri Lanka

[Thishan Channa Yahathugoda¹](#), [Nirmitha Lalindi De Silva¹](#), [Janaka Ruben¹](#), [Sharmini Gunawardena²](#), [Mirani Vasanthamala Weerasooriya¹](#), [John Horton³](#), [Philip Budge⁴](#), [Eric Ottesen⁵](#), [Sarah Mary Sullivan⁵](#), [Mariana Stephens⁵](#), [John Shen⁵](#), [Ute Klarmann-Schulz⁶](#), [Achim Hoerauf⁶](#), [Joseph Patrick Shott⁷](#), [Charles Mackenzie⁵](#)

Abstract

Morbidity management of filarial lymphedema remains a challenge even during the post-lymphatic filariasis elimination era in Sri Lanka despite provision of the predominantly hygiene-based WHO Essential Package of Care. Because prior studies have suggested that 6 weeks of doxycycline may reduce progression of limb lymphedema, we conducted a randomized, placebo-controlled, superiority study to evaluate this possibility in Sri Lanka. Patients aged 14 to 65 years with lymphedema in one or both legs received either 200 mg of doxycycline daily for 6 weeks or matching placebo. The primary efficacy endpoint was improvement or lack of progression in lymphedema stage at 24 months postenrollment. Secondary endpoints included change in lymphedema stage at 12 and 24 months, frequency of acute adenolymphangitis episodes, and perceived disability measured by the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0). Training and supplies for limb hygiene were provided throughout the study. Two hundred participants (100 in each arm) with lymphedema of Dreyer stages 1 to 3 were enrolled. By the end of the 2-year study, 29% of the doxycycline patients and 34% of those on placebo showed improvement (i.e., a decrease in lymphedema stage), whereas 11% and 15% of the two groups showed worsening of the lymphedema. Adenolymphangitis rates were comparable in the two groups (43 doxycycline and 38 placebo recipients), although attacks lasted slightly longer in placebo patients (6.5

days versus 5.2 days). In both groups, perceived disability improved initially, with partial rebound in the second year. Only 34 adverse events affecting 24 patients (11%) occurred during the 6-week treatment period. Although doxycycline did not significantly impact lymphedema progression in this study, the results clearly indicate that clinical and personal benefits can be obtained from intensive hygiene management alone.

Am J Trop Med Hyg. 2024 Oct 1;111(4_Suppl):83-93.

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Efficacy and Safety of Adding 6 Weeks of Doxycycline to the Essential Package of Care to Treat Filarial Lymphedema: A Double-Blind, Randomized, Controlled Trial in Southern India

[Suma Krishnasastri¹](#), [Anuja Ashok¹](#), [Ammu Devidas¹](#), [Sarah Sullivan²](#), [Mariana Stephens²](#), [Jayla Norman²](#), [Elianna Paljug²](#), [Andrew Deathe²](#), [Andrew Majewski²](#), [John Horton³](#), [Joseph P Shott⁴](#), [Ute Klarmann-Schulz⁵](#), [Achim Hoerauf⁵](#), [Eric Ottesen²](#), [Charles D Mackenzie^{2,6}](#)

Abstract

Finding additional ways to manage lymphedema due to lymphatic filariasis (LF) is a primary concern for the Global Program to Eliminate Lymphatic Filariasis. The WHO-recommended Essential Package of Care (EPC) consists of skin hygiene, elevation of affected limbs, exercise, protective shoe ware, wound care, and supportive therapy for acute phases. The care program has been successful but often hard to maintain. A double-blind study reexamined previous findings that doxycycline treatment could improve the lymphedematous changes in LF patients. The present study was carried out in a semi-urban location of Kerala, southern India, where *Brugia* sp. is the predominant parasite, and LF mass drug administration had ceased in many areas. Two hundred individuals (aged 14-65 years; 142 females and 58 males) with lymphedema of stages 1-3 were instructed in the EPC and were randomly administered either 200 mg doxycycline or an identical-appearing placebo daily for 6 weeks. Data were collected at 0, 3, 6, 12, 18, and 24 months and included the state of the lymphedema (size, cleanliness, skin thickness and changes), occurrence of adenolymphangitis (ADL) attacks, and patients' quality of life (QOL). The results demonstrated no difference over time between the two arms of the study; virtually all patients of both groups showed either improvement or "no worsening" in the parameters during the 2-year study period. Importantly, this rigorous trial confirmed that the EPC is of substantial benefit to lymphedema patients by reducing acute ADL and improving their QOL and clinical condition.

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Adherence to Hygiene Protocols and Doxycycline Therapy in Ameliorating Lymphatic Filariasis Morbidity in an Endemic Area Post-Interruption of Disease Transmission in Ghana

[Linda Batsa Debrah^{1,2,3}](#), [Ute Klarmann-Schulz^{4,5,6}](#), [Jubin Osei-Mensah^{1,7}](#), [Janina M Kuehlwein^{4,5}](#), [Yusif Mubarik¹](#), [Jennifer Nadal^{4,6}](#), [Nana Kwame Ayisi-Boateng⁸](#), [Arcangelo Ricchiuto^{4,6}](#), [Vera Serwaa Opoku¹](#), [Sarah M Sullivan⁹](#), [Derrick Adu Mensah^{1,2}](#), [John](#)

[Horton¹⁰](#), [Abu Abudu Rahamani^{1,2}](#), [Philip J Budge¹¹](#), [Stephen Gbedema¹²](#), [Patricia Jebett Korir^{4,5}](#), [John Opoku¹](#), [Kenneth Pfarr^{4,5}](#), [Derrick Boateng Kontoh¹²](#), [Angelika Kellings¹³](#), [Charles Gyasi¹](#), [Michael Agyemang Obeng¹](#), [Barbara Gruetzmacher⁴](#), [Fatima Amponsah Fordjour¹⁴](#), [Inge Kroidl^{15,16}](#), [Sacha Horn¹⁵](#), [Eunice Kyaakyile Kuutiero¹](#), [Caroline Wauschkuhn^{4,5}](#), [Abdallah Ngenya¹⁷](#), [Charles Mackenzie⁹](#), [Samuel Wanji¹⁸](#), [Akili Kalinga¹⁷](#), [Eric A Ottesen⁹](#), [Achim Hoerauf^{4,5,19}](#), [Alexander Yaw Debrah^{1,3,20}](#)

Abstract

Filarial lymphedema (LE) remains a significant global problem despite the progress made toward elimination of lymphatic filariasis (LF). In Ghana, the main approach to LF is preventive chemotherapy, but this has minimal impact on individuals who have already developed LE. In 2018-2020, a 24-month randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy of stringent hygiene measures using the Essential Package of Care with or without additional administration of doxycycline (DOX) to improve filarial leg LE. This study enrolled 356 participants with LE stages 1-3 from two districts in the Upper East Region of Ghana. In addition to regular training on appropriate care for their affected legs, participants were randomized to receive 6 weeks of either 200 mg/day DOX (n = 117), 100 mg/day DOX (n = 120), or matching placebo (n = 119). Participants were seen every 2 months, with clinical measurements done at 6, 12, 18, and 24 months to assess the status of affected legs. There was a trend toward later appearance of acute attacks after DOX, but surprisingly, DOX showed no effect on LE stage progression. In all groups, leg LE improvement was more common (DOX 200 mg: n = 23 [20%]; DOX 100 mg: n = 23 [19.5%]; placebo: n = 32 [27.4%]) than LE worsening (DOX 200 mg: n = 2 [1.7%]; DOX 100 mg: n = 3 [2.5%]; placebo: n = 2 [1.7%]). Overall, these data show a strong benefit from adherence to a strict hygiene protocol, with some added potential benefit for DOX in preventing acute attacks.

Leprosy

Malaria

Malaria diagnosis

Insecticide-treated bed nets and other materials

BMC Public Health. 2025 Jan 28;25(1):346.

doi: 10.1186/s12889-025-21586-x.

[**Community benefits of mass distribution of three types of dual-active-ingredient long-lasting insecticidal nets against malaria prevalence in Tanzania: evidence from a 3-year cluster-randomized controlled trial**](#)

[Eliud Andrea Lukole^{1,2}](#), [Jackie Cook³](#), [Jacklin F Mosha⁴](#), [Nancy S Matowo⁵](#), [Manisha A Kulkarni⁶](#), [Elizabeth Mallya⁷](#), [Tatu Aziz⁴](#), [Jacklin Martin⁷](#), [Mark Rowland⁵](#), [Immo Kleinschmidt^{3,8,9}](#), [Alphaxard Manjurano⁴](#), [Franklin W Mosha⁷](#), [Natacha Protopopoff⁵](#)

Abstract

Background: Long-lasting insecticidal nets (LLINs) were once fully effective for the prevention of malaria; however, mosquitoes have developed resistance to pyrethroids, the main class of insecticides used on nets. Dual active ingredient LLINs (dual-AI LLINs) have been rolled out as an alternative to pyrethroid (PY)-only LLINs to counteract this. Understanding the minimum community usage at which these LLINs elicit an effect that also benefits non-users against malaria infection is important.

Methods: We conducted a secondary analysis of a 3-year randomized controlled trial (RCT) in 84 clusters in North-western Tanzania to evaluate the effectiveness of three dual-AI LLINs: pyriproxyfen and alpha(α)-cypermethrin, chlorfenapyr and α -cypermethrin, and the piperonyl-butoxide (PBO) and permethrin compared to α -cypermethrin only LLINs. We measured malaria infection prevalence using 5 cross-sectional surveys between 2020 and 2022. We assessed net usage at the cluster level and malaria infection in children aged from 6 months to 14 years in 45 households per cluster. The trial was registered as a clinical trial on www.clinicaltrials.gov.

Clinicaltrials: gov : ClinicalTrials.gov ([NCT03554616](https://clinicaltrials.gov/ct2/show/study/NCT03554616)) on 2018-06-13.

Results: A total of 22,479 children from 12,654 households were tested for malaria using rapid diagnostic tests in January 2020, 2021, & 2022 and July 2020 & 2021. Among non-users, community-level usage of > 40% of dual-AI LLIN was significantly associated with protection against malaria infection: chlorfenapyr arm (OR: 0.44 (95% CI: 0.27-0.71), $p = 0.0009$), PBO arm (OR: 0.55 (95% CI: 0.33-0.94), $p = 0.0277$) and pyriproxyfen arm (OR: 0.61 (95% CI: 0.37-0.99), $p = 0.0470$) compared with non-users in clusters with > 40% usage of pyrethroid-only LLINs. There were indications of some protection against malaria infection to non-users in the chlorfenapyr arm when community-level usage was $\leq 40\%$ (OR: 0.65 (95% CI: 0.42-1.01), $p = 0.0528$) compared to those living in clusters with > 40% usage of pyrethroid-only LLINs.

Conclusion: Our study demonstrated that at a community usage of 40% or more of dual-AI LLINs non-users benefited from the presence of these nets. Noticeably, even when usage was $\leq 40\%$ in the chlorfenapyr arm, non-users were better protected than non-users in the higher coverage pyrethroid-only arm. The greater difference in malaria risk observed between users and non-users indicates that LLINs play a crucial role in providing personal protection against malaria infection for the people using the net.

Malar J. 2025 Jun 8;24(1):182.

doi: 10.1186/s12936-025-05434-2.

[A household randomized-control trial of insecticide-treated screening for malaria control in unimproved houses in Tanzania](#)

[Olukayode G Odufuwa^{1,2,3,4}](#), [Sarah Jane Moore^{5,6,7,8}](#), [Zawadi Mageni Mboma^{5,8}](#), [Rehema Mwanga⁵](#), [Fatuma Matwewe⁵](#), [Lorenz Martin Hofer^{6,7}](#), [Isaya Matanila⁵](#), [Said Abbasi⁵](#), [Mohammed Ally Rashid⁵](#), [Rose Philipo⁵](#), [Fadhila Kihwele⁵](#), [Jason Moore^{5,6,7}](#), [Hien Nguyen⁹](#), [Rune Bosselmann¹⁰](#), [Ole Skovmand¹¹](#), [Jennifer C Stevenson^{5,6,7}](#), [Joseph B Muganga⁵](#), [John Bradley¹²](#)

Abstract

Background: Installing insecticidal netting on open eaves, windows, and holes in walls of unimproved houses is a potential malaria control tool. It prevents mosquito house-entry, induces lethal and sub-lethal effects on malaria vectors, and may reduce malaria transmission. Therefore, a household epidemiological trial was conducted to assess the efficacy of insecticide-treated screening (ITS) on malaria infection and indoor vectors in Tanzania.

Methods: In Chalinze district, Tanzania, 421 households were randomized into two arms. In June-July 2021, one group of households' houses was fitted with ITS (incorporated with deltamethrin and piperonyl butoxide) on eaves, windows, and wall holes, while the second group did not receive screening. After installation, consenting household members (aged ≥ 6 months) were tested for malaria infection using quantitative polymerase chain reaction after the long rainy season (June/July 2022, primary outcome) and the short rainy season (January/February 2022, secondary outcome). Secondary outcomes included indoor total mosquito per trap/night (June-July 2022), adverse effects after one month of ITS installation (August 2021), and chemical bioavailability and retention of ITS samples after one year of field use (June/July 2022). At the end of the trial, the control group received ITS.

Results: Malaria prevalence among residents in the ITS arm was 19.9% (50/251) and 28.3% (65/230) in the control arm after the long rains, however, this difference was not significant [adjusted odds ratio (OR) 0.67 (95% CI 0.35-1.28), $p = 0.227$]. Similarly, no protection was seen for ITS after the short rains, [OR 1.27 (95% CI 0.68-2.38), $p = 0.452$]. However, school-age children in the ITS arm had lower malaria after the long rains [OR 0.11 (95% CI 0.02-0.73), $p = 0.022$]. No serious adverse effects were reported. The mean number of female Anopheles mosquitoes caught per trap/night was not significantly different between arms [1.7 vs 2.4, crude relative risk: 0.71 (95% CI 0.16-3.09), $p = 0.650$]. ITS showed reduced chemical bioavailability and retention post-field use. The trial reported high household refusals (17-30%) in both arms in both surveys.

Conclusion: The trial was inconclusive because households' refusal resulted in low power. A large cluster randomized trial of the intervention, preferably with screens treated with longer-lasting insecticides installed in houses, is needed.

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Inter-cluster contamination: a semivariance analysis of community effect ranges of malaria vector control interventions in a four-armed malaria trial in Muleba, Tanzania

Charles Thickstun¹, Eliud Lukole², Jacklin F Mosha², Alphaxard Manjurano², Immo Kleinschmidt^{3,4,5}, Franklin W Mosha⁶, Jacques Derek Charlwood^{7,8}, Mark Rowland⁷, Ann Jolly⁹, Alice Zwerling⁹, Natacha Protopopoff^{7,10,11}, Manisha Kulkarni⁹

Abstract

Background: The presence of a community effect in cluster randomized trials of malaria vector control interventions has led to the implementation of "buffer zones" around clusters to limit the potential for contamination between interventions. No consensus has been reached on how large these buffers need to be to encapsulate the effect.

Methods: Nested within a phase-III cluster randomized malaria vector control trial in Northwest Tanzania, this study aims to determine the presence and spatial range of community effects from long-lasting insecticidal net (LLIN) and indoor residual spraying (IRS)

interventions on household-level malaria infection in trial clusters four months post-intervention. Effective spatial range estimates of intervention community effects were compared to the 300m buffer distance implemented to limit intervention spillover between clusters in the trial. Geographically-weighted adjusted odds of malaria infection in children aged 0.5-14 years were determined four months post community-level intervention with a randomized allocation comprising one of two LLIN products (Olyset™ LN: 1000mg/m² permethrin or Olyset™ Plus LN: 400 + permethrin 800mg/m²) with either IRS (Actellic®300CS: 1000mg/m² micro-encapsulated pirimiphos-methyl) or no IRS. Robust semivariograms were calculated for each of 48 intervention clusters and fit to semivariogram models by Weighted Least Squares.

Results: 6440 children from 2785 households were included in the geographically-weighted logistic regression. Prevalence of *Plasmodium falciparum* infection was 45.9% in the study population. Twenty (20) clusters had significant residual effect ranges, 13 of which were fit to Sine Wave Effect models, indicating periodicity in the study area. Effective range estimates for the study area had a median value of 1210 m (IQR: 958-1691). Clusters with IRS had a higher median range value: 1535 m (IQR: 976-3398) than those without IRS: 1168m (IQR: 829-1504).

Conclusions: Significant semivariogram model range estimates extended beyond the trial buffer sizes by a median average of 868 m in LLIN intervention clusters and 1235 m for IRS clusters. This presents a contamination, or spillover, potential for all trialed intervention types that may reduce the statistical power to detect difference between trial arms. Future studies should consider the ranges of intervention effects and contamination potential between trial arms when designing buffer areas.

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Evaluating the impact of two next-generation long-lasting insecticidal nets on malaria incidence in Uganda: an interrupted time-series analysis using routine health facility data

[Adrienne Epstein¹](#), [Samuel Gonahasa²](#), [Jane Frances Namuganga²](#), [Martha J Nassali²](#), [Catherine Maiteki-Sebuguzi^{2,3}](#), [Isaiah Nabende²](#), [Katherine Snyman^{2,4}](#), [Joaniter I Nankabirwa^{2,5}](#), [Jimmy Opigo³](#), [Martin J Donnelly⁶](#), [Sarah G Staedke⁶](#), [Moses R Kamya^{2,7}](#), [Grant Dorsey⁸](#)

Abstract

Introduction: Malaria remains a significant public health challenge globally, particularly in sub-Saharan Africa, where progress has stalled in recent years. Long-lasting insecticidal nets (LLINs) are a critical preventive tool against malaria. This study investigated the effectiveness of newer-generation LLINs following a universal coverage campaign in Uganda.

Methods: Health facility data collected 36 months prior to LLIN distribution and 24 months after LLIN distribution were used from 64 sites that took part in a cluster-randomised trial comparing two newer-generation LLINs (pyrethroid-piperonyl butoxide and pyrethroid-pyriproxyfen). Using an interrupted time-series approach, we compared observed malaria incidence with counterfactual scenarios if no LLINs were distributed, adjusting for precipitation, vegetation, seasonality and care-seeking behaviour. Analyses were also stratified by LLIN type and study-site level estimates of transmission intensity.

Results: Overall, malaria incidence decreased from 827 cases per 1000 person-years in the predistribution period to 538 per 1000 person-years in the postdistribution period. Interrupted time-series analyses estimated a 23% reduction in malaria incidence (incidence rate ratio [IRR]=0.77, 95% CI 0.65 to 0.91) in the first 12 months following distribution relative to what would be expected had no distribution occurred, which was not sustained in the 13-24 month post-distribution period (IRR=0.97, 95% CI 0.75 to 1.28). Findings were similar when stratified by LLIN type. In the first 12 months following distribution, LLIN effectiveness was greater in the high-transmission sites (IRR=0.67, 95% CI 0.54 to 0.86) compared with the medium- (IRR=0.74, 95% CI 0.59 to 0.92) and low-transmission sites (IRR=0.87, 95% CI 0.56 to 1.32).

Conclusion: This study demonstrated a modest reduction in malaria incidence following the distribution of newer-generation LLINs that was sustained for only 12 months, highlighting the need for improved strategies to maintain net effectiveness. Adjusting the frequency of universal coverage campaigns based on local malaria transmission intensity may enhance control efforts.

PLOS Glob Public Health. 2025 Feb 26;5(2):e0003558.

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LLIN Evaluation in Uganda Project (LLINEUP2) - Effect of long-lasting insecticidal nets (LLINs) treated with pyrethroid plus pyriproxyfen vs LLINs treated with pyrethroid plus piperonyl butoxide in Uganda: A cluster-randomised trial

[Samuel Gonahasa^{1,2}](#), [Jane Frances Namuganga¹](#), [Martha J Nassali¹](#), [Catherine Maiteki-Sebuguzi^{1,3}](#), [Isaiah Nabende¹](#), [Adrienne Epstein⁴](#), [Katherine Snyman^{1,5,6}](#), [Joaniter I Nankabirwa^{1,7}](#), [Jimmy Opigo³](#), [Martin J Donnelly^{2,8}](#), [Grant Dorsey⁴](#), [Moses R Kamya^{1,7}](#), [Sarah G Staedke^{2,6,9}](#)

Abstract

Long-lasting insecticidal nets (LLINs) are the cornerstone of malaria control, but their effectiveness is threatened by pyrethroid resistance. We embedded a pragmatic, cluster-randomised trial into Uganda's national LLIN distribution campaign in 2020-2021, comparing pyrethroid-piperonyl butoxide (PBO) LLINs to pyrethroid-pyriproxyfen LLINs. Target communities surrounding public health facilities (clusters, n=64), covering 32 districts were included. Clusters were randomised 1:1 in blocks of two by district to receive: (1) pyrethroid-PBO LLINs (PermaNet 3.0, n=32) or (2) pyrethroid-pyriproxyfen LLINs (Royal Guard, n=32). LLINs were delivered from 7 November 2020 to 26 March 2021. Malaria surveillance data were collected from health facilities from 1 November 2019 until 31 March 2023. Cluster-level estimates of malaria incidence in residents of all ages (primary outcome) were generated from enhanced health facility surveillance data. Cross-sectional community surveys were conducted in randomly selected households (at least 50 per cluster) at 12-months (24 November 2021 to 1 April 2022) and 24-months (23 November 2022 to 21 March 2023) post-LLIN distribution. Overall, 186,364 clinical malaria episodes were diagnosed in cluster residents during 398,931 person-years of follow-up. At 24-months, malaria incidence was lower than baseline in both arms (pyrethroid-PBO: 465 vs 676 episodes per 1000 person-years; pyrethroid-pyriproxyfen: 469 vs 674 episodes per 1000 person-years); but there was no evidence of a difference between the arms (incidence rate ratio 1.06, 95% confidence interval [CI] 0.91-1.22, p=0.47). Two years post-distribution, ownership of at least one LLIN for every

two household residents was low in both arms (41.1% pyrethroid-PBO vs 38.6% pyrethroid-pyriproxyfen). Parasite prevalence in children aged 2-10 years was no different between the arms in either survey (24-months: 26.1% pyrethroid-PBO; 29.5% pyrethroid-pyriproxyfen; odds ratio 1.29 [95% CI: 0.81-2.05], $p=0.29$). The effectiveness of pyrethroid-PBO LLINs and pyrethroid-pyriproxyfen LLINs was no different in Uganda, but two years after mass distribution, LLIN coverage was inadequate.

Parasit Vectors. 2024 Jul 13;17(1):303.

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Malaria prevalence and transmission in the Zakpota sub-district of central Benin: baseline characteristics for a community randomised trial of a new insecticide for indoor residual spraying

[Renaud Govoetchan^{1,2,3}](#), [Augustin Fongnikin^{4,5}](#), [Corneille Hueha^{4,5}](#), [Juniace Ahoga^{4,5}](#), [Chantal Boko⁴](#), [Thomas Syme^{6,4,5}](#), [Riliwanou Issiakou^{4,5}](#), [Abel Agbevo^{6,4,5}](#), [Rock Aikpon⁷](#), [Graham Small⁸](#), [Janneke Snetselaar⁸](#), [Razaki Ossè⁴](#), [Filemon Tokponnon⁴](#), [Germain Gil Padonou⁴](#), [Corine Ngufor^{9,10,11}](#)

Abstract

Background: Malaria transmission is known to be perennial and heterogeneous in Benin. Studies assessing local malaria prevalence, transmission levels and vector characteristics are critical for designing, monitoring and evaluating new vector control interventions in community trials. We conducted a study in the Zakpota sub-district of central Benin to collect baseline data on household characteristics, malaria prevalence, vector characteristics and transmission dynamics in preparation for a randomised controlled trial to evaluate the community impact of VECTRON™ T500, a new broflanilide indoor residual spraying (IRS) product.

Methods: A total of 480 children under 5 years of age from the 15 villages of the sub-district were tested for malaria by rapid diagnostic tests (RDTs). Mosquitoes were collected by human landing catches (HLCs), pyrethrum spray catches (PSCs) and Centers for Disease Control and Prevention miniature light traps (CDC-LTs) in selected houses in each village to assess vector density, composition, vector infectivity and prevalence of insecticide resistance markers. Bioassays were performed to detect vector susceptibility to pyrethroids, broflanilide (6 µg/bottle) and clothianidin (90 µg/bottle).

Results: A total of 9080 households were enumerated in the 15 study villages. Insecticide-treated net (ITN) usage was > 90%, with 1-2 ITNs owned per household. Houses were constructed mainly with cement (44%) and mud (38%) substrates or a mixture of cement and mud (18%), and 60% of them had open eaves. The overall prevalence of *P. falciparum* infection was 19% among surveyed children: 20% among females and 18% among males. The haemoglobin rate showed an anaemia (< 11 g/dl) prevalence of 66%. *Anopheles coluzzii* and *An. gambiae sensu stricto* (s.s.) were the two vector species present at an overall proportion of 46% versus 54%, respectively. The human biting rate was 2.3 bites per person per night (b/p/n) and biting occurred mostly indoors compared with outdoors (IRR = 0.776; $P = 0.001$). The overall proportion of outdoor biting was 44% and exceeded indoor biting in three villages. The sporozoite rate was 2% with a combined yearly entomological inoculation rate (EIR) of 16.1 infected bites per person per year (ib/p/y). There was great variability in malaria transmission risk across the villages, with EIR ranging from 0 to 29.3 ib/p/y. The

vector population showed a high intensity of resistance to pyrethroids across the study villages but was largely susceptible to broflanilide and clothianidin.

Conclusions: This study found high levels of malaria prevalence, vector density and transmission in the Zakpota sub-district despite the wide use of insecticide-treated nets. The vector population was mostly indoor resting and showed a high intensity of pyrethroid resistance but was generally fully susceptible to broflanilide. These findings demonstrated the suitability of the study area for the assessment of VECTRON™ T500 in a community randomised trial.

Lancet. 2025 Jan 11;405(10473):147-156.

doi: 10.1016/S0140-6736(24)02253-0. Epub 2024 Dec 19.

Effect of a spatial repellent on malaria incidence in an area of western Kenya characterised by high malaria transmission, insecticide resistance, and universal coverage of insecticide treated nets (part of the AEGIS Consortium): a cluster-randomised, controlled trial

[Eric O Ochomo¹](#), [John E Gimnig²](#), [Quentin Awori³](#), [Bernard Abong'o³](#), [Prisca Oria³](#), [Nickline K Ashitiba³](#), [Brian Polo³](#), [Vincent Moshi³](#), [Hilda Otanga³](#), [Ferdinand Adung'o³](#), [Eunice A Ouma³](#), [Susan Outa⁴](#), [Edith Ramaita⁵](#), [Rebecca Levine²](#), [Wycliffe Odongo²](#), [Steven A Harvey⁶](#), [April Monroe⁷](#), [Ashley Hudson⁸](#), [Bradley Sandberg⁹](#), [Jared Hendrickson⁹](#), [Xingyuan Zhao¹⁰](#), [Ruyu Zhou¹⁰](#), [Fang Liu¹⁰](#), [Nicole L Achee¹¹](#), [John P Grieco⁸](#)

Abstract

Background: Spatial repellent products are used for prevention of insect bites, and a body of evidence exists on spatial repellent entomological efficacy. A new option for vector control, spatial repellent products are designed to release active ingredient into the air for disruption of human-vector contact thereby reducing human exposure to mosquito-borne pathogens. Clinical trials have shown spatial repellent epidemiological efficacy against Aedes-borne viruses but inconclusive outcomes against malaria. We aimed to show and quantify the protective efficacy of spatial repellents in reducing malaria infection incidence in Busia County, Kenya.

Methods: A prospective, cluster-randomised, controlled trial in Busia County, western Kenya was done to quantify the efficacy of a transfluthrin-based spatial repellent against human malaria infection following mass distribution of insecticide treated nets. Investigators, staff, and study participants were masked to cluster allocation. Infection incidence was measured by microscopy in children aged 6 months to younger than 10 years during a 4-month baseline (March-July 2021) and 24-month follow-up period with intervention (October, 2021-October, 2023). From 58 clusters (29 intervention, 29 placebo), a total of 1526 and 1546 participants from two consecutive, 12-month cohorts were assessed for first-time malaria infection (primary endpoint) by survival analysis at interim and end-of-trial timepoints, respectively. This trial is registered with ClinicalTrials.gov, [NCT04766879](#) and is complete.

Findings: The outcome of the primary endpoint indicated that spatial repellents significantly reduced the hazard rate of first-time malaria infection by 33·4% (95% CI 11·1-50·1; p=0·0058) and the hazard rate of overall new malaria infections by 32·1% (15·9-45·2; p=0·0004). No reported adverse events and serious adverse events were deemed to be associated with the spatial repellent.

Interpretation: Our trial provides the first evidence of a demonstrative spatial repellent protective efficacy in reducing risk of malaria infection in an African setting characterised by high malaria transmission, pyrethroid resistant malaria vectors, and high coverage of insecticide treated nets. Results support spatial repellent products as a beneficial component of malaria prevention.

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Evaluation of Attractive Targeted Sugar Baits, a new outdoor vector control strategy against malaria: Results from a cluster randomised open-label parallel arm controlled trial in Southwestern Mali

[Sophie Sarrassat¹](#), [Mahamoudou Toure²](#), [Ayouba Diarra²](#), [Makan Keita²](#), [Hamady Coulibaly²](#), [Abdoul Zamilou Arou²](#), [Mohamed Traore²](#), [Cheick Oumar Tangara²](#), [John Bradley³](#), [Gunter Muller²](#), [Silas Majambere⁴](#), [John C Beier⁵](#), [John Vontas⁶](#), [Sekou F Traore²](#), [Samba Diop²](#), [Immo Kleinschmidt⁷](#), [Seydou Doumbia²](#)

Abstract

Background: The Attractive Targeted Sugar Bait (ATSB) is a new malaria outdoor vector control tool targeting sugar-feeding behaviours of vector mosquitoes. In Mali, a two-year open-label two-arm cluster randomised controlled trial compared the efficacy and safety of ATSB plus insecticide treated mosquito nets (ITN) versus ITN alone on malaria burden.

Methods: 76 clusters were formed, of which 38 were randomly allocated to the intervention. Cohort studies and household surveys were performed to assess clinical malaria incidence (primary outcome) in children aged 5 to 14 years and malaria infection prevalence in individuals aged 6 months or older, respectively. Primary analyses were performed on an intention-to-treat basis. The trial was designed to detect a minimum 30% reduction in the two outcomes over a two-year period with a power of at least 80%. The trial is registered at ClinicalTrial.gov ([NCT04149119](#)).

Findings: The proportion of sleeping buildings with at least 2 ATSB ranged between 70% and 80%. Coverage of ATSB in good condition was lower (50% or less). Over the two-year trial period, the clinical malaria incidence rate in the control and intervention arm was 0.726 and 0.660 cases per person-year, respectively, with no statistical evidence for an intervention effect (Incidence Rate Ratio (IRR) = 0.90; 95%CI 0.77, 1.05; p = 0.188). Malaria infection prevalence was approximately 37% in both arms (Odds Ratio (OR) = 0.96; 95%CI 0.76, 1.21; p = 0.729). In clusters with coverage of stations in good condition above 80%, there was evidence for a 26% reduction in malaria incidence compared to control clusters after controlling for confounders (adjusted IRR = 0.74; 95%CI 0.61, 0.90; p = 0.002).

Interpretation: Overall, the trial did not demonstrate evidence of additional protection against malaria of ATSB compared to using ITN alone. Suboptimal coverage and maintenance of ATSB in good condition in the field may explain the lack of an intervention effect.

doi: 10.1186/s13071-024-06457-5.

Why does malaria transmission continue at high levels despite universal vector control? Quantifying persistent malaria transmission by Anopheles funestus in Western Province, Zambia

[Ruth A Ashton¹](#), [Benjamin Chanda²](#), [Chama Chishya²](#), [Rayford Muyabe²](#), [Tresford Kaniki²](#), [Patricia Mambo²](#), [Mwansa Mwenya²](#), [Gift Mwaanga³](#), [Annie Arnzen⁴](#), [Erica Orange⁴](#), [Kochelani Saili^{2,3}](#), [Handrinah Banda Yikona²](#), [John Chulu²](#), [Chanda Chitoshi²](#), [Irene Kyomuhangi^{5,6}](#), [John Miller⁷](#), [Kafula Silumbe⁷](#), [Busiku Hamainza⁸](#), [Megan Littrell⁹](#), [Joshua Yukich⁵](#), [Immo Kleinschmidt¹⁰](#), [Javan Chanda⁶](#), [Joseph Wagman^{#8}](#), [Thomas P Eisele^{#5}](#)

Abstract

Background: Some settings continue to experience a high malaria burden despite scale-up of malaria vector control to high levels of coverage. Characterisation of persistent malaria transmission in the presence of standard control measures, also termed residual malaria transmission, to understand where and when individuals are exposed to vector biting is critical to inform refinement of prevention and control strategies.

Methods: Secondary analysis was performed using data collected during a phase III cluster randomized trial of attractive targeted sugar bait stations in Western Province, Zambia. Two seasonal cohorts of children aged 1-14 years were recruited and monitored monthly during the malaria transmission season, concurrent with entomological surveillance using a combination of human landing catch (HLC) and Centres for Disease Control (CDC) light traps at randomly selected households in study clusters. Behavioural data from cohort participants were combined with measured *Anopheles funestus* landing rates and sporozoite positivity to estimate the human behaviour-adjusted entomological inoculation rate (EIR).

Results: Behavioural data from 1237 children over 5456 child-visits in 20 entomology surveillance clusters were linked with hourly landing rates from 8131 female *An. funestus* trapped by HLC. Among all *An. funestus* tested by enzyme-linked immunosorbent assay (ELISA), 3.3% were sporozoite-positive. Mean EIR directly measured from HLC was 0.07 infectious bites per person per night (ib/p/n). When accounting for child locations over the evening and night, the mean behaviour-adjusted EIR was 0.02 ib/p/n. Children not sleeping under insecticide-treated nets (ITNs) experienced 13.6 infectious bites per person per 6 month season, 8% of which occurred outdoors, while ITN users received 1.3 infectious bites per person per 6 month season, 86% of which were received outdoors. Sleeping under an ITN can prevent approximately 90% of potential *An. funestus* bites among children.

Conclusions: In this setting ITNs have a high personal protective efficacy owing to peak *An. funestus* biting occurring indoors while most individuals are asleep. However, despite high household possession of ITNs (>90%) and high individual use (>70%), children in this setting experience more than one infectious bite per person per 6 month transmission season, sufficient to maintain high malaria transmission and burden. New tools and strategies are required to reduce the malaria burden in such settings.

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Efficacy of attractive targeted sugar bait stations against malaria in Western Province Zambia: epidemiological findings from a two-arm cluster randomized phase III trial

[Ruth A Ashton¹](#), [Kochelani Saili^{2,3}](#), [Chama Chishya²](#), [Handrinah Banda Yikona²](#), [Annie Arnzen⁴](#), [Erica Orange⁴](#), [Chanda Chitoshi²](#), [John Chulu²](#), [Titus Tobolo²](#), [Frank](#)

[Ndalama²](#), [Irene Kyomuhangi^{5,6}](#), [Willy Ngulube⁷](#), [Hawela Moonga⁷](#), [Jacob Chirwa⁷](#), [Laurence Slutsker⁸](#), [Joseph Wagman⁹](#), [Javan Chanda¹⁰](#), [John Miller¹⁰](#), [Kafula Silumbe¹⁰](#), [Busiku Hamainza⁷](#), [Thomas P Eisele⁵](#), [Joshua Yukich⁵](#), [Megan Littrell⁸](#)

Abstract

Background: Attractive targeted sugar bait (ATSB) stations containing bait (to attract) and ingestion toxicant (to kill) sugar-foraging mosquitoes are hypothesized to reduce malaria transmission by shortening the lifespan of Anopheles vectors.

Methods: A two-arm cluster-randomized controlled trial (cRCT) was conducted in Western Province Zambia. Seventy clusters of 250-350 households were assigned (1:1) by restricted randomization to an intervention arm (ATSB) or control arm (no ATSB) in the context of standard of care vector control (insecticide-treated nets and/or indoor residual spraying). Two ATSB stations (Westham Sarabi, 0.11% dinotefuran w/w) were maintained on exterior walls of eligible household structures for a 7-month deployment period (December-June) during the high malaria transmission season. The primary outcome was clinical malaria incidence among two consecutive seasonal cohorts of children aged 1-14 years, followed-up monthly from January-June in 2022 and 2023. Secondary outcome was Plasmodium falciparum prevalence among individuals aged over six months. Analysis compared clinical malaria incidence and prevalence between arms among the intention-to-treat population.

Results: ATSB coverage, assessed by cross-sectional survey, was 98.3% in March-April 2022 and 89.5% in March-April 2023. 4494 children contributed any follow-up time to the cohort, with 2313 incident malaria cases in the intervention arm (1.28 per child per six-month transmission season), and 2449 in the control arm (1.38 per child-season). The incidence rate ratio between the two arms was 0.91 (95% CI 0.72-1.15, $p = 0.42$). 2536 individuals participated in cross-sectional surveys, with prevalence of *P. falciparum* 50.7% in the intervention arm and 53.5% in the control arm. The odds ratio between the two arms was 0.89 (95% CI 0.66-1.18, $p = 0.42$). Secondary covariable-adjusted and subgroup analyses did not substantially alter the findings. No serious adverse events associated with the intervention were reported.

Conclusions: Two ATSB stations deployed per eligible structure for two consecutive transmission seasons did not result in a statistically significant reduction in clinical malaria incidence among children aged 1-14 years or in *P. falciparum* prevalence in rural western Zambia. Further studies are needed to assess the efficacy of ATSB stations in different settings and with different deployment strategies.

Intermittent preventative treatment and seasonal malaria prophylaxis

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[Effectiveness of sulfadoxine-pyrimethamine plus amodiaquine and dihydroartemisinin-piperaquine for seasonal malaria chemoprevention in Uganda: a three-arm, open-label, non-inferiority and superiority, cluster-randomised, controlled trial](#)

[Anthony Nuwa¹](#), [Kevin Baker²](#), [Richard Kajubi³](#), [Chukwudi A Nnaji⁴](#), [Katherine Theiss-Nyland⁴](#), [Musa Odongo³](#), [Tonny Kyagulanyi³](#), [Jane Nabakooza⁵](#), [David Salandini³](#), [Victor Asua⁶](#), [Maureen Nakirunda³](#), [Christian Rassi⁴](#), [Damian Rutazaana⁵](#), [Richard Achuma⁷](#), [Patrick Sagaki⁷](#), [John Baptist Bwanika³](#), [Godfrey Magumba³](#), [Adoke Yeka⁸](#), [Sam Nsohya⁹](#), [Moses R Kanya¹⁰](#), [James Tibenderana⁴](#), [Jimmy Opigo⁵](#)

Abstract

Background: Seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine combined with amodiaquine (SPAQ) effectively protects eligible children from malaria in areas of high and seasonal transmission. However, concerns about parasite resistance to sulfadoxine-pyrimethamine in East and Southern Africa necessitate evaluating alternative drug regimens. This study assessed the effectiveness of SPAQ and dihydroartemisinin-piperaquine for SMC in Uganda.

Methods: This three-arm, open-label, non-inferiority and superiority, cluster-randomised, controlled trial was conducted in Karamoja subregion, Uganda, among children aged 3-59 months and 6-59 months for SPAQ and dihydroartemisinin-piperaquine, respectively. Of 427 villages, 380 were randomly assigned (1:1) to the SPAQ group and dihydroartemisinin-piperaquine group, and 47 were assigned to the control group (no SMC). The superiority component compared the SPAQ and dihydroartemisinin-piperaquine groups with the control group, whereas the non-inferiority component compared the dihydroartemisinin-piperaquine group with the SPAQ group. The primary endpoint was confirmed malaria incidence using rapid diagnostic tests or microscopy. Survival analyses were done on an intention-to-treat basis (in all randomised participants), with adjustments made for covariate imbalances at baseline. Additionally, molecular markers associated with resistance to sulfadoxine-pyrimethamine and amodiaquine were analysed on 750 malaria-positive blood samples from children younger than 5 years before and after five SMC cycles. This trial was registered with ClinicalTrials.gov, [NCT05323721](#), and has been completed.

Findings: During June 18-30, 2022, 3881 children were enrolled; 1755 in SPAQ, 1736 in dihydroartemisinin-piperaquine, and 390 in control villages. Of these children, 3629 were analysed. Incidence rates were 0.90 cases per 100 person-months in the SPAQ group, 0.80 cases per 100 person-months in the dihydroartemisinin-piperaquine group, and 18.26 cases per 100 person-months in the control group. SPAQ and dihydroartemisinin-piperaquine reduced malaria risk by 94% (hazard ratio [HR] 0.06 [95% CI 0.04-0.08]; $p<0.001$) and 96% (0.04 [0.03-0.06]; $p<0.001$), respectively. Based on the prespecified non-inferiority margin of 1.4, there was non-inferiority between the protective effectiveness of dihydroartemisinin-piperaquine and that of SPAQ (HR 0.90 [95% CI 0.58-1.39]). Prevalence of mutations linked to moderate (*Plasmodium falciparum* dihydrofolate reductase [PfDHFR] and *P falciparum* dihydropteroate synthetase reductase [PfDHPS]) and high (PfDHFR Ile164Leu and PfDHPS Ala581Gly) sulfadoxine-pyrimethamine resistance were more than 88% and less than 5%, respectively. Mutations associated with 4-aminoquinolone resistance (*P falciparum* multidrug resistance protein-1 [PfMDR1] Asp1246Tyr and PfMDR1 Asn86Tyr) were less than 1%. There was no significant increase in the prevalence of antifolate and artemisinin partial resistance-associated mutations, but a decrease was observed for key aminoquinoline resistance-associated alleles: *P falciparum* chloroquine resistance transporter protein Lys76Thr, *P falciparum* multidrug resistance protein Asn86Tyr, and PfMDR1 Asp1246Tyr ($p<0.001$). No serious or fatal adverse events were reported.

Interpretation: SPAQ and dihydroartemisinin-piperaquine effectively reduced malaria in children younger than 5 years, with no safety concerns. There was no evidence of resistance

selection by SMC. Although these findings support SPAQ-based SMC in Eastern and Southern Africa, ongoing resistance surveillance and efficacy monitoring are essential for sustained impact.

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Effect of mass drug administration on malaria incidence in southeast Senegal during 2020-22: a two-arm, open-label, cluster-randomised controlled trial

[El-Hadji Konko Ciré Ba¹](#), [Michelle E Roh²](#), [Abdoulaye Diallo¹](#), [Tidiane Gadiaga³](#), [Amadou Seck¹](#), [Sylla Thiam¹](#), [Ari Fogelson⁴](#), [Seynabou Gaye⁵](#), [Ibrahima Diallo⁵](#), [Aminata Colle Lo¹](#), [Elhadji Diouf⁶](#), [Oumar Gallo Ba¹](#), [Alioune Badara Gueye⁷](#), [Xue Wu²](#), [Paul Milligan⁴](#), [Tabitha Kibuka⁸](#), [Moustapha Hama⁸](#), [Erin Eckert⁸](#), [Julie Thwing⁹](#), [Adam Bennett¹⁰](#), [Roly Gosling¹¹](#), [Jimee Hwang¹²](#), [Doudou Sene⁵](#), [Fatou Ba⁵](#), [Bayal Cissé³](#), [Katharine Sturm-Ramirez⁷](#), [Michelle S Hsiang¹³](#), [Jean Louis Ndiaye¹](#)

Abstract

Background: In Africa, the scale-up of malaria-control interventions has reduced malaria burden, but progress towards elimination has stalled. Mass drug administration (MDA) is promising as a transmission-reducing strategy, but evidence from low-to-moderate transmission settings is needed. We aimed to assess the safety, coverage, and effect of three cycles of MDA with dihydroartemisinin-piperaquine plus single, low-dose primaquine on *Plasmodium falciparum* incidence and prevalence in southeast Senegal.

Methods: We conducted a two-arm, open-label, cluster-randomised controlled trial in villages in the Tambacounda health district of southeast Senegal. Eligible villages had a population size of 200-800, were within a health-post catchment area with an annual malaria incidence of 60-160 cases per 1000 people, and had an established or planned Prise en Charge à Domicile Plus model. We randomly assigned villages (1:1) using a stratified, constrained randomisation approach to receive either three cycles of MDA with oral dihydroartemisinin-piperaquine plus single, low-dose primaquine administered at 6-week intervals (intervention) or to standard of care, which included three cycles of seasonal malaria chemoprevention (SMC) with oral sulfadoxine-pyrimethamine plus amodiaquine administered at 4-week intervals (control). Participants, the field team, and all investigators, including those who assessed outcomes and analysed data, were unmasked to allocation assignment. Laboratory technicians were masked to intervention assignment. The primary outcome was village-level, *P falciparum*-confirmed malaria incidence in the post-intervention year (ie, July to December, 2022). Secondary outcomes included malaria incidence during the intervention year (ie, July to December, 2021), coverage and safety of MDA, and adverse events. We conducted analyses using an intention-to-treat approach. The trial is registered with ClinicalTrials.gov ([NCT04864444](#)) and is completed.

Findings: Between Sept 1 and Oct 25, 2020, 523 villages were geolocated and screened for eligibility; 111 met the inclusion criteria. Of these, 60 villages were randomly selected and assigned to the intervention arm or control arm. Distribution coverage of all three doses of dihydroartemisinin-piperaquine was 6057 (73·6%) of 8229 participants in the first cycle, 6836 (78·8%) of 8673 participants in the second cycle, and 7065 (81·3%) of 8690 participants in the third cycle. Distribution coverage of single, low-dose primaquine was 6286 (78·6%) of 7999 participants in the first cycle, 6949 (82·1%) of 8462 participants in the second cycle, and 7199

(84.0%) of 8575 participants in the third cycle. Distribution coverage of all three doses of SMC was 3187 (92.2%) of 3457 children aged 3-120 months in the first cycle, 3158 (91.8%) of 3442 children aged 3-120 months in the second cycle, and 3139 (91.4%) of 3434 children aged 3-120 months in the third cycle. In the intervention year (ie, July to December, 2021), the adjusted effect of MDA was 55% (95% CI 28 to 71). In the post-intervention year (ie, July to December 2022), the adjusted MDA effect was 26% (-17 to 53). Malaria incidence during the transmission season of the post-intervention year was 126 cases per 1000 population in the intervention arm and 146 cases per 1000 population in the control arm. No serious adverse events were reported.

Interpretation: In southeast Senegal, a low-to-moderate transmission setting where malaria-control measures have been scaled up, three cycles of MDA with dihydroartemisinin-piperaquine plus single, low-dose primaquine was safe and reduced malaria burden during the intervention year. However, its sustained effect was weak and continuation of MDA or another transmission-reducing strategy could be required.

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The effect of intermittent preventive treatment for malaria with dihydroartemisinin-piperaquine on vaccine-specific responses among schoolchildren in rural Uganda (POPVAC B): a double-blind, randomised controlled trial

[Ludoviko Zirimenya¹](#), [Agnes Natukunda²](#), [Jacent Nassuuna³](#), [Gyaviira Nkurunungi⁴](#), [Christopher Zziwa³](#), [Caroline Ninsiima³](#), [Christine Kukundakwe³](#), [Christine M Nankabirwa³](#), [Charity Katushabe³](#), [Loyce K Namusobya³](#), [Gloria Oduru³](#), [Grace Kabami³](#), [Joel Kabali³](#), [John Kayiwa⁵](#), [Joyce Kabagenyi³](#), [Govert J van Dam⁶](#), [Paul L A M Corstjens⁷](#), [Stephen Cose¹](#), [Anne Wajja⁸](#), [Sarah G Staedke⁹](#), [Pontiano Kaleebu³](#), [Alison M Elliott¹](#), [Emily L Webb¹⁰](#); [POPVAC trial team](#)

Abstract

Background: Several important vaccines differ in immunogenicity and efficacy between populations. We hypothesised that malaria suppresses responses to unrelated vaccines and that this effect can be reversed—at least partially—by monthly malaria intermittent preventive treatment (IPT) in high-transmission settings.

Methods: We conducted an individually randomised, double-blind, placebo-controlled trial of the effect of malaria IPT with dihydroartemisinin-piperaquine on vaccine responses among schoolchildren aged 9-17 years in Jinja district, Uganda. Participants were recruited from two schools and did not have exposure to vaccines of interest after the age of 5 years, with the exception of human papillomavirus (HPV). Computer-generated 1:1 randomisation was implemented in REDCap. 3-day courses of dihydroartemisinin-piperaquine (dosage by weight) or placebo were administered monthly, including twice before the first vaccination. Trial participants were vaccinated with the live parenteral BCG vaccine (Serum Institute of India, Pune, India) at week 0; yellow fever vaccine (YF-17D; Sanofi Pasteur, Lyon, France); live oral typhoid vaccine (Ty21a; PaxVax, London, UK), and quadrivalent virus-like particle HPV vaccine (Merck, Rahway, NJ, USA) at week 4; and toxoid vaccines (tetanus-diphtheria; Serum Institute of India) and an HPV booster at week 28. An additional HPV vaccination at week 8 was provided to female participants older than 14 years who had not previously been

vaccinated, and a tetanus-diphtheria booster was given after completion of the trial at week 52. Primary outcomes were vaccine responses at week 8 and, for tetanus-diphtheria, at week 52, and analysis was done in the intention-to-treat population. Malaria parasite prevalence at enrolment and during follow-up was determined retrospectively by PCR. The safety population comprised all randomly allocated participants. The trial was registered at the ISRCTN Registry (ISRCTN62041885) and is complete.

Findings: Between May 25 and July 14, 2021, we assessed 388 potential participants for eligibility. We enrolled and randomly allocated 341 participants to the two groups (170 [50%] to dihydroartemisinin-piperaquine and 171 [50%] to placebo); 192 (56%) were female and 149 (44%) participants were male. 145 (85%) participants in the dihydroartemisinin-piperaquine group and 140 participants (82%) in the placebo group were followed up until the week 52 endpoint. At enrolment, 109 (64%) of all participants in the dihydroartemisinin-piperaquine group and 99 (58%) of 170 participants in the placebo group had malaria; this reduced to 6% or lower at all follow-up visits in the dihydroartemisinin-piperaquine group. There was no effect of dihydroartemisinin-piperaquine versus placebo on primary outcomes: BCG-specific IFN γ ELISpot response had a geometric mean ratio (GMR) of 1.09 (95% CI 0.93-1.29), $p=0.28$; yellow fever neutralising antibody was 1.19 (0.91-1.54), $p=0.20$ for plaque reduction neutralising reference tests (PRNT₅₀) titres (the reciprocal of the last plasma dilution that reduced by 50%) and 1.24 (0.97-1.58), $p=0.09$ for PRNT₉₀ titres (reciprocal of the last plasma dilution that reduced by 90%); and IgG to Salmonella enterica serovar Typhi O-lipopolysaccharide was 1.09 (0.81-1.46), $p=0.58$, HPV-16 was 0.72 (0.44-1.77), $p=0.19$, HPV-18 was 0.71 (0.47-1.09), $p=0.11$; tetanus toxoid was 1.22 (0.91-1.62), $p=0.18$, and diphtheria toxoid was 0.97 (0.83-1.13), $p=0.72$. There was some evidence that dihydroartemisinin-piperaquine reduced waning of the yellow fever response.

Interpretation: IPT for malaria with dihydroartemisinin-piperaquine did not improve peak vaccine responses, despite reducing malaria prevalence. Possible longer-term effects on response waning should be further explored.

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Safety and efficacy of repeat ivermectin mass drug administrations for malaria control (RIMDAMAL II): a phase 3, double-blind, placebo-controlled, cluster-randomised, parallel-group trial

[A Fabrice Somé¹](#), [Anthony Somé¹](#), [Emmanuel Sougué¹](#), [Cheick Oumar W Ouédraogo¹](#), [Ollo Da¹](#), [S Rodrigue Dah¹](#), [Frederic Nikiéma¹](#), [Tereza Magalhaes²](#), [Lyndsey I Gray³](#), [Will Finical³](#), [Greg Pugh³](#), [Paula Lado³](#), [Jenna C Randall³](#), [Timothy A Burton³](#), [Molly E Ring³](#), [Anna-Sophia Leon³](#), [McKenzie Colt⁴](#), [Fangyong Li⁵](#), [Kaicheng Wang⁵](#), [Martina Wade⁴](#), [Audun J Lier⁶](#), [Kacey Richards⁴](#), [Hannah Sprock⁴](#), [Elizabeth Zhang⁴](#), [Julia Ellman⁴](#), [Ijeamaka Achebe⁴](#), [Conner L Jackson⁷](#), [Mengli Xiao⁷](#), [Emma J Wu⁸](#), [Teun Bousema⁹](#), [Hannah C Slater¹⁰](#), [Brian D Foy³](#), [Sunil Parikh¹¹](#), [Roch K Dabiré¹](#)

Abstract

Background: The success of crucial vector control efforts in Africa (eg, long-lasting insecticide-treated nets [ITNs] and indoor residual spraying) are threatened by widespread insecticide resistance and insufficient effect on outdoor mosquito biting. Studies have shown that ivermectin, used for the treatment of parasitic diseases, can kill malaria vectors that

feed on the blood of treated people and thus might be an effective complementary vector control tool if administered widely to communities in malaria endemic regions. We aimed to test the safety of repeated, high-dose ivermectin mass drug administration (MDA) and its efficacy for reducing malaria incidence among children when integrated with seasonal malaria chemoprevention (SMC) delivery.

Methods: We conducted a phase 3, double-blind, placebo-controlled, cluster-randomised, parallel-group trial in southwest Burkina Faso over two consecutive rainy seasons (2019-20). 14 villages or village sectors (clusters) were randomly assigned (1:1) to ivermectin or placebo MDA by random draw, and study-eligible participants (those who regularly lived in the cluster and provided written informed consent) from all households were enrolled in July, 2019 and July, 2020. Participants were eligible for MDA if they were 90 cm in height or taller and not excluded for other safety reasons (eg, pregnancy or taking SMC drugs). There were no age restrictions for participants. Each rainy season (July to October), eligible participants from the intervention group clusters received monthly high-dose oral ivermectin MDA (three daily doses, approximately 300 µg/kg dosed by height bands) and those from the control group received monthly oral placebo MDA for up to eight treatment rounds. MDA was performed by study staff alongside community health worker administration of monthly SMC to children aged 3-59 months in both groups. All participants and study personnel, apart from the pharmacist, were masked to group assignment. The primary outcome was weekly malaria incidence in children aged 10 years and younger, as assessed by weekly active case detection until week 16 of year 2, by intention to treat. Adverse events were monitored in all MDA participants through active and passive surveillance. Blood was sampled for secondary parasitological outcomes, including analysis of parasite species distribution among malaria cases. Mosquitoes were sampled from pre-selected households in three clusters per group for secondary entomological outcomes, including analysis of blood-fed mosquito survivorship, mosquito biting rates, and entomological inoculation rates. Changes in haemoglobin pre-intervention and post-intervention in children aged 10 years and younger were assessed in 2020. The trial is registered with ClinicalTrials.gov ([NCT03967054](https://clinicaltrials.gov/ct2/show/study/NCT03967054)) and the Pan African Clinical Trials Registry (PACT201907479787308) and is completed.

Findings: The study took place from July 13, 2019, to Nov 8, 2020, with seven villages assigned to the control group and seven to the intervention group. Participants were enrolled from households in both groups in July, 2019, and July, 2020. In the intervention group, 1928 participants in 2019 and 2163 participants in 2020 were followed up, and 703 children in 2019 and 686 children in 2020 were analysed. In the control group, 1604 participants in 2019 and 1921 participants in 2020 were followed up, and 605 children in 2019 and 641 children in 2020 were analysed. MDA coverage (receiving ≥ 1 dose) in the enrolled population (including those who were ineligible) varied over the intervention period (68-74%), with 86-95% of participants who were eligible receiving ivermectin or placebo over the study period. 288 (47.2%) of 610 children in the control group and 312 (44.2%) of 706 children in the ivermectin group received SMC, and all clusters received new dual-chemistry Interceptor G2 ITNs containing chlorfenapyr and α -cypermethrin by government authorities in October, 2019. The average estimated weekly malaria incidence rate per 100 person-weeks among children in the intervention group was 1.78 (95% CI 1.24-2.53) and 1.84 (1.29-2.64) in the control group, and the incidence rate ratio was 0.96 (95% CI 0.58-1.59; $p=0.8723$). The risk of adverse events among eligible participants in the intervention group was lower than in the control group (risk ratio 0.63, 95% CI 0.46-0.87; $p=0.0049$). The distribution of *Plasmodium* spp detected in children with clinical malaria was unexpectedly diverse with

non-*Plasmodium falciparum* species detected in 56 (11%) of 505 symptomatic children; however, species distribution did not differ between groups ($p=0.15$). Blood-fed *Anopheles gambiae* species complex mosquitoes captured in intervention group clusters the week after MDA in 2019 had decreased survival relative to those captured from control group clusters ($p<0.0001$), but this effect was not seen in mosquitoes captured 3 weeks after MDA. Overall entomological inoculation rates (EIRs; infectious bites per person per night) did not differ between groups (intervention EIR 0.010; control EIR 0.011; between-group ratio 0.91, 95% CI 0.56-1.30; $p=0.45$). In 2020, children aged 10 years and younger in the intervention group had a significantly higher increase in haemoglobin pre-intervention versus post-intervention than children in the control group ($p=0.007$).

Interpretation: Repeated high-dose ivermectin MDA integrated with SMC distributions at the study site did not reduce malaria incidence among children relative to placebo MDA, despite evidence that, compared with the control group, mosquito survivorship in the first year was reduced in the intervention group the week following MDA and overall improvements in haemoglobin were greater in children in the intervention group. Confounding factors, including unexpectedly low malaria incidence over the trial period, possibly due to government distribution of dual-chemistry ITNs to all trial clusters in the middle of the intervention period, overdispersion of the primary incidence outcome between clusters, and high parasite and mosquito species diversity, might have influenced the primary outcome.

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Comparing approaches for chemoprevention for school-based malaria control in Malawi: an open label, randomized, controlled clinical trial

Alick Sixpence^{1,2}, Maclean Vokhiwa³, Wangisani Kumalakwaan², Nicola J Pitchford⁴, Karl B Seydel^{5,6}, Laurence S Magder⁷, Miriam K Laufer⁸, Don P Mathanga^{2,9}, Lauren M Cohee^{8,10}

Abstract

Background: School-age children in sub-Saharan Africa suffer an underappreciated burden of malaria which threatens their health and education. To address this problem, we compared the efficacy of two school-based chemoprevention approaches: giving all students intermittent preventive treatment (IPT) or screening and treating only students with detected infections (IST).

Methods: In a three-arm, open-label, randomized, controlled trial ([NCT05244954](#)) in Malawi, 746 primary school students, aged 5-19 years, were individually randomized within each grade-level to IPT ($n = 249$), IST with a high-sensitivity rapid diagnostic test (hs-RDT, $n = 248$), or control ($n = 249$). At six-week intervals three times within the peak malaria transmission season (February-June 2022) treatment with dihydroartemisinin-piperazine (DP) was administered to girls <10 years and all boys, and chloroquine to older girls. The primary outcome was *Plasmodium falciparum* (Pf) infection detected by PCR 6-8 weeks after the final intervention. Secondary outcomes included anaemia, clinical malaria, and scores on tests of attention, literacy, and math. Analysis was by modified intention-to-treat.

Findings: Outcomes analyses included 727 (97%) participants. At the end of the study, prevalence of Pf infection was 17% (41/243) in the IPT arm, 24% (58/244) in the IST arm, and

53% (127/240) in the control arm. Compared to controls, IPT and IST reduced the odds of *Pf* infection (IPT adjusted odds ratio [aOR]: 0.18 (95% CI: 0.11, 0.27); $p < 0.0001$; IST aOR: 0.27 (95% CI: 0.18, 0.40); $p < 0.0001$). However, only participants receiving IPT had a lower incidence of clinical malaria (0.19 cases per person per six months (95% CI: 0.14, 0.27) vs 0.56 (95% CI: 0.46, 0.68); incidence rate ratio: 0.38 (95% CI: 0.26, 0.55); $p < 0.0001$) and prevalence of anaemia (8% [20/243] vs 15% [36/240]; aOR: 0.49 (95% CI: 0.27, 0.91); $p = 0.023$) compared to controls. Literacy scores were higher in both intervention arms. No between group differences in tests of attention or math or number of serious adverse events were found.

Interpretation: Results support implementation of IST with hs-RDTs or IPT for reduction in the prevalence of infection. Based on reductions in clinical malaria, IPT may provide additional benefits warranting further consideration by school-based malaria chemoprevention programs.

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Effect of weekly fever-screening and treatment and monthly RDT testing and treatment on the infectious reservoir of malaria parasites in Burkina Faso: a cluster-randomised trial

[Katharine A Collins¹](#), [Alphonse Ouedraogo²](#), [Wamdaogo Moussa Guelbeogo²](#), [Issiaka Soulama²](#), [Maurice S Ouattara²](#), [Salif Sombie²](#), [Nicolas Ouedraogo²](#), [Aboubacar S Coulibaly²](#), [Apollinaire Nombre²](#), [Kjerstin Lanke¹](#), [Jordache Ramjith¹](#), [Shehu S Awandu¹](#), [Samuel S Serme²](#), [Noelie Henry²](#), [Will Stone³](#), [Issa N Ouedraogo²](#), [Amidou Diarra²](#), [Tobias M Holden⁴](#), [Sodiomon B Sirima⁵](#), [John Bradley⁶](#), [Seyi Soremekun³](#), [Prashanth Selvaraj⁷](#), [Jaline Gerardin⁸](#), [Chris Drakeley³](#), [Teun Bousema⁹](#), [Alfred B Tiono²](#)

Abstract

Background: The majority of *Plasmodium* spp infections in endemic countries are asymptomatic and a source of onward transmission to mosquitoes. We aimed to examine whether *Plasmodium falciparum* transmission and malaria burden could be reduced by improving early detection and treatment of infections with active screening approaches.

Methods: In this 18-month cluster randomised study in Sapone, Burkina Faso, households were enrolled and randomly assigned (1:1:1) to one of three groups: group 1 (control) received standard of care only, group 2 received active weekly, at home, fever screening by a community health worker regardless of symptoms, participants with a fever received a rapid diagnostic test (RDT) and treatment if RDT positive, and group 3 received active weekly fever screening (as in group 2) plus a monthly RDT regardless of symptoms, and treatment if RDT positive. Eligible households had a minimum of three eligible residents, one in each age group (<5 years, 5-15 years, and >15 years). The primary outcome was parasite prevalence by quantitative PCR (qPCR) in the end-of-study cross-sectional survey. Secondary outcomes included parasite and gametocyte prevalence and density in all three end-of-season cross-sectional surveys, incidence of infection, and the transmissibility of infections to mosquitoes. This trial was registered at ClinicalTrials.gov ([NCT03705624](#)) and is completed.

Findings: A total of 906 individuals from 181 households were enrolled during two phases, and participated in the study. 412 individuals were enrolled between Aug 9 and 17, 2018, and participated in phase 1 and 494 individuals were enrolled between Jan 10 and 31, 2019, in phase 2. In the end-of-study cross-sectional survey (conducted between Jan 13 and 21, 2020), *Pfalciparum* prevalence by qPCR was significantly lower in group 3 (29.26%; 79 of 270),

but not in group 2 (45·66%; 121 of 265), when compared with group 1 (48·72%; 133 of 273; risk ratio 0·65 [95% CI 0·52-0·81]; $p=0·0001$). Total parasite and gametocyte prevalence and density were also significantly lower in group 3 in all surveys. The largest differences were seen at the end of the dry season, with gametocyte prevalence 78·4% and predicted transmission potential 98·2% lower in group 3 than in group 1.

Interpretation: Active monthly RDT testing and treatment can reduce parasite carriage and the infectious reservoir of *P falciparum* to less than 2% when used during the dry season. This insight might inform approaches for malaria control and elimination.

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Artemether-lumefantrine with or without single-dose primaquine and sulfadoxine-pyrimethamine plus amodiaquine with or without single-dose tafenoquine to reduce Plasmodium falciparum transmission: a phase 2, single-blind, randomised clinical trial in Ouelessebouyou, Mali

[Almahamoudou Mahamar¹](#), [Merel J Smit²](#), [Koualy Sanogo³](#), [Youssof Sinaba³](#), [Sidi M Niambele³](#), [Adama Sacko³](#), [Oumar M Dicko³](#), [Makonon Diallo³](#), [Seydina O Maguiraga³](#), [Yaya Sankaré³](#), [Sekouba Keita³](#), [Siaka Samake³](#), [Adama Dembele³](#), [Kjerstin Lanke²](#), [Rob Ter Heine⁴](#), [John Bradley⁵](#), [Yahia Dicko³](#), [Sekou F Traore³](#), [Chris Drakeley⁶](#), [Alassane Dicko³](#), [Teun Bousema²](#), [Will Stone⁶](#)

Abstract

Background: Artemether-lumefantrine is widely used for uncomplicated *Plasmodium falciparum* malaria; sulfadoxine-pyrimethamine plus amodiaquine is used for seasonal malaria chemoprevention. We aimed to determine the efficacy of artemether-lumefantrine with and without primaquine and sulfadoxine-pyrimethamine plus amodiaquine with and without tafenoquine for reducing gametocyte carriage and transmission to mosquitoes.

Methods: In this phase 2, single-blind, randomised clinical trial conducted in Ouelessebouyou, Mali, asymptomatic individuals aged 10-50 years with *P falciparum* gametocytaemia were recruited from the community and randomly assigned (1:1:1:1) to receive either artemether-lumefantrine, artemether-lumefantrine with a single dose of 0·25 mg/kg primaquine, sulfadoxine-pyrimethamine plus amodiaquine, or sulfadoxine-pyrimethamine plus amodiaquine with a single dose of 1·66 mg/kg tafenoquine. All trial staff other than the pharmacist were masked to group allocation. Participants were not masked to group allocation. Randomisation was done with a computer-generated randomisation list and concealed with sealed, opaque envelopes. The primary outcome was the median within-person percent change in mosquito infection rate in infectious individuals from baseline to day 2 (artemether-lumefantrine groups) or day 7 (sulfadoxine-pyrimethamine plus amodiaquine groups) after treatment, assessed by direct membrane feeding assay. All participants who received any trial drug were included in the safety analysis. This study is registered with ClinicalTrials.gov, [NCT05081089](#).

Findings: Between Oct 13 and Dec 16, 2021, 1290 individuals were screened and 80 were enrolled and randomly assigned to one of the four treatment groups (20 per group). The median age of participants was 13 (IQR 11-20); 37 (46%) of 80 participants were female and 43 (54%) were male. In individuals who were infectious before treatment, the median percentage reduction in mosquito infection rate 2 days after treatment was 100·0% (IQR 100·0-100·0; $n=19$; $p=0·0011$) with artemether-lumefantrine and 100·0% (100·0-100·0; $n=19$;

$p=0.0001$) with artemether-lumefantrine with primaquine. Only two individuals who were infectious at baseline infected mosquitoes on day 2 after artemether-lumefantrine and none at day 5. By contrast, the median percentage reduction in mosquito infection rate 7 days after treatment was 63.6% (IQR 0.0-100.0; $n=20$; $p=0.013$) with sulfadoxine-pyrimethamine plus amodiaquine and 100% (100.0-100.0; $n=19$; $p<0.0001$) with sulfadoxine-pyrimethamine plus amodiaquine with tafenoquine. No grade 3-4 or serious adverse events occurred.

Interpretation: These data support the effectiveness of artemether-lumefantrine alone for preventing nearly all mosquito infections. By contrast, there was considerable post-treatment transmission after sulfadoxine-pyrimethamine plus amodiaquine; therefore, the addition of a transmission-blocking drug might be beneficial in maximising its community impact.

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Collateral benefits of ivermectin mass drug administration designed for malaria against headlice in Mopeia, Mozambique: a cluster randomised controlled trial

[Joanna Furnival-Adams^{1,2}](#), [Amelia Houana³](#), [Patricia Nicolas^{4,5,3}](#), [Julia Montaña^{4,5,3}](#), [Samuel Martinho³](#), [Aina Casellas⁴](#), [Hansel Mundaca⁴](#), [Jenisse Mbanze³](#), [Arlindo Soares³](#), [Saimado Imputiua³](#), [Paula Ruiz-Castillo⁴](#), [Marta Ribes^{4,5}](#), [Almudena Sanz⁴](#), [Mussa Mamudo Salé³](#), [Antonio Macucha³](#), [Eldo Elobolobo³](#), [Vegovito Vegove³](#), [Victor Mutepa³](#), [Humberto Munguambe³](#), [Aida Xerinda³](#), [Felisbela Materula³](#), [Regina Rabinovich^{4,6}](#), [Francisco Saute³](#), [Carlos Chaccour^{4,7,8}](#)

Abstract

Background: Headlice are prevalent worldwide, with a higher burden in rural, lower-middle income settings. They can cause intense itchiness, discomfort, and secondary bacterial infections with potentially serious consequences. Ivermectin is efficacious against headlice, and is also being evaluated as a malaria vector control tool. In this study, we explored risk factors for headlice, and assessed the efficacy of ivermectin mass drug administration (MDA) designed for malaria against headlice.

Methods: We conducted an open-label, assessor-blind, cluster-randomized controlled trial in Mopeia, Mozambique. A single dose of ivermectin was given monthly to eligible humans or humans and livestock (humans: 400 µg/kg, livestock: 1% injectable 200 µg/kg) in 3 consecutive months during the rainy season. The control group received albendazole (humans only). Thirty-nine clusters (13 per arm) were randomly selected for the nested assessment of headlice prevalence. 1341 treated participants were followed up at least once, 1, 2 and 3 months and 382 untreated (ineligible) participants at 3 and 6 months after the first MDA round. Headlice diagnosis was determined by scalp examination. Logistic regression was used to identify risk factors for headlice at baseline, and to estimate the treatment effect at each time point.

Results: A total of 1309 participants were included in the main analysis assessing ivermectin MDA efficacy, and 1332 in the risk factor analysis. The baseline headlice prevalence was 11%. Risk factors included living with a household member with head itch [adjusted odds ratio (aOR) = 48.63, 95% confidence interval (CI): 28.7-82.3, P -value < 0.0001], being female (aOR = 2.25, 95% CI: 1.33-3.80, P -value < 0.01), and using surface water as the main water (aOR = 2.37, 95% CI: 1.12-5.33, P -value = 0.04). The treated population receiving ivermectin had significantly lower odds of having headlice at 3 months compared to those receiving

albendazole (aOR = 0.19, 95% CI: 0.04-0.91, P-value = 0.04). There was no indirect effect on headlice among children ineligible for treatment.

Conclusions: In a highly endemic setting, mass drug administration with ivermectin significantly reduces headlice infestation prevalence among those who receive the drug for three sequential months. The lack of effect among untreated, ineligible children implies that additional interventions would be needed to interrupt local transmission.

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Adjunctive ivermectin mass drug administration for malaria control on the Bijagos Archipelago of Guinea-Bissau (MATAMAL): a quadruple-blinded, cluster-randomised, placebo-controlled trial

[Harry Hutchins¹](#), [Elizabeth Pretorius²](#), [John Bradley³](#), [Eunice Teixeira da Silva⁴](#), [Hristina Vasileva⁵](#), [Mamadou Ousmane Ndiath⁶](#), [Robert T Jones²](#), [Harouna Dit Massire Soumare⁶](#), [Haddy Nyang⁶](#), [Aurelia Prom⁶](#), [Sarata Sambou⁶](#), [Fatima Ceesay⁶](#), [Sainey Ceesay⁶](#), [Sophie Moss¹](#), [David Mabey¹](#), [Paulo Djata⁷](#), [Jose Ernesto Nante⁷](#), [Cesario Martins⁸](#), [James G Logan⁹](#), [Hannah Slater¹⁰](#), [Kevin Tetteh¹¹](#), [Chris Drakeley¹²](#), [Umberto D'Alessandro⁶](#), [Amabelia Rodrigues⁴](#), [Anna Last¹³](#)

Free article

Abstract

Background: Arthropod vectors feeding on the blood of individuals treated with ivermectin have substantially increased mortality. Whether this effect will translate into a useful tool for reducing malaria burden at scale is not clear. Our trial aimed to assess whether using ivermectin as an adjunct to mass drug administration (MDA) with dihydroartemisinin-piperaquine would further reduce malaria prevalence.

Methods: MATAMAL was a quadruple-blinded, cluster-randomised, placebo-controlled trial, conducted on the Bijagos Archipelago, Guinea-Bissau, an area of seasonal malaria transmission. All residents were invited to participate, with exclusions for drug safety. 24 clusters were randomised in a 1:1 ratio, using restriction randomisation, to either MDA with three daily oral doses of dihydroartemisinin-piperaquine and ivermectin (300 µg/kg per day) in three sequential months during the transmission season in 2021 and 2022, or MDA with dihydroartemisinin-piperaquine and placebo in the same schedule. The primary outcome was quantitative PCR prevalence of *Plasmodium falciparum* parasitaemia in all age groups, during peak transmission, after the second year of intervention. The primary entomological outcome was anopheline parity rate. The trial is registered with ClinicalTrials.gov ([NCT04844905](#)).

Findings: Participants were recruited between June 7, 2021 and Sept 21, 2022. The baseline population was 25 882 (12 634 [50.6%] were female individuals and 12 317 [49.4%] were male individuals): 13 832 were in the intervention group and 12 050 in the control group. Cluster-level coverage for dihydroartemisinin-piperaquine ranged from 60.4% to 78.7%, and for ivermectin or ivermectin-placebo from 58.1 to 77.1%. Following the intervention, the prevalence of *P falciparum* infection was 118 (5.05%) of 2300 in the control group and 141 (6.64%) of 2083 in the intervention group. The adjusted risk difference was 1.67% (95% CI -1.44 to 4.78; p=0.28). There were 124 adverse events in the control group (1.0% of participants) and 267 in the intervention group (1.9% of participants). Two serious adverse

events were reported, neither related to the intervention, and no treatment-related deaths. The anopheline parity rate was 1679 (67.8%) of 2475 in control clusters and 1740 (72.3%) of 2414 in intervention clusters. The adjusted risk difference was -1.32 (95% CI -14.77 to 12.12; $p=0.84$).

Interpretation: Adding ivermectin to dihydroartemisinin-piperaquine MDA had no additional effect on reducing malaria prevalence or vector parity in this setting. The intervention was well tolerated. To our knowledge, this trial is the first to be designed to assess whether ivermectin has an additive effect on malaria when coadministered with dihydroartemisinin-piperaquine MDA.

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Relationship between red blood cell polymorphisms and effectiveness of seasonal malaria chemoprevention in 2020 in Dangassa, Mali

[Ilo Dicko¹²](#), [Drissa Konaté³⁴](#), [Seidina Aboubacar Samba Diakité⁴⁵](#), [Bourama Keita⁴](#), [Ibrahim Sanogo⁶](#), [Aboubacar Fomba⁴](#), [Abdouramane Traoré⁴](#), [Job Koné⁴](#), [Salimata Kanté⁴](#), [Oumarou Tessougué⁷](#), [Sory Ibrahima Diawara³⁴](#), [Seydou Doumbia⁶³](#), [Mahamadou Diakité⁶⁴](#)

Abstract

Treatment failure with amodiaquine was reported in Dangassa, where red blood cell (RBC) polymorphisms are found and seasonal malaria chemoprevention (SMC) is underway. Here, we aimed at assessing the influence of RBC polymorphisms on SMC effectiveness. This was a secondary analysis of data from a study conducted in Dangassa. Children aged 5 to 14 years enrolled in an open randomized study were assigned either to receive SMC (intervention arm) or not (control arm). SMC was implemented from July to November. For all children, hemoglobin type and blood group were determined at enrolment in July, and parasitemia and hemoglobin level were monthly monitored by finger-prick. Overall, 166 children were enrolled among which 82 (49.40%) in the control arm and 84 (50.60%) in the SMC arm. The prevalence of HbAS was 10.24% (17/166) with 12.20% in the control and 8.33% in the SMC arm. O group was the most common overall (45%) and in the SMC arm (54%), but the control arm had more B (39.02%) than O (36.59%). In the SMC arm, no case of Plasmodium infection and malaria disease was observed in the 7 HbAS children while in Non-HbAS children, peaks of infection and disease prevalence were respectively observed in October (24.66%) and November (7.14%). For the SMC arm, in group O and Non-group O, Plasmodium infection cases were observed from August to December. Plasmodium infection and malaria disease were more frequently observed in HbAS children in the control arm than in the SMC arm. Further studies are needed to assess factors associated with the asymptomatic carriage of parasites during SMC in Dangassa

Nat Med. 2024 Oct;30(10):2813-2820.

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Extension of efficacy range for targeted malaria-elimination interventions due to spillover effects

[Jade Benjamin-Chung¹²](#), [Haodong Li³](#), [Anna Nguyen⁴](#), [Gabriella Barratt Heitmann⁴](#), [Adam Bennett⁵⁶](#), [Henry Ntuku⁵](#), [Lisa M Prach⁵](#), [Munyaradzi Tambo⁷](#), [Lindsey Wu⁸](#), [Chris](#)

[Drakeley⁸](#), [Roly Gosling^{5,9}](#), [Davis Mumbengegwi¹⁰](#), [Immo Kleinschmidt^{11,12,13}](#), [Jennifer L Smith^{5,14}](#), [Alan Hubbard³](#), [Mark van der Laan³](#), [Michelle S Hsiang^{15,5,14}](#)

Abstract

Malaria-elimination interventions aim to extinguish hotspots and prevent transmission to nearby areas. Here, we re-analyzed a cluster-randomized trial of reactive, focal interventions (chemoprevention using artemether-lumefantrine and/or indoor residual spraying with pirimiphos-methyl) delivered within 500 m of confirmed malaria index cases in Namibia to measure direct effects (among intervention recipients within 500 m) and spillover effects (among non-intervention recipients within 3 km) on incidence, prevalence and seroprevalence. There was no or weak evidence of direct effects, but the sample size of intervention recipients was small, limiting statistical power. There was the strongest evidence of spillover effects of combined chemoprevention and indoor residual spraying. Among non-recipients within 1 km of index cases, the combined intervention reduced malaria incidence by 43% (95% confidence interval, 20-59%). In analyses among non-recipients within 3 km of interventions, the combined intervention reduced infection prevalence by 79% (6-95%) and seroprevalence, which captures recent infections and has higher statistical power, by 34% (20-45%). Accounting for spillover effects increased the cost-effectiveness of the combined intervention by 42%. Targeting hotspots with combined chemoprevention and vector-control interventions can indirectly benefit non-recipients up to 3 km away.

Treatment of uncomplicated malaria

Malar J. 2025 Mar 11;24(1):77.

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[Comparing HemoCue® and Quantitative Buffy Coat® and Coulter Counter-measured haemoglobin concentrations in African children with acute uncomplicated malaria: a Bland-Altman analysis](#)

[Dhol S Ayuen¹](#), [Peter Olupot-Olupot^{2,3}](#), [Rita Muhindo²](#), [Marie A Onyamboko⁴](#), [Seun Ajayi¹](#), [Natenapa Chimjinda⁵](#), [Chiraporn Taya⁵](#), [Sophie Uyoga⁶](#), [Thomas N Williams^{6,7}](#), [Kathryn Maitland^{6,7}](#), [Caterina Fanello^{1,5}](#), [Nicholas P J Day^{1,5}](#), [Walter R Taylor^{#1,5}](#), [Mavuto Mukaka^{#8,9}](#)

Abstract

Background: Anaemia is a deleterious consequence of malaria, and its accurate diagnosis is crucial for effective management. However, laboratory methods for measuring haemoglobin (Hb) concentration, like the Coulter Counter and the Quantitative Buffy Coat® (QBC®), are costly and not widely accessible in resource-limited settings. The point-of-care HemoCue® test is a cheaper alternative and suitable in rural areas. The study aimed to determine the level of agreement between Coulter Counter/QBC® vs. HemoCue®-measured Hb concentrations by Bland-Altman analysis.

Methods: As part of a randomized, placebo-controlled trial of single low-dose primaquine in Ugandan and Congolese children with acute uncomplicated *Plasmodium falciparum* malaria, Hb concentrations were measured on days 0, 3, 7, and 28 using Coulter Counter (Uganda, n = 1880 paired values), QBC® (DR Congo, n = 1984 paired values) and HemoCue® Hb-301™. The predefined clinically acceptable limits were set at ± 0.5 g/dL.

Results: The Bland-Altman analysis showed that the HemoCue® minus Coulter Counter mean Hb difference was - 0.15 g/dL with lower and upper limits of agreement of - 3.68 g/dL and 3.39 g/dL, respectively. Corresponding HemoCue® minus QBC® values were - 0.23 g/dL, - 1.66 g/dL and 1.22 g/dL. Linear regression of Hb concentration differences vs. mean Hb concentrations showed negative correlations: $r = - 0.43$ and $r = - 0.34$ for HemoCue® vs. Coulter Counter and HemoCue® vs. QBC®, respectively.

Conclusions: Compared to Coulter and QBC®, mean HemoCue® measured Hb concentrations were lower and, compared to the Coulter or QBC® methods, had an overall tendency to measure lower Hb concentrations with increasing Hb concentrations. Upper and lower limits of agreement were wider than the predefined clinically acceptable limits of ± 0.5 g/dL. HemoCue® should be used with caution in settings where decisions about blood transfusions are made.

Treatment of severe malaria

Lancet Microbe. 2025 Feb;6(2):100966.

doi: 10.1016/j.lanmic.2024.100966. Epub 2024 Dec 17.

[Artemether-lumefantrine-amodiaquine or artesunate-amodiaquine combined with single low-dose primaquine to reduce Plasmodium falciparum malaria transmission in Ouélessébougou, Mali: a five-arm, phase 2, single-blind, randomised controlled trial](#)
[Almahamoudou Mahamar¹](#), [Leen N Vanheer²](#), [Merel J Smit³](#), [Koualy Sanogo¹](#), [Youssef Sinaba¹](#), [Sidi M Niambele¹](#), [Makonon Diallo¹](#), [Oumar M Dicko¹](#), [Richard S Diarra¹](#), [Seydina O Maguiraga¹](#), [Ahamadou Youssouf¹](#), [Adama Sacko¹](#), [Sekouba Keita¹](#), [Siaka Samake¹](#), [Adama Dembele¹](#), [Karina Teelen³](#), [Yahia Dicko¹](#), [Sekou F Traore¹](#), [Arjen Dondorp⁴](#), [Chris Drakeley⁵](#), [William Stone⁵](#), [Alassane Dicko¹](#)

Abstract

Background: Triple artemisinin-based combination therapies (TACTs) can delay the spread of antimalarial drug resistance. Artesunate-amodiaquine is widely used for uncomplicated *Plasmodium falciparum* malaria. We therefore aimed to determine the safety and efficacy of artemether-lumefantrine-amodiaquine and artesunate-amodiaquine with and without single low-dose primaquine for reducing gametocyte carriage and transmission to mosquitoes.

Methods: We did a five-arm, single-blind, phase 2 randomised controlled trial at the Ouélessébougou Clinical Research Unit of the Malaria Research and Training Centre of the University of Sciences, Techniques and Technologies of Bamako in Mali. Eligible participants were aged 10-50 years, with asymptomatic *P falciparum* microscopy-detected gametocyte carriage. Eligible participants were randomly allocated (1:1:1:1:1) to receive either artemether-lumefantrine, artemether-lumefantrine-amodiaquine, artemether-lumefantrine-amodiaquine plus primaquine, artesunate-amodiaquine, or artesunate-amodiaquine plus primaquine. Treatment regimens were administered on days 0, 1, and 2; primaquine was given as a single dose on day 0. All staff except the trial pharmacist and participants were masked to the treatment allocation. The primary outcome was the median percentage change in mosquito infection rate between pretreatment and 2 days after treatment

initiation, assessed by direct membrane feeding assay. Data were analysed using a per-protocol analysis. This study is registered with ClinicalTrials.gov, [NCT05550909](https://clinicaltrials.gov/ct2/show/study/NCT05550909).

Findings: Between Oct 16, 2022, and Dec 28, 2022, a total of 1249 individuals were screened; of whom, 100 were enrolled and randomly assigned to one of the five treatment groups (20 per group). Before treatment, 61 (61%) of 100 participants were infectious to mosquitoes, with a median of 7.3% (IQR 3.2 to 23.5) of mosquitoes becoming infected. Among infectious participants, the median percentage reduction in mosquito infection rate between pretreatment and 2 days after treatment was 100% (IQR 100 to 100) in the artemether-lumefantrine ($p=0.0018$), artemether-lumefantrine-amodiaquine ($p=0.0018$), and artemether-lumefantrine-amodiaquine plus primaquine ($p=0.0009$) treatment groups. In the artesunate-amodiaquine group the median percentage reduction in mosquito infection rate was only 32% (IQR -10.9 to 79.4; $p=0.19$), whereas a 100% median reduction was seen in the artesunate-amodiaquine plus primaquine group (IQR 100 to 100; $p=0.0009$). At day 2, two (10%) of 20 participants in the artemether-lumefantrine group, two (11%) of 19 in the artemether-lumefantrine-amodiaquine group, and 15 (75%) of 20 in the artesunate-amodiaquine group infected any number of mosquitoes whereas no infected mosquitoes were observed at this timepoint in the groups with primaquine. 85 (85%) of 100 participants had a total of 262 adverse events during follow-up; of which, 181 (69%) were categorised as mild and 81 (31%) as moderate. No serious adverse events were reported.

Interpretation: Our findings support the effectiveness of artemether-lumefantrine alone or as part of TACT for preventing nearly all human-mosquito malaria parasite transmission within 48 h. By contrast, substantial transmission was observed following treatment with artesunate-amodiaquine. The addition of a single low dose of primaquine blocks transmission to mosquitoes rapidly regardless of schizonticide.

BMC Med. 2024 Nov 6;22(1):516.

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Azithromycin in severe malaria bacterial co-infection in African children (TABS-PKPD): a phase II randomised controlled trial

[Roisin Connon](#)^{#1}, [Peter Olupot-Olupot](#)^{#2,3}, [Arthur M A Pistorius](#)^{#4}, [William Okiror](#)^{2,3}, [Tonny Ssenyondo](#)^{2,3}, [Rita Muhindo](#)^{2,3}, [Sophie Uyoga](#)⁵, [Ayub Mpoya](#)⁵, [Thomas N Williams](#)^{5,6}, [Diana M Gibb](#)¹, [A Sarah Walker](#)¹, [Rob Ter Heine](#)⁴, [Elizabeth C George](#)¹, [Kathryn Maitland](#)^{7,8}

Abstract

Background: African children with severe malaria are at increased risk of non-typhoidal salmonellae co-infection. Broad-spectrum antibiotics are recommended by guidelines but the optimal class and dose have not been established. We investigated the optimal dose of oral dispersible azithromycin and whether simple clinical criteria and point-of-care biomarkers could target antibiotics to those at greatest risk of bacterial co-infection.

Methods: We conducted a phase I/II trial in Ugandan children with severe malaria comparing a 5-day course of azithromycin: 10, 15 and 20 mg/kg of azithromycin (prescribed by weight bands) spanning the dose-range effective for other salmonellae infection. We generated relevant pharmacokinetic (PK) data by sparse sampling during dosing intervals and investigated associations between azithromycin exposure and potential mechanisms (PK-pharmacodynamics) using change in C-reactive protein (CRP), a putative marker of sepsis, at 72 h (continuous) and microbiological cure (7-day) (binary), alone and as a composite with 7-

day and 90-day survival. To assess whether clinical or biomarkers could identify those at risk of sepsis, a non-severe malaria control was concurrently enrolled.

Results: Between January 2020 and January 2022, 105 cases were randomised azithromycin doses: 35 to 10 mg/kg, 35 to 15 mg/kg and 35 to 20 mg/kg. Fifty non-severe malaria controls were concurrently enrolled. CRP reduced in all arms by 72 h with a mean reduction of 65.8 mg/L (95% CI 57.1, 74.5) in the 10 mg/kg arm, 64.8 mg/L (95% CI 56.5, 73.1; $p = 0.87$) in the 20 mg/kg arm and a smaller reduction 51.2 mg/L (95% CI 42.9, 59.5; $p = 0.02$) in the 15 mg/kg arm. Microbiological cure alone outcome was not analysed as only one pathogen was found among cases. Three events contributed to the composite outcome of 7-day survival and microbiological cure, with no events in the 15 mg/kg arm. The odds ratio comparing 20 vs 10 mg/kg was 0.50 (95% CI 0.04, 5.79); $p = 0.58$. Due to the low number of pathogens identified, it was not possible to identify better methods for targeting antibiotics including both the cases and controls.

Conclusions: We found no evidence for an association between systemic azithromycin exposure and reduction in CRP. Further work is needed to better identify children at highest risk from bacterial co-infection.

Malnutrition

(Papers in past years listed in this section refer to the management of protein-energy malnutrition. For other relevant studies of nutrition see also Nutrition, Vitamin A, Vitamin D, Zinc, Maternal health, Anaemia and iron deficiency)

Sci Transl Med. 2024 Oct 2;16(767):eadn2366.

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[**A microbiome-directed therapeutic food for children recovering from severe acute malnutrition**](#)

[Steven J Hartman^{1,2}](#), [Matthew C Hibberd^{1,2,3}](#), [Ishita Mostafa⁴](#), [Nurun N Naila⁴](#), [Md Munirul Islam⁴](#), [Mahabub Uz Zaman⁴](#), [Sayeeda Huq⁴](#), [Mustafa Mahfuz⁴](#), [Md Tazul Islam⁵](#), [Kallol Mukherji⁵](#), [Vaha Akbary Moghaddam⁶](#), [Robert Y Chen^{1,2}](#), [Michael A Province⁶](#), [Daniel M Webber^{1,2,3}](#), [Suzanne Henrissat^{1,2}](#), [Bernard Henrissat⁷](#), [Nicolas Terrapon⁸](#), [Dmitry A Rodionov⁹](#), [Andrei L Osterman⁹](#), [Michael J Barratt^{1,2,3}](#), [Tahmeed Ahmed⁴](#), [Jeffrey I Gordon^{1,2,3}](#)

Abstract

Globally, severe acute malnutrition (SAM), defined as a weight-for-length z-score more than three SDs below a reference mean ($WLZ < -3$), affects 14 million children under 5 years of age. Complete anthropometric recovery after standard, short-term interventions is rare, with children often left with moderate acute malnutrition (MAM; $WLZ -2$ to -3). We conducted a randomized controlled trial (RCT) involving 12- to 18-month-old Bangladeshi children from urban and rural sites, who, after initial hospital-based treatment for SAM, received a 3-month intervention with a microbiome-directed complementary food (MDCF-2) or a calorically more dense, standard ready-to-use supplementary food (RUSF). The rate of WLZ improvement was significantly greater in MDCF-2-treated children ($P = 8.73 \times 10^{-3}$), similar to our previous RCT of Bangladeshi children with MAM without antecedent SAM ($P = 0.032$). A correlated meta-analysis of plasma levels of 4520 proteins in both RCTs revealed 215 positively associated with WLZ (largely representing musculoskeletal and central nervous system development)

and 44 negatively associated (primarily related to immune activation). Moreover, the positively associated proteins were significantly enriched by MDCF-2 ($q = 1.1 \times 10^{-6}$). Characterizing the abundances of 754 bacterial metagenome-assembled genomes in serially collected fecal samples disclosed the effects of acute rehabilitation for SAM on the microbiome and how, during treatment for MAM, specific strains of *Prevotella copri* function at the intersection between MDCF-2 glycan metabolism and anthropometric recovery. These results provide a rationale for further testing the generalizability of MDCF efficacy and for identifying biomarkers to define treatment responses.

Health Policy Plan. 2025 Mar 7;40(3):273-286.

doi: 10.1093/heapol/czae106.

Cost-effectiveness of a simplified acute malnutrition program: a secondary analysis of the OptiMA randomized clinical trial in the Democratic Republic of the Congo

[Stephen C Resch¹](#), [Ryoko Sato¹](#), [Kevin Phelan²](#), [Cécile Cazes³](#), [Abdramane Ombotimbe⁴](#), [Victoire Hubert⁴](#), [Harouna Boubacar⁴](#), [Liévin Izie Bozama⁵](#), [Gilbert Tshibangu Sakubu⁶](#), [Béatrice Kalenga Tshiala⁵](#), [Toussaint Tusuku⁵](#), [Rodrigue Alitanou⁴](#), [Antoine Kouamé⁷](#), [Cyrille Yao⁷](#), [Delphine Gabillard³](#), [Moumouni Kinda⁸](#), [Renaud Becquet³](#), [Susan Shepherd⁸](#), [Robert M Hecht⁹](#)

Abstract

Acute malnutrition (AM) causes large loss of life and disability in children in Africa. Researchers are testing innovative approaches to increase the efficiency of treatment programs. This paper presents results of a cost-effectiveness analysis of one such program in the Democratic Republic of the Congo (DRC) based on a secondary analysis of a randomized controlled trial Optimizing Treatment for Acute Malnutrition (OptiMA), conducted in DRC in 2018-20. A total of 896 children aged 6-59 months with a mid-upper arm circumference (MUAC) <125 mm or with oedema were treated and followed for 6 months. The cost-effectiveness of OptiMA using ready-to-use therapeutic food (RUTF) at a tapered dose was compared with the standard national program in which severe cases (SAM) received RUTF proportional to weight, and moderate cases (MAM) were referred to another clinic for a fixed dose regimen of ready-to-use supplementary food. Cost analysis from the provider perspective used data collected during the trial and from administrative records. Statistical differences were derived using t-tests. The mean cost per enrolled child under OptiMA was \$123 [95% confidence interval (CI): 114-132], not statistically different from the standard group [\$127 (95%CI: 118-136), $P = 0.549$], while treatment success (i.e. recovery to MUAC > 125 mm and no relapse for 6 months) under OptiMA was 9% higher (72 vs 63%, $P = 0.004$). Among children with SAM at enrollment, there was no significant difference in treatment success between OptiMA and standard care (70 vs 62%, $P = 0.12$), but OptiMA's mean cost per enrolled child was 23% lower (\$128 vs \$166, $P < 0.0001$). OptiMA was more effective at preventing progression to SAM among those enrolled with MAM (5 vs 16%, $P < 0.0001$), with an incremental cost-effectiveness ratio of \$234 per progression to SAM prevented. Overall, OptiMA had significantly better outcomes and was no more expensive than standard care. Its adoption could enable more children to be successfully treated in contexts where therapeutic food products are scarce.

Br J Nutr. 2025 Feb 13:1-10.

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Serum insulin-like growth factor 1 in young children with moderate acute malnutrition: secondary analysis of a randomised trial in Burkina Faso

[Thora W Helt¹](#), [Bernardette Cichon²](#), [Christian Fabiansen²](#), [Ann-Sophie Iuel-Brockdorff²](#), [Charles W Yaméogo^{2,3}](#), [Christian Ritz⁴](#), [André Briend^{2,5}](#), [Kim F Michaelsen²](#), [Suzanne Filteau⁶](#), [Henrik Friis²](#), [Vibeke B Christensen^{1,7}](#), [Benedikte Grenov²](#)

Abstract

Insulin-like growth factor 1 (IGF-1) is an important growth factor in childhood. We aimed to investigate the impact of food supplements for the treatment of moderate acute malnutrition (MAM) on serum IGF-1 (sIGF-1). Secondary analysis of a randomised 2 × 2 × 3 factorial nutrition trial was performed. Children aged 6-23 months with MAM received 2093 kJ/d as lipid-based nutrient supplement (LNS) or corn soy blend (CSB), containing either dehulled soya or soya isolate and different quantities of dried skimmed milk (0 %, 20 % or 50 % of total protein) for 12 weeks. The trial was double-blind with regard to soya and milk but not to matrix (LNS v. CSB). sIGF-1 was measured at inclusion and after 12 weeks of supplementation. Of 1609 children enrolled, 1455 (90 %) had sIGF-1 measured at both time points. During supplementation, sIGF-1 increased 6.7 (95 % CI 6.1, 7.3) ng/ml compared with an expected age-dependent decrease of 0.3 (95 % CI 0.2, 0.4) ng/ml. Children who received LNS v. CSB had a lower increase in sIGF-1 (-8 %, 95 % CI -12, -3). The effect of LNS was partly attenuated when sIGF-1 was corrected for inflammation. Children who received soya isolate compared with dehulled soya had a higher increase in sIGF-1 (6 %, 95 % CI 1, 12). Milk content did not affect sIGF-1. Overall, sIGF-1 increased during supplementation. The lower increase with LNS v. CSB was only partly explained by increased inflammation with LNS and needs further investigation. Isolate v. dehulled soya led to a higher increase which may be due to antinutrients in dehulled soya.

J Nutr. 2024 Nov 5:S0022-3166(24)01133-7.

doi: 10.1016/j.tjnut.2024.11.001. Online ahead of print.

Acceptability of Microbiota-Directed Complementary Foods in Treating Indian Children with Moderate Acute Malnutrition: eACT-MAM Pre-Proof-of-Concept Study

[Sam Marconi¹](#), [Bireshwar Sinha²](#), [Aditi Apte³](#), [Midhun Sasikumar⁴](#), [Gunjan Aggarwal⁵](#), [Rashmi Chabukswar³](#), [Akshaya Vasudevan⁶](#), [Zavid Miyandad⁶](#), [Sowndharya Pandian⁶](#), [Pranita Shambharkar³](#), [Himani Bhardwaj⁵](#), [Girish Dayma³](#), [Dhiraj Agarwal³](#), [Sunita Taneja⁵](#), [Venkata Raghava Mohan⁶](#)

Abstract

Background: In India, currently, there are no standard guidelines for the management of moderate acute malnutrition (MAM). Previous research in Bangladesh has shown that children with MAM have impaired gut microbiota development, and microbiota-directed complementary foods (MDCF) can potentially repair their gut microbiota.

Objectives: The objectives of this study were to evaluate the acceptability and safety of supplementing shelf-stable formulation of MDCF in Indian children with MAM as compared

with a locally prepared ready-to-use supplementary food (RUSF) in 3 geographically distinct Indian populations and to establish and pilot systems of intervention delivery, collection, transport, and storage of stool samples using stringent protocols.

Methods: This pre-proof-of-concept (prePOC), multicentric, open-labeled, age-stratified, randomized controlled trial was done in children aged 6-18 mo with MAM. After a run-in period of 2 wk, the participants were supplemented with MDCF or RUSF for 4 wk through direct observation and followed up for another 2 wk post intervention. Maternal responses to the acceptability of the organoleptic properties of supplements were recorded weekly during the intervention phase of 4 wk. Compliance was reported based on the amount of supplement consumed by the children. Feasibility of weekly stool sample collection (except 7th week) within 30 min of passage was recorded. Anthropometric measurements were done at baseline and endline. Monitoring for adverse events was done throughout the course of the study.

Results: A total of 240 children with MAM were randomly selected to receive either MDCF or RUSF, of which 221 (92.1%) completed follow-up. The overall acceptability for >80% of the maternal responses was reported as good or very good for all organoleptic properties in both MDCF and RUSF arms. MDCF and RUSF interventions had good-to-high compliance in 83.0% and 79.8% of participants, respectively. At the end of the intervention phase, 53.2% (58/109) of children in MDCF arm against 42.0% (47/112) in RUSF arm had weight-for-length Z score >-2. The overall incidence of acute gastroenteritis reported was low; higher in MDCF compared with RUSF but not statistically significant.

Conclusion: The prePOC study demonstrates good acceptability and safety of MDCF among Indian children with MAM including the age group of 6-12 mo of age. The study demonstrates the feasibility of conducting a long-term supplementation study in this population. The study was registered at the clinical trial registry of India as CTRI/2023/01/048716.

Br J Nutr. 2024 Aug 14;132(3):372-381.

doi: 10.1017/S0007114524000837. Epub 2024 Jun 4.

Legume-supplemented feed for children hospitalised with severe malnutrition: a phase II trial

[Kevin Walsh](#)^{#12}, [Akglinta Kiosa](#)^{#1}, [Peter Olupot-Olupot](#)³, [Florence Alaroker](#)⁴, [William Okiror](#)³, [Margaret Nakuya](#)⁴, [Tonny Tsseniyondo](#)³, [Denis Aromut](#)⁴, [Bernard Charles Okalebo](#)³, [Rita Muhindo](#)³, [Ayub Mpoya](#)⁵, [Elizabeth C George](#)^{#6}, [Gary S Frost](#)^{#1}, [Kathryn Maitland](#)^{#3 5 7}

Abstract

Children hospitalised with severe malnutrition have high mortality and readmission rates post-discharge. Current milk-based formulations target restoring ponderal growth but not the modification of gut barrier integrity or microbiome which increases the risk of gram-negative sepsis and poor outcomes. We propose that legume-based feeds rich in fermentable carbohydrates will promote better gut health and improve overall outcomes. We conducted an open-label phase II trial at Mbale and Soroti Regional Referral Hospitals, Uganda, involving 160 children aged 6 months to 5 years with severe malnutrition (mid-upper arm circumference (MUAC) < 11.5 cm and/or nutritional oedema). Children were randomised to a lactose-free, chickpea-enriched legume paste feed (LF) (*n* 80) v. WHO

standard F75/F100 feeds (n 80). Co-primary outcomes were change in MUAC and mortality to day 90. Secondary outcomes included weight gain (> 5 g/kg/d), *de novo* development of diarrhoea, time to diarrhoea and oedema resolution. Day 90 MUAC increase was marginally lower in LF v. WHO arm (1.1 cm (interquartile range (IQR) 1.1) v. 1.4 cm (IQR 1.40), $P = 0.09$); day 90 mortality was similar (11/80 (13.8 %) v. 12/80 (15 %), respectively, OR 0.91 (95 % CI 0.40, 2.07), $P = 0.83$). There were no differences in any of the other secondary outcomes. Owing to initial poor palatability of the LF, ten children switched to WHO feeds. Per-protocol analysis indicated a trend to lower day 90 mortality and readmission rates in the LF (6/60 (10 %) and 2/60 (3 %) v. WHO feeds (12/71 (17.5 %) and 4/71 (6 %)). Further refinement of LF and clinical trials are warranted, given the poor outcomes in children with severe malnutrition.

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doi: 10.1136/bmjopen-2023-079448.

Lactoferrin and lysozyme to promote nutritional, clinical and enteric recovery: a protocol for a factorial, blinded, placebo-controlled randomised trial among children with diarrhoea and malnutrition (the Boresha Afya trial)

[Ruchi Tiwari¹](#), [Kirkby D Tickell²](#), [Emily Yoshioka¹](#), [Joyce Otieno³](#), [Adeel Shah⁴](#), [Barbra A Richardson^{1,5}](#), [Lucia Keter⁶](#), [Maureen Okello³](#), [Churchil Nyabinda⁶](#), [Indi Trehan¹](#), [Christine J McGrath¹](#), [Arianna Rubin Means¹](#), [Eric R Houpt⁷](#), [Jie Liu⁸](#), [James A Platts-Mills⁷](#), [James M Njunge⁹](#), [Doreen Rwigy^{6,10}](#), [Mareme M Diakhate¹](#), [Julius Nyaoke⁶](#), [Eric Ochola⁶](#), [Grace John-Stewart^{1,11,12}](#), [Judd L Walson^{11,13}](#), [Patricia B Pavlinac¹](#), [Benson O Singa³](#)

Abstract

Introduction: Children with moderate or severe wasting are at particularly high risk of recurrent or persistent diarrhoea, nutritional deterioration and death following a diarrhoeal episode. Lactoferrin and lysozyme are nutritional supplements that may reduce the risk of recurrent diarrhoeal episodes and accelerate nutritional recovery by treating or preventing underlying enteric infections and/or improving enteric function.

Methods and analysis: In this factorial, blinded, placebo-controlled randomised trial, we aim to determine the efficacy of lactoferrin and lysozyme supplementation in decreasing diarrhoea incidence and improving nutritional recovery in Kenyan children convalescing from comorbid diarrhoea and wasting. Six hundred children aged 6-24 months with mid-upper arm circumference <12.5 cm who are returning home after an outpatient visit or inpatient hospital stay for diarrhoea will be enrolled. Children will be randomised to 16 weeks of lactoferrin, lysozyme, a combination of the two, or placebo and followed for 24 weeks, with biweekly home visits by community health workers and clinic visits at 4, 10, 16 and 24 weeks. The primary analysis will compare the incidence of moderate-to-severe diarrhoea and time to nutritional recovery between each intervention arm and placebo. The trial will also test whether these interventions reduce enteric pathogen carriage, decrease enteric permeability and/or increase haemoglobin concentration in enrolled children. Finally, we will evaluate the acceptability, adherence and cost-effectiveness of lactoferrin and/or lysozyme.

Ethics and dissemination: The trial has been approved by the institutional review boards of the Kenya Medical Research Institute, the University of Washington, the Kenyan Pharmacy and Poisons Board, and the Kenyan National Commission on Science, Technology and Innovation. The results of this trial will be shared with local and international stakeholders

and published in peer-reviewed journals, and the key findings will be presented at relevant conferences.

Matern Child Nutr. 2024 Jul;20(3):e13649.

doi: 10.1111/mcn.13649. Epub 2024 Apr 10.

Three-arm clinical trial of improved flour targeting intestinal microbiota (MALINEA)

Muriel Vray¹, Laura Tondeur¹, Boris G Hedible², Rindra Vatosoa Randremanana³, Alexandre Manirakiza⁴, Ramatoulaye Hamidou Lazoumar⁵, Cassandre Van Platen⁶, Antonio Vargas⁷, André Briend^{8,9}, Ronan Jambou¹⁰; Malinea Clinical Trial Group

Abstract

The main objective of this project was to compare in the field conditions two strategies of re-nutrition of children with moderate acute malnutrition (MAM) aged from 6 to 24 months, targeting the microbiota in comparison with a standard regimen. A three-arm, open-label, pragmatic randomised trial was conducted in four countries (Niger, CAR, Senegal and Madagascar). Children received for 12 weeks either fortified blended flour (FBF control) = arm 1, or FBF + azithromycin (oral suspension of 20 mg/kg/day daily given with a syringe) for the first 3 days at inclusion = arm 2 or mix FBF with inulin/fructo-oligosaccharides (6 g/day if age ≥ 12 months and 4 g if age < 12 months) = arm 3. For each arm, children aged from 6 to 11 months received 100 g $\times$ 2 per day of flours and those aged from 12 to 24 months received 100 g $\times$ 3 per day of FBF. The primary endpoint was nutritional recovery, defined by reaching a weight-for-height z-score (WHZ) ≥ -1.5 within 12 weeks. Overall, 881 children were randomised (297, 290 and 294 in arm 1, arm 2 and arm 3, respectively). Three hundred and forty-four children were males (39%) and median/mean age were 14.6/14.4 months (SD = 4.9, IQR = 10.5-18.4). At inclusion, the three arms were comparable for all criteria, but differences were observed between countries. Overall, 44% (390/881) of the children recovered at week 12 from MAM, with no significant difference between the three arms (41.4%, 45.5% and 45.9%, in arm 1, arm 2 and arm 3, respectively, $p = 0.47$). This study did not support the true advantages of adding a prebiotic or antibiotic to flour. When using a threshold of WHZ ≥ -2 as an exploratory endpoint, significant differences were observed between the three arms, with higher success rates in arms with antibiotics or prebiotics compared to the control arm (66.9%, 66.0% and 55.2%, respectively, $p = 0.005$).

Narra J. 2024 Aug;4(2):e846.

doi: 10.52225/narra.v4i2.846. Epub 2024 Jul 15.

Effects of Formula-100 therapeutic milk and Bregas Nutriroll ready-to-use therapeutic food on Indonesian children with severe acute malnutrition: A randomized controlled trial study

Anwar Lubis^{1,2}, Hadi Riyadi³, Ali Khomsan³, Rimbawan Rimbawan³, Indhira Shagti⁴

Abstract

Severe acute malnutrition (SAM) is a global health concern that affects children and leads to delayed growth. The aim of this study was to compare the impact of F100 milk and *Bregas Nutriroll*, a local ready-to-use therapeutic food (RUTF), on SAM children. An unmasked, non-blinded, two-group, and simple randomized controlled trial was conducted. Indonesian

children aged 12-59 months with SAM were randomly assigned to receive either F100 milk or *Bregas Nutriroll*. After eight weeks, the increase in the mean weight gain in both groups was assessed. The *Bregas Nutriroll* group (n=19) had a mean weight gain of 1.07 ± 0.09 kg, while the F100 group (n=17) had a mean weight gain of 1.05 ± 0.11 kg. The *Bregas Nutriroll* group had a slightly higher gain of mid-upper arm circumference (MUAC) than the F100 group (0.62 ± 0.34 cm vs 0.50 ± 0.37 cm). The gain of children's height of the *Bregas Nutriroll* group was 0.96 ± 0.42 cm, while the F100 group was shorter at a mean of 0.81 ± 0.44 cm. Statistically significant differences ($p < 0.001$) in nutritional status were observed based on weight, MUAC, and height/length after F100 and *Bregas Nutriroll* interventions. The intervention with F100 increased hemoglobin (Hb) levels of 0.71 ± 1.25 mg/dL, while the *Bregas Nutriroll* intervention led to an increase of 0.11 ± 1.39 mg/dL. In conclusion, our study showed that community-based treatment with F100 milk or *Bregas Nutriroll* resulted in nutritional status in children with SAM. These findings suggested that both treatments could be effective in treating SAM in improving nutritional status and child health outcomes.

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Predictors of change in early child development among children with stunting: Secondary analysis of a randomized trial in Uganda

[Joseph Mbabazi^{1,2}](#), [Hannah Pesu¹](#), [Roland Mutumba^{1,2}](#), [Gareth McCray³](#), [Christian Ritz⁴](#), [Suzanne Filteau⁵](#), [André Briend^{1,6}](#), [Ezekiel Mupere²](#), [Benedikte Grenov¹](#), [Henrik Friis¹](#), [Mette F Olsen^{1,7}](#)

Abstract

Millions of children under 5 years in low- and middle-income countries fail to attain their development potential with accruing short- and long-term consequences. Low length/height for age (stunting) is known to be a key factor, but there is little data on how child characteristics are linked with developmental changes among children with stunting. We assessed the socioeconomic, household, anthropometric, and clinical predictors of change in early child development (ECD) among 1-5-year-old children with stunting. This was a prospective cohort study nested in a randomized trial testing effects of lipid-based nutrient supplementation among children with stunting in Uganda. Development was assessed using the Malawi Development Assessment Tool (MDAT). Multiple linear regression analysis was used to assess for predictors of change. We included 750 children with mean $\pm$ SD age of 30.2 ± 11.7 months 45% of whom were female. After 12 weeks, total MDAT z-score increased by 0.40 (95%CI: 0.32; 0.48). Moderate vs severe stunting, higher fat-free mass, negative malaria test and no inflammation (serum α -1-acid glycoprotein < 1 g/l) at baseline predicted greater increase in ECD scores. Older age and fat mass gain predicted a lesser increase in ECD. Our findings reinforce the link between stunting and development with more severely stunted children having a lesser increase in ECD scores over time. Younger age, freedom from malaria and inflammation, and higher fat-free mass at baseline, as well as less gain of fat mass during follow-up predicted a higher increase in developmental scores in this study. Thus, supporting fat-free mass accretion, focusing on younger children, and infection prevention may improve development among children with stunting.

BMJ Glob Health. 2025 Mar 28;10(3):e017643.

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Seasonality of underweight among infants 1-11 months old in Niger: an exploratory analysis of data from a cluster-randomised trial

[Brittany Peterson¹](#), [Ahmed Mamane Arzika²](#), [Ramatou Maliki³](#), [Amza Abdou⁴](#), [Bawa Aichatou²](#), [Ismael Sara²](#), [Diallo Beidi²](#), [Nasser Galo⁵](#), [Nasser Harouna²](#), [Alio Karamba Mankara²](#), [Sani Mahamadou²](#), [Moustapha Abarchi²](#), [Almou Ibrahim⁴](#), [Elodie Lebas¹](#), [Jeremy David Keenan¹](#), [Catherine E Oldenburg¹](#), [Travis C Porco¹](#), [Benjamin Arnold¹](#), [Thomas M Lietman¹](#), [Kieran S O'Brien⁶](#)

Abstract

Introduction: Malnutrition is a risk factor for child mortality, with around 45% of deaths in children under 5 globally linked to malnutrition. Seasonality of malnutrition has important implications for the timing of child health programme activities, but evidence is mixed on the nature of such patterns. Moreover, the bulk of the existing evidence is focused on wasting and stunting in children 6-59 months, despite increasing evidence that younger children also face a high risk, and that underweight alone is an important predictor of mortality.

Methods: This study used data from the cluster-randomised AVENIR trial which compared the effect of biannual distribution of azithromycin vs placebo on mortality in children 1-59 months old in Niger. AVENIR included a biannual census conducted on a rolling basis over 2 years. A subset of 133 781 infants aged 1-11 months from 2904 communities were included in this study, and weight-for-age z-score (WAZ) was calculated at each census. The exposure for this analysis is the day of the year weight was captured. Harmonic regression was used to determine primary and secondary peaks and nadirs of WAZ over time.

Results: Overall, the primary peak of WAZ occurred in late February and the primary nadir occurred in mid-May, aligning with a seasonal temperature increase before the rainy season. A secondary peak in August and a secondary nadir in November were also seen, aligning with the postrainy season.

Health Policy Plan. 2024 Aug 8;39(7):710-721.

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The impacts of task shifting on the management and treatment of malnourished children in Northern Kenya: a cluster-randomized controlled trial

[Hermann Pythagore Pierre Donfouet¹](#), [Tewoldeberhan Daniel²](#), [Calistus Wilunda³](#), [Elizabeth Mwaniki³](#), [James Njiru⁴](#), [Emily Keane⁵](#), [Lily Schofield⁵](#), [Lucy Maina⁶](#), [Edward Kutondo⁶](#), [Olivia Agutu⁶](#), [Peter Okoth⁶](#), [Judith Raburu⁶](#), [Betty Samburu⁶](#), [Bonventure Mwangi³](#), [Taddese Alemu Zerfu^{3,7}](#), [Jemimah Wekhomba Khamadi⁸](#), [Pilar Charle Cuellar⁹](#), [Daniel Kavoo¹⁰](#), [Lydia Karimurio¹⁰](#), [Charles Matanda¹⁰](#), [Alex Mutua¹⁰](#), [Grace Gichohi¹⁰](#), [Martin Chabi¹¹](#), [Patrick Codjia⁶](#), [Saul Guerrero Oteyza¹²](#), [Elizabeth Kimani-Murage³](#)

Abstract

Treating children with acute malnutrition can be challenging, particularly regarding access to healthcare facilities during treatment. Task shifting, a strategy of transferring specific tasks to health workers with shorter training and fewer qualifications, is being considered as an effective approach to enhancing health outcomes in primary healthcare. This study aimed to assess the effectiveness of integrating the treatment of acute malnutrition by community

health volunteers into integrated community case management in two sub-counties in northern Kenya (Loima and Isiolo). We conducted a two-arm non-inferiority cluster-randomized controlled trial across 20 community health units. Participants were children aged 6-59 months with uncomplicated acute malnutrition. In the intervention group, community health volunteers used simplified tools and protocols to identify and treat eligible children at home and provided the usual integrated community case management package. In the control group, community health volunteers provided the usual integrated community case management package only (screening and referral of the malnourished children to the health facilities). The primary outcome was recovery (MUAC ≥ 12.5 cm for 2 consecutive weeks). Results show that children in the intervention group were more likely to recover than those in the control group [73 vs 50; risk difference (RD) = 26% (95% CI 12 to 40) and risk ratio (RR) = 2 (95% CI 1.2 to 1.9)]. The probability of defaulting was lower in the intervention group than in the control group: RD = -21% (95% CI -31 to -10) and RR = 0.3 (95% CI 0.2 to 0.5). The intervention reduced the length of stay by about 13 days, although this was not statistically significant and varied substantially by sub-county. Integrating the treatment of acute malnutrition by community health volunteers into the integrated community case management programme led to better malnutrition treatment outcomes. There is a need to integrate acute malnutrition treatment into integrated community case management and review policies to allow community health volunteers to treat uncomplicated acute malnutrition.

Nutrients. 2024 Sep 15;16(18):3118.

doi: 10.3390/nu16183118.

Investigating the Effects of Dietary Supplementation and High-Intensity Motor Learning on Nutritional Status, Body Composition, and Muscle Strength in Children with Moderate Thinness in Southwest Ethiopia: A Cluster-Randomized Controlled Trial

Melese Sinaga Teshome^{1,2}, Evi Verbecque², Sarah Mingels^{2,3}, Marita Granitzer², Teklu Gemechu Abessa^{2,4}, Liesbeth Bruckers⁵, Tefera Belachew¹, Eugene Rameckers^{2,6,7}

Abstract

Background: In Ethiopia, moderate thinness (MT) is a persistent issue among children. Yet, evidence on the effects of dietary supplementation and motor skills training in these children is limited.

Objective: This study aimed to assess the effect of Ready-to-Use Supplementary Food (RUSF), whether or not combined with high-intensity motor learning (HiML), on weight, height, body composition, and muscle strength in children 5-7 years old with MT living in Jimma Town, Ethiopia.

Methods: A cluster-randomized controlled trial was carried out among 69 children (aged 5-7) with MT assigned to receive RUSF (n = 23), RUSF + HiML (n = 25), or no intervention (control group, n = 21). A multivariable Generalized Estimating Equations model was used and the level of significance was set at $\alpha < 0.05$.

Results: At baseline, there were no significant differences in the outcome measurements between the RUSF, RUSF + HiML, and control groups. However, after 12 weeks of intervention, there were significant mean differences in differences (DIDs) between the RUSF group and the control arm, with DIDs of 1.50 kg for weight ($p < 0.001$), 20.63 newton (N) for elbow flexor ($p < 0.001$), 11.00 N for quadriceps ($p = 0.023$), 18.95 N for gastrocnemius sup flexor of the leg ($p < 0.001$), and 1.03 kg for fat-free mass ($p = 0.022$). Similarly, the mean

difference in differences was higher in the RUSF + HiML group by 1.62 kg for weight ($p < 0.001$), 2.80 kg for grip strength ($p < 0.001$), 15.93 for elbow flexor ($p < 0.001$), 16.73 for quadriceps ($p < 0.001$), 9.75 for gastrocnemius sup flexor of the leg ($p = 0.005$), and 2.20 kg for fat-free mass ($p < 0.001$) compared the control arm.

Conclusion: RUSF alone was effective, but combining it with HiML had a synergistic effect. Compared to the control group, the RUSF and RUSF + HiML interventions improved the body composition, height, weight, and muscle strength of the studied moderately thin children. The findings of this study suggest the potential that treating moderately thin children with RUSF and combining it with HiML has for reducing the negative effects of malnutrition in Ethiopia. Future research should explore these interventions in a larger community-based study.

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Cost- effectiveness of a simplified acute malnutrition program: a secondary analysis of the OptiMA randomized clinical trial in the Democratic Republic of the Congo

Stephen C Resch¹, Ryoko Sato¹, Kevin Phelan², Cécile Cazes³, Abdramane Ombotimbe⁴, Victoire Hubert⁴, Harouna Boubacar⁴, Liévin Izie Bozama⁵, Gilbert Tshibangu Sakubu⁶, Béatrice Kalenga Tshiala⁵, Toussaint Tusuku⁵, Rodrigue Alitanou⁴, Antoine Kouamé⁷, Cyrille Yao⁷, Delphine Gabillard³, Moumouni Kinda⁸, Renaud Becquet³, Susan Shepherd⁸, Robert M Hecht⁹

Abstract

Acute malnutrition (AM) causes large loss of life and disability in children in Africa. Researchers are testing innovative approaches to increase efficiency of treatment programs. This paper presents results of a cost-effectiveness analysis of one such program in the Democratic Republic of the Congo (DRC) based on a secondary analysis of a randomized controlled trial Optimizing Treatment for Acute Malnutrition (OptiMA), conducted in DRC in 2018-20. 896 children aged 6-59 months with a mid-upper arm circumference (MUAC) <125 mm or with oedema were treated and followed for six months. Cost-effectiveness of OptiMA using ready-to-use therapeutic food (RUTF) at a tapered dose was compared with the standard national program in which severe cases (SAM) received RUTF proportional to weight, and moderate cases (MAM) were referred to another clinic for a fixed dose regimen of ready-to-use supplementary food. Cost analysis from provider perspective used data collected during the trial and from administrative records. Statistical differences were derived using t-tests. The mean cost per enrolled child under OptiMA was \$123 [95%CI: 114-132], not statistically different from the standard group (\$127 [95%CI: 118-136], $p=0.549$), while treatment success (i.e. recovery to MUAC >125 mm and no relapse for 6 months) under OptiMA was 9 percentage points higher (72% vs 63%, $p=0.004$). Among children with SAM at enrollment, there was no significant difference in treatment success between OptiMA and standard (70% vs 62%, $p=0.12$) but OptiMA's mean cost per enrolled child was 23% lower (\$128 vs \$166, $p<0.0001$). OptiMA was more effective at preventing progression to SAM among those enrolled with MAM (5% vs 16%, $p<0.0001$) with an incremental cost-effectiveness ratio (ICER) of \$234 per progression to SAM prevented. Overall, OptiMA had significantly better outcomes and was no more expensive than standard care. Its adoption could enable more children to be successfully treated in contexts where therapeutic food products are scarce.

PLoS Med. 2025 May 16;22(5):e1004606.

doi: 10.1371/journal.pmed.1004606. eCollection 2025 May.

Effectiveness of a reduced dose of ready-to-use therapeutic food in community-based management of severe acute malnutrition: A non-inferiority randomized controlled trial in the Democratic Republic of Congo

[Julien Ntaongo Alendi¹](#), [Cécile Salpeteur²](#), [Steve Botomba³](#), [Alemayehu Argaw⁴](#), [Victor Nikièma²](#), [Jean-Baptiste Mayavanga⁵](#), [Benjamin Guesdon²](#), [Marie Petry⁶](#), [Uwimana Sebinwa⁶](#), [Sophie Bruneau⁶](#), [Aimée Mupuala Masaya⁷](#), [Florence Mbiya Muadi⁸](#), [Samuel Mampunza Ma Miezi⁸](#), [Marie-Claire Muyer³](#)

Abstract

Introduction: The reduced Ready-to-use Therapeutic Food (RUTF) dose strategy was demonstrated effective in recovering children with Severe Acute Malnutrition (SAM) in ideal conditions and in a context of food security. The present study was conducted to provide further evidence on the effectiveness of reduced RUTF dose in a context of high food insecurity and post conflict humanitarian crisis, and with routine health staff.

Methods and findings: An individually randomized non-inferiority trial was conducted in 968 children aged 6-59 months suffering from SAM without medical complications in 14 health centers in the Bonzola and Nzaba health zones of Kasai Oriental, Democratic Republic of Congo (DRC). Children were randomly assigned to either a control group receiving the standard WHO (World Health Organization) RUTF dose at the time or an intervention group receiving a reduced RUTF dose starting from the third week of treatment. The primary outcome was weight gain velocity from admission to discharge from treatment, while secondary outcomes included anthropometry measurements, programmatic outcomes and relapse. Mixed effects linear and logistic regression models with the health center as random intercept were used to compare differences between the two study groups. Close to 94% of the children were from severely food insecure households. There was no difference in weight gain velocity between the two groups (4.88 ± 2.36 g/kg/d reduced dose group versus 5.09 ± 2.28 g/kg/d standard dose group; difference -0.09 g/kg/d (95% CI $[-0.33, 0.15]$; $p = 0.46$). Programmatic outcomes were also similar between the two groups: recovery rate (64.3% versus 67.0%), loss to follow-up (4.69% versus 5.23%), defaulter rate (2.65% and 1.88%), relapse rate over 3 months (2.86% versus 2.40%) and mean length of stay (42 versus 43 days). Nevertheless, the rate of mid-upper arm circumference (MUAC) gain from the third week onwards was lower in the reduced-dose group than in the standard-dose group, with a mean difference of -0.13 mm/week (95% CI $[-0.25, -0.01]$; $p = 0.04$). There was no difference in terms of serious adverse events, in the reduced versus standard dose: weight loss (2.24% versus 1.26%), weight stagnation (14.9% versus 17.0%), and medical complications (4.08% versus 3.77%). Important effect modifiers identified were: child sex, child age, season of admission and missed treatment visits.

Conclusions: The strategy of a reduced RUTF dose starting from the third week of treatment is as effective as the standard dose strategy on weight gain velocity and programmatic outcomes in a context of severe food insecurity. However, MUAC gain velocity was lower in the reduced dose group. Future studies should investigate the effectiveness of a reduced dose strategy among sub group of children with high risk factors.

BMC Public Health. 2025 Jan 20;25(1):233.

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Cost-effectiveness of decentralising acute malnutrition treatment with a standard or simplified treatment protocol: an economic evaluation in the region of Gao, Mali

[Bernardette Cichon¹](#), [Noemí López-Ejeda²](#), [Salimata Samake³](#), [Cornelia Aton⁴](#), [Abdias Ogobara Dougnon⁵](#), [Mahamadou N'tji Samake⁶](#), [Aliou Bagayoko⁶](#), [Magloire Bunkembo³](#), [Alexandra Rutishauser-Perera⁴](#), [Pilar Charle-Cuellar⁷](#)

Abstract

Background: Acute malnutrition treatment coverage remains low worldwide, causing significant morbidity and mortality. Decentralisation of treatment to Community Health Worker (CHW) sites has shown to be an effective strategy to improve access and increase coverage, but evidence on the cost and cost-effectiveness of this approach as well the use of simplified treatment protocols in conflict settings is lacking. The objective of this study was to determine cost per child treated as well as the cost-effectiveness of the hybrid model of treatment delivery (where treatment is provided at both health facilities and CHW sites) using either a standard protocol (Intervention 1) or simplified protocol (Intervention 2) compared to standard treatment at health facilities only (Control) in the conflict affected region of Gao in Northern Mali.

Methods: This economic evaluation was part of a three-arm cluster randomized controlled trial which enrolled 2038 children with moderate and severe acute malnutrition. Outcomes assessed were cost per child treated as well as average and incremental cost-effectiveness ratios for cost per child cured and disability adjusted life year (DALY) averted. A within study trial horizon, from March 2020 to July 2021, was used. Cost data were collected from accountancy records and through key informant interviews using a societal perspective. Treatment admission and outcome data were obtained from the main trial.

Results: In the base case scenario the cost per child treated was 272 US\$, 179 US\$ and 210US\$ in the Control, Intervention 1 and 2 groups, respectively. Cost per child cured was 356 US\$ in the Control, 219 US\$ in the Intervention 1 and 226 US\$ Intervention 2 groups. Ready-to-use therapeutic foods (RUTF) costs among SAM children treated with a simplified protocol were 5.7 US\$ less per child. The average cost per DALY averted was 173.1 US\$ in the Control compared to 60.3 US\$ in the Intervention 1 and 53 US\$ in the Intervention 2.

Conclusion: This study shows that involving CHWs in acute malnutrition treatment reduces the cost per child treated and is a cost-effective strategy, due to lower treatment costs and greater coverage in the decentralised model. Switching to a simplified protocol in a conflict setting can lead to cost savings particularly in terms of RUTF, and should be considered where weight-based admission, monitoring or dosage is not possible or RUTF stocks are running low.

Maternal health

BMC Med Educ

Experiences, barriers and perspectives of midwifery educators, mentors and students implementing the updated emergency obstetric and newborn care-enhanced pre-service midwifery curriculum in Kenya: a nested qualitative study

[Duncan N Shikuku^{1,2}](#), [Sarah Bar-Zeev³](#), [Alice Norah Ladur⁴](#), [Helen Allott⁴](#), [Catherine Mwaura⁵](#), [Peter Nandikove⁶](#), [Alphonse Uyara⁷](#), [Edna Tallam⁸](#), [Eunice Ndirangu⁹](#), [Lucy Waweru⁵](#), [Lucy Nyaga⁵](#), [Issak Bashir¹⁰](#), [Carol Bedwell⁴](#), [Charles Ameh^{4,11,12}](#)

Abstract

Introduction: To achieve quality midwifery education, understanding the experiences of midwifery educators and students in implementing a competency-based pre-service curriculum is critical. This study explored the experiences of and barriers to implementing a pre-service curriculum updated with emergency obstetric and newborn care (EmONC) skills by midwifery educators, students and mentors in Kenya.

Methods: This was a nested qualitative study within the cluster randomised controlled trial investigating the effectiveness of an EmONC enhanced midwifery curriculum delivered by trained and mentored midwifery educators on the quality of education and student performance in 20 colleges in Kenya. Following the pre-service midwifery curriculum EmONC update, capacity strengthening of educators through training (in both study arms) and additional mentoring of intervention-arm educators was undertaken. Focus group discussions were used to explore the experiences of and barriers to implementing the EmONC-enhanced curriculum by 20 educators and eight mentors. Debrief/feedback sessions with 6-9 students from each of the 20 colleges were conducted and field notes were taken. Data were analysed thematically using Braun and Clarke's six step criteria.

Results: Themes identified related to experiences were: (i) relevancy of updated EmONC-enhanced curriculum to improve practice, (ii) training and mentoring valued as continuous professional development opportunities for midwifery educators, (iii) effective teaching and learning strategies acquired - peer teaching (teacher-teacher and student-student), simulation/scenario teaching and effective feedback techniques for effective learning and, (iv) effective collaborations between school/academic institution and hospital/clinical staff promoted effective training/learning. Barriers identified were (i) midwifery faculty shortage and heavy workload vs. high student population, (ii) infrastructure gaps in simulation teaching - inadequate space for simulation and lack of equipment inventory audits for replenishment (iii) inadequate clinical support for students due to inadequate clinical sites for experience, ineffective supervision and mentoring support, lack/shortage of clinical mentors and untrained hospital/clinical staff in EmONC and (iv) limited resources to support effective learning.

Conclusion: Findings reveal an overwhelmed midwifery faculty and an urgent demand for students support in clinical settings to acquire EmONC competencies for enhanced practice. For quality midwifery education, adequate resources and regulatory/policy directives are needed in midwifery faculty staffing and development. A continuous professional development specific for educators is needed for effective student teaching and learning of a competency-based pre-service curriculum.

Effectiveness of intrapartum azithromycin to prevent infections in planned vaginal births in low-income and middle-income countries: a post-hoc analysis of data from a multicentre, randomised, double-blind, placebo-controlled trial

[Waldemar A Carlo¹](#), [Alan T N Tita²](#), [Janet L Moore³](#), [Musaku Mwenechanya⁴](#), [Elwyn Chomba⁴](#), [Jennifer J Hemingway-Foday³](#), [Avinash Kavi⁵](#), [Mrityunjay C Metgud⁵](#), [Shivaprasad S Goudar⁵](#), [Richard J Derman⁶](#), [Adrien Lokangaka⁷](#), [Antoinette Tshefu⁷](#), [Melissa Bauserman⁸](#), [Jackie K Patterson⁸](#), [Poonam Shivkumar⁹](#), [Manju Waikar¹⁰](#), [Archana Patel¹¹](#), [Patricia L Hibberd¹²](#), [Paul Nyongesa¹³](#), [Fabian Esamai¹³](#), [Osayame Austine Ekhuagure¹⁴](#), [Sherri Bucher¹⁴](#), [Saleem Jessani¹⁵](#), [Shiyam Sunder Tikmani¹⁵](#), [Sarah Saleem¹⁵](#), [Robert L Goldenberg¹⁶](#), [Sk Masum Billah¹⁷](#), [Ruth Lennox¹⁸](#), [Rashidul Haque¹⁹](#), [William Petri²⁰](#), [Manolo Mazariegos²¹](#), [Nancy F Krebs²²](#), [Denise C Babineau³](#), [Elizabeth M McClure³](#), [Marion Koso-Thomas²³](#); [A-PLUS Trial Group](#)

Abstract

Background: In 2023, the Azithromycin Prevention in Labor Use (A-PLUS) trial showed intrapartum azithromycin reduces maternal sepsis or death in women with planned vaginal delivery in low-resource settings, but whether it reduces maternal infection is unknown. We aimed to evaluate the effectiveness of intrapartum azithromycin in reducing maternal infection.

Methods: We performed a post-hoc analysis of the multicentre, facility-based, randomised, double-blind, placebo-controlled A-PLUS trial. This trial compared prophylactic intrapartum single oral dose of 2 g azithromycin versus placebo on maternal morbidity and mortality in low-resource settings in southeast Asia and Africa from Sept 9, 2020, to Aug 18, 2022. The trial enrolled women in labour at 28 weeks' gestation (or later) at eight sites in the Democratic Republic of the Congo, Kenya, Zambia, Bangladesh, India, Pakistan, and Guatemala and found that azithromycin reduced the incidence of maternal sepsis or death. The primary outcome of the present analysis was the incidence of any maternal infection in the azithromycin versus placebo groups, which was defined as one or more of these infections after randomisation: chorioamnionitis, endometritis, perineal or caesarean wound infection, abdominopelvic abscess, mastitis or breast abscess, and other infections. Any neonatal infection was also analysed. All analyses were by intention to treat in all those with data available for that outcome. Relative risks (RRs) and 95% CIs were estimated with a Poisson model adjusted for treatment group and site. Subgroup analyses included a two-way interaction test between intervention group and subgroup. A-PLUS was registered at ClinicalTrials.gov, number [NCT03871491](#).

Findings: 29 278 women were randomly assigned to groups: 14 590 to receive azithromycin, 14 688 to receive placebo. Baseline characteristics were similar between the azithromycin and placebo groups (43·3% vs 43·4% primiparous, 8·5% vs 8·7% high risk for infection). The presence of any maternal infection occurred less often in the azithromycin group (580 [4·0%] of 14 558) compared with the placebo group (824 [5·6%] of 14 661 women; RR 0·71, 95% CI 0·64-0·79, $p<0·0001$). Any neonatal infection did not differ between treatment groups. Adverse events were not detected.

Interpretation: Among women planning vaginal delivery, this analysis provides evidence indicating that intrapartum azithromycin is associated with a lower incidence of maternal infections than placebo.

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Cost-effectiveness of intrapartum azithromycin to prevent maternal infection, sepsis, or death in low-income and middle-income countries: a modelling analysis of data from a randomised, multicentre, placebo-controlled trial

[Jackie K Patterson¹](#), [Simon Neuwahl²](#), [Sydney Kirsch²](#), [Janet L Moore²](#), [Alan T N Tita³](#), [Waldemar A Carlo³](#), [Adrien Lokangaka⁴](#), [Antoinette Tshetu⁴](#), [Musaku Mwenechanya⁵](#), [Elwyn Chomba⁵](#), [Avinash Kavi⁶](#), [Mrityunjay C Metgud⁶](#), [Shivaprasad S Goudar⁶](#), [Richard J Derman⁷](#), [Poonam Shivkumar⁸](#), [Manju Waikar⁹](#), [Archana Patel¹⁰](#), [Patricia L Hibberd¹¹](#), [Paul Nyongesa¹²](#), [Fabian Esamai¹²](#), [Osa A Ekhaguere¹³](#), [Sherri Bucher¹³](#), [Saleem Jessani¹⁴](#), [Shiyam S Tikmani¹⁴](#), [Sarah Saleem¹⁴](#), [Blair J Wylie¹⁵](#), [Robert L Goldenberg¹⁵](#), [Sk Masum Billah¹⁶](#), [Ruth Lennox¹⁷](#), [Rashidul Haque¹⁶](#), [William A Petri¹⁸](#), [Manolo Mazariegos¹⁹](#), [Nancy F Krebs²⁰](#), [Jennifer J Hemingway-Foday²](#), [Denise Babineau²](#), [Marion Koso-Thomas²¹](#), [Elizabeth M McClure²](#), [Melissa Bauserman²²](#)

Abstract

Background: Sepsis is one of the leading causes of maternal mortality globally. In 2023, the Azithromycin Prevention in Labor Use (A-PLUS) trial showed intrapartum azithromycin for women planning a vaginal birth reduced the risk of maternal sepsis or death and infection. We aimed to evaluate the cost-effectiveness of intrapartum azithromycin for pregnant people planning a vaginal birth in low-income and middle-income countries (LMICs) using A-PLUS trial data.

Methods: We compared the benefits and costs of intrapartum azithromycin versus standard care across 100 000 model simulations using data from the A-PLUS trial and a probabilistic decision tree model that included 24 mutually exclusive scenarios. A-PLUS was a randomised, double-blind, placebo-controlled trial that enrolled 29 278 women in labour at 28 weeks' gestation or more at eight sites in the Democratic Republic of the Congo, Kenya, Zambia, Bangladesh, India, Pakistan, and Guatemala. Women randomly assigned to azithromycin received a single intrapartum 2 g oral dose. In this cost-effectiveness analysis, we considered the cost of azithromycin treatment and its effects on a composite outcome of maternal infection, sepsis, or death and its individual components, and health-care use. Our analysis had a health-care sector perspective. We summarised results as an average and 95% CI of the model simulations. We also conducted sensitivity analyses. A-PLUS was registered at ClinicalTrials.gov, number [NCT03871491](#).

Findings: In model simulations, intrapartum azithromycin resulted in 1592·0 (95% CI 1139·7 to 2024·1) cases of maternal infection, sepsis, or death averted per 100 000 pregnancies, yielding 248·5 (95·3 to 403·7) facility readmissions averted, 866·8 (537·8 to 1193·2) unplanned clinic visits averted, and 1816·2 (1324·5 to 2299·7) antibiotic regimens averted. Using mean health-care costs across the A-PLUS sites, intrapartum azithromycin resulted in net savings of US\$32 661 (-52 218 to 118 210) per 100 000 pregnancies and 13·2 (8·3 to 17·9) disability-adjusted life-years averted. The cost of facility readmission, cost of azithromycin, and probability of infection had the greatest impact on the incremental cost.

Interpretation: In most cases, intrapartum azithromycin is a cost-saving intervention for the prevention of maternal infection, sepsis, or death in LMICs. This evidence supports global consideration of intrapartum azithromycin as an economically efficient preventive therapy to reduce infection, sepsis, or death among women planning a vaginal birth in LMICs.

Antenatal care

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[The impact of group antenatal care on newborns: Results of a cluster randomized control trial in Eastern Region, Ghana](#)

[Veronica Apetorgbor¹](#), [Elizabeth Awini¹](#), [Bidisha Ghosh²](#), [Ruth Zielinski²](#), [Georgina Amankwah¹](#), [Vida A Kukula¹](#), [Katherine James³](#), [John E O Williams¹](#), [Jody R Lori¹](#), [Cheryl A Moyer⁴](#)

Abstract

Background: Maternal recognition of neonatal danger signs following birth is a strong predictor of care-seeking for newborn illness, which increases the odds of newborn survival. However, research suggests that maternal knowledge of newborn danger signs is low. Similarly, maternal knowledge of optimal newborn care practices has also been shown to be low. Since both issues are typically addressed during antenatal care, this study sought to determine whether group antenatal care (G-ANC) could lead to improvements in maternal recognition of danger signs and knowledge of healthy newborn practices, as well as boosting postnatal care utilization.

Methods: This cluster randomized controlled trial of G-ANC compared to routine individual antenatal care (I-ANC) was conducted at 14 health facilities in Ghana, West Africa, from July 2019 to July 2023. Facilities were randomized to intervention or control, and pregnant participants at each facility were recruited into groups and followed for the duration of their pregnancies. 1761 participants were recruited: 877 into G-ANC; 884 into I-ANC. Data collection occurred at enrollment (T0), 34 weeks' gestation to 3 weeks postdelivery (T1) and 6-12 weeks postpartum (T2). Comparisons were made across groups and over time using logistic regression adjusted for clustering.

Results: Overall, knowledge of newborn danger signs was significantly higher for women in G-ANC, both in aggregate (13-point scale) and for many of the individual items over time. Likewise, knowledge of what is needed to keep a newborn healthy was higher among women in G-ANC compared to I-ANC over time for the aggregate (7-point scale) and for many of the individual items. Women in G-ANC were less likely to report postnatal visits for themselves and their babies within 2 days of delivery than women in I-ANC, and there was no difference between groups regarding postnatal visits at one week or 6 weeks after birth.

Conclusion: This study illustrates that group ANC significantly improves knowledge of newborn danger signs and healthy newborn practices when compared to routine care, suggesting that the impact of G-ANC extends beyond impacts on maternal health. Further research elucidating care pathways for ill newborns and maternal behaviors around healthy newborn practices is warranted.

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Group antenatal care positively transforms the care experience: Results of an effectiveness trial in Malawi

[Crystal L Patil¹](#), [Kathleen F Norr²](#), [Esnath Kapito³](#), [Li C Liu²](#), [Xiaohan Mei²](#), [Elizabeth Chodzaza³](#), [Genesis Chorwe-Sungani³](#), [Ursula Kafulafula³](#), [Elizabeth T Abrams¹](#), [Allissa Desloge⁴](#), [Ashley Gresh⁵](#), [Rohan D Jeremiah²](#), [Dhruvi R Patel⁶](#), [Anne Batchelder⁵](#), [Heidy Wang²](#), [Jocelyn Faydenko²](#), [Sharon S Rising⁷](#), [Ellen Chirwa³](#)

Abstract

Background: We developed and tested a Centering-based group antenatal (ANC) model in Malawi, integrating health promotion for HIV prevention and mental health. We present effectiveness data and examine congruence with only the Group ANC theory of change model, which identifies key processes as supportive relationships, empowered partners in learning and care, and meaningful services, leading to better ANC experiences and outcomes.

Methods: We conducted a hybrid effectiveness-implementation trial at seven clinics in Blantyre District, Malawi, comparing outcomes for 1887 pregnant women randomly assigned to Group ANC or Individual ANC. Group effects on outcomes were summarized and evaluated using t-tests, Mann-Whitney, or Chi-squared tests. Adjusted for seven individual and two clinic-level baseline covariates, point estimates are reported for continuous outcomes using multivariable linear regression models. Adjusted for the same covariates, odds ratios are reported for categorical outcomes using logistic regression models. All statistical tests were two-sided, controlling for a Type I error probability of 0.01 due to multiple testing.

Findings: Women in Group ANC had higher peer connectedness and pregnancy-related empowerment, recalled receiving more services, and discussed more health promotion topics. They experienced less wait time, greater satisfaction with care (Estimate = 1.21, 99% CI = 0.07, 2.35), and had a higher mean number of ANC contacts (Estimate = 0.74, 99% CI = 0.50, 0.98). Most women preferred Group ANC for a future pregnancy (81% in Individual ANC; 95% in Group ANC). Women in Group ANC had more diverse diets (Estimate = 0.35, 99% CI = 0.17, 0.53), were better prepared for birth (Estimate 0.32, 99% CI = 0.16, 0.48), more likely to use condoms consistently (OR= 1.07, 99% CI = 1.00, 1.14) and communicated more with partners. They reported less mental distress in late pregnancy (Estimate = -0.61, 99% CI = -1.20, -0.02). Exclusive breastfeeding, partner HIV testing and disclosure, facility-based delivery, postnatal care attendance, postpartum family planning, and low birth weight did not differ by ANC type.

Conclusions: This effectiveness study of Malawi Group ANC, the first trial with individual randomization in a low-income country, maps outcomes to the theory of change, enhancing our understanding of Group ANC's diverse positive impacts. The integration of typically neglected health promotion topics into the model highlights its flexibility to address changing local and global needs. Based on study results, the Malawi Ministry of Health is introducing Group ANC at district-level trainings and exploring the logistics for nationwide adoption. With momentum and political will, better care and a positive healthcare experience can be achieved for women, infants, and families in Malawi and globally.

The impact of enhancing nutrition and antenatal infection treatment on birth outcomes in Amhara, Ethiopia: a pragmatic factorial, cluster-randomised clinical effectiveness study

[Anne Cc Lee^{1,2}](#), [Firehiwot Workneh³](#), [Yunhee Kang⁴](#), [Kalkidan Yibeltal⁵](#), [Nebiyou Fasil⁶](#), [Sitota Tsegaye⁷](#), [Estifanos Baye²](#), [Workagegnehu Tarekegn Kidane⁷](#), [Yoseph Yemane Berhane³](#), [Mulatu Melese Derebe⁸](#), [Fred Van Dyk⁴](#), [Michelle Eglovitch²](#), [Ingrid Olson²](#), [Mandefro M Mengistie⁸](#), [Fisseha Shiferie³](#), [Tigest Shifraw⁵](#), [Chunling Lu^{9,10}](#), [Krysten North^{2,9}](#), [Grace J Chan^{11,12}](#), [Sheila Isanaka¹³](#), [Rose L Molina^{9,14}](#), [Amare Worku Tadesse^{7,15}](#), [Blair J Wylie¹⁴](#), [Parul Christian⁴](#), [Luke C Mullany⁴](#), [Alemayehu Worku³](#), [Yemane Berhane³](#)

Abstract

Introduction: We aimed to determine the impact of antenatal interventions to optimise maternal nutrition and infection management on birth outcomes in Ethiopia.

Methods: We conducted a pragmatic, open-label, 2×2 factorial randomised clinical effectiveness study among pregnant women enrolled <24 weeks gestation in 12 rural health centres in Amhara, Ethiopia. Eligible health centres were randomised to deliver an enhanced nutrition package (ENP) (iron-folic acid, iodised salt and targeted micronutrient fortified balanced energy protein (BEP) supplementation for undernourished women) or routine nutrition care (iron-folic acid only). Individual women were randomised to receive an enhanced infection management package (EIMP) (genitourinary tract infection screening-treatment and enhanced deworming) or routine infection care (syndromic management). The primary outcomes were birth weight and length; secondary outcomes were gestational age, preterm delivery, small-for-gestational-age, low birth weight, stillbirth, newborn weight-for-age and length-for-age z-scores, newborn head circumference, and maternal anemia. Analysis was intention to treat.

Results: From August 2020 to December 2021, 2392 women were randomised (604 ENP+EIMP, 600 ENP alone, 593 EIMP alone and 595 neither package) and followed until June 2022, with 2170 pregnancy outcomes analysed (565 ENP+EIMP, 549 ENP, 525 EIMP, 531 neither). In the ENP arm, 427 (36%) women were eligible for BEP and consumed on average 74 days. The prevalence of genitourinary tract infection was low (4.9%), while parasitic stool infections were common (31%). There was no difference in birth weight (ENP vs not-ENP: adjusted mean difference -4 g (-83 to 75); EIMP vs not-EIMP: 18 g (-35 to 70); ENP+EIMP vs neither: 14 g (-81 to 109)) or birth length (ENP: -0.3 cm (-1.1 to 0.5); EIMP: 0.2 cm (-0.1 to 0.5); ENP+EIMP: -0.1 cm (-1.2 to 1.1)) between study arms. In the ENP+EIMP group, the stillbirth rate was lower compared with the arm receiving neither package (7.1/1000 vs 24.7/1000 births; adjusted relative risk: 0.29 (0.09 to 0.94)). The packages did not significantly affect other secondary outcomes.

Conclusions: In this pragmatic study implemented within the Ethiopian health system, enhanced nutrition and infection packages did not affect birth weight or length. While stillbirth rates were lower in the group receiving both packages, these findings need to be supported by additional studies.

Effectiveness of targeted social and behavior change communication on maternal health knowledge, attitudes, and institutional childbirth: a cluster-randomized trial in Jimma Zone, Ethiopia

[Lakew Abebe Gebretsadik¹](#), [Abebe Mamo¹](#), [Zewdie Birhanu Koricha¹](#), [Sudhakar Morankar¹](#)

Abstract

Maternal mortality remains a critical global health challenge, with 95% of deaths occurring in low-income countries. While progress was made from 2000 to 2015, regions such as Ethiopia continue to experience high maternal mortality rates, impeding the achievement of the sustainable development goal to reduce maternal deaths to 70 per 100 000 live births by 2030. This study evaluated the effectiveness of a Social and Behavior Change Communication (SBCC) intervention to improve maternal health behaviors. A community-randomized trial was conducted in three districts of Jimma Zone, rural Ethiopia, involving 5057 women. Sixteen primary healthcare units were randomly assigned to either the intervention (SBCC) or control (standard care) group. Data on socio-demographics, antenatal care (ANC) visits, maternal health knowledge, attitudes, and institutional childbirth rates were collected at baseline and endline. Statistical analyses included t-tests, effect sizes, and generalized estimating equations. The intervention group demonstrated significant improvements. Maternal health knowledge increased from 5.68 to 7.70 ($P < .001$, effect size = 0.34), attitudes improved from 37.49 to 39.73 ($P < .001$, effect size = 0.29), and ANC visits rose from 3.27 to 4.21 ($P < .001$, effect size = 0.50). Institutional childbirth rates increased from 0.52 to 0.71 ($P < .001$, effect size = 0.18). ANC attendance ($B = 0.082$, $P = .002$) and positive attitudes ($B = 0.055$, $P < .001$) were significant predictors of institutional childbirth. The SBCC intervention significantly enhanced maternal health knowledge, attitudes, ANC utilization, and institutional childbirth rates, highlighting the value of community-based strategies in improving maternal health behaviors.

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It takes a village: A pilot cross-randomized trial to enhance pregnancy care and support in northern Ghana

[Aleksandra Jakubowski¹](#), [Raymond Akawire Aborigo²](#), [Irene Kuwolamo²](#), [Jesse D Meredith³](#), [Aaron Asibi Abuosi⁴](#)

Abstract

Background: Maternal mortality remains a challenge in Ghana, where 263 women per 100 000 live births die during pregnancy or childbirth. Barriers to reaching the recommended antenatal care (ANC) include poor access to quality health care, cultural factors, and lack of support for pregnant women.

Methods: We piloted two cross-randomized interventions: durbars, or local community meetings that incorporated education about ANC and supporting pregnant women, and an enhanced ANC model that added phone calls and a home visit to standard care. The study took place in 30 villages in the Upper East Region of Ghana between August 2021 and November 2022.

Results: We tracked 277 women during pregnancy, with 120 women randomly assigned to the enhanced ANC intervention and 142 women living in villages randomized to the durbar

intervention. Women who were randomized to the enhanced ANC intervention were 13.2 percentage points (pp) (95% confidence interval (CI) = 0.1, 24.3) more likely to have average or above average knowledge of pregnancy danger signs, 22.1 pp (95% CI = 9.1, 36.5) more likely to have a birth plan, 28.2 pp (95% CI = 13.0, 42.4) more likely to prepare the plan with their partners, and 16.4 pp (95% CI = 0.9, 29.3) more likely to pay for delivery with funds set aside in birth plan. They were also 35 pp (95% CI = 16.1, 48.1) more likely to make blood donor arrangements than control women who made birth plans. We found no impact of the durbar intervention on study outcomes.

Conclusions: Evidence from this pilot suggests that interventions that increase interactions between health providers and pregnant women outside of the health facility may substantially improve women's experience during pregnancy and maternal health outcomes. Providing structured ways for men to get engaged in ANC increased their involvement. Although we found no evidence the community meetings improved study outcomes, larger studies with repeated meetings and community-wide surveys are needed to make causal conclusions.

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Evaluating the effectiveness of the global position system beaded bracelets to improve the uptake of antenatal care, health facility delivery, and post-natal care services among pastoralist women in Kenya

[Dahabo Adi Galgalo](#)¹, [Patrick Nyamemba Nyakundi](#)², [Ákos Várnagy](#)³, [Viktória Prémusz](#)⁴

Abstract

Background: Antenatal Care (ANC), Health Facility Delivery (HFD), and Postnatal Care (PNC) are the leading indicators of improving maternal and child healthcare globally. This study investigated the effectiveness of a prototyped Global Position System (GPS) beaded bracelet intervention in enhancing maternal healthcare services uptake among pastoralist communities.

Methods: In this Randomized Control Trial (RCT), one hundred and seven pregnant women in their first trimester were randomly allocated to the intervention group (n = 52) and control group (n = 55). A GPS-beaded bracelet was given to the intervention group for the study duration of 16 months (6 months before delivery and 10 months after delivery). Meanwhile, the non-intervention group received routine ante- and postnatal care. The Pearson X² test and multivariate logistic regression analysis were conducted using IBM SPSS version 27.0, following the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Model fit was assessed using, the Omnibus test of model Co-efficient, classification table, Nagelkerke R Square, and the Hosmer-Lemeshow test. The significance level was set at p < 0.05. RCT was registered (ISRCTN15438206), and the GPS beaded bracelet was patented by Kenya Industrial Property Institutes (KIPI) NO: KE/UM/19/1211.

Results: Women in the intervention group have nine-fold higher likelihood of having more than four ANC visits (AOR 9.13, 95 % CI 1.75-47.54), three-fold higher likelihood of having postnatal care (AOR 2.71, 95 % CI 0.74-9.96), and a fourfold higher of giving live birth (AOR 3.56, 95 % CI 0.47-27.07) compared to women in the control group. No significant differences were noted between groups when it comes to place of delivery, indicating that while GPS may facilitate access to health facilities, it did not markedly change delivery outcomes based

on location, but there is likelihood of delivering in a health facility (OR 2.0, 95 % CI 0.39-8.21). Other variables like age group, literacy level, and distance from health facility didn't exhibit a statistically significant association. All three methods of model fit assessment indicated good model fit.

Conclusion: The study result showed the effectiveness of GPS-beaded bracelets by significantly improving ANC, HFD, and PNC attendance and reducing infant mortality. Future studies should focus on refining these technologies to explore the long-term impacts and scalability of such interventions across diverse pastoralist populations to improve maternal and child healthcare.

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Antenatal Care Interventions to Increase Contraceptive Use Following Birth in Low- and Middle-Income Countries: Systematic Review and Narrative Synthesis

[Ona L McCarthy¹](#), [Nasser Fardousi²](#), [Vandana Tripathi³](#), [Renae Stafford³](#), [Karen Levin³](#), [Farhad Khan³](#), [Maxine Pepper²](#), [Oona M R Campbell²](#)

Abstract

Introduction: Health risks associated with short interpregnancy intervals, coupled with women's desires to avoid pregnancy following childbirth, underscore the need for effective postpartum family planning programs. The antenatal period provides an opportunity to intervene; however, evidence is limited on the effectiveness of interventions aimed at reaching women in the antenatal period to increase voluntary postpartum family planning in low- and middle-income countries (LMICs). This systematic review aimed to identify and describe interventions in LMICs that attempted to increase postpartum contraceptive use via contacts with pregnant women in the antenatal period.

Methods: Studies published from January 2012 to July 2022 were considered if they were conducted in LMICs, evaluated an intervention delivered during the antenatal period, were designed to affect postpartum contraceptive use, were experimental or quasi-experimental, and were published in French or English. The main outcome of interest was postpartum contraceptive use within 1 year after birth, defined as the use of any method of contraception at the time of data collection. We searched EMBASE, Global Health, and Medline and manually searched the reference lists from studies included in the full-text screening.

Results: We double-screened 771 records and included 34 reports on 31 unique interventions in the review. Twenty-three studies were published from 2018 on, with 21 studies conducted in sub-Saharan Africa. Approximately half of the study designs (n=16) were randomized controlled trials, and half (n=15) were quasi-experimental. Interventions were heterogeneous. Among the 24 studies that reported on the main outcome of interest, 18 reported a positive intervention effect, with intervention recipients having greater contraceptive use in the first year postpartum.

Conclusion: While the studies in this systematic review were heterogeneous, the findings suggest that interventions that included a multifaceted package of initiatives appeared to be most likely to have a positive effect.

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[Exploring the association between multidimensional poverty and antenatal care utilization in two provinces of Papua New Guinea: a cross-sectional study](#)

[Olga P M Saweri^{1,2}](#), [William S Pomat^{3,4}](#), [Andrew J Vallely^{3,4}](#), [Virginia Wiseman^{#3,5}](#), [Neha Batura^{#6}](#); [WANTAIM Study Group](#)

Abstract

Background: Although global poverty rates have declined in the last decade, the fall in the Asia-Pacific region has been slow relative to the rest of the world. Poverty continues to be a major cause of poor maternal and newborn health, and a barrier to accessing timely antenatal care. Papua New Guinea has one of the highest poverty rates and some of the worst maternal and neonatal outcomes in the Asia-Pacific region. Few studies have investigated equity in antenatal care utilization in this setting. We explored equity in antenatal care utilization and the determinants of service utilization, which include a measure of multidimensional poverty in Papua New Guinea.

Methods: To explore the association between poverty and antenatal care utilization this study uses data from a ten-cluster randomized controlled trial. The poverty headcount, average poverty gap, adjusted poverty headcount, and multidimensional poverty index of antenatal clinic attendees are derived using the Alkire-Foster method. The distribution of service utilization is explored using the multidimensional poverty index, followed by multivariate regression analyses to evaluate the determinants of service utilization.

Results: The poverty headcount was 61.06%, the average poverty gap 47.71%, the adjusted poverty headcount 29.13% and the average multidimensional poverty index was 0.363. Further, antenatal care utilization was regressive with respect to poverty. The regression analyses indicated that older women; being a widow (small number of widows (n = 3) asserts interpreting result with caution); or formally employed increase the likelihood of accessing antenatal care more often in pregnancy. Travelling for over an hour to receive care was negatively associated with utilization.

Conclusion: This study indicated high levels of multidimensional poverty in PNG and that ANC utilization was regressive; highlighting the need to encourage pregnant women, especially those who are economically more vulnerable to visit clinics regularly throughout pregnancy.

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[Effectiveness of engaging religious leaders in maternal health education for improving maternal health service utilization in Ethiopia: cluster randomized controlled trial](#)

[Abinet Arega Sadore^{1,2}](#), [Yohannes Kebede¹](#), [Zewdie Birhanu¹](#)

Abstract

Introduction: High mortality rates for pregnant women and their new-borns are one of Africa's most intractable public health issues today, and Ethiopia is one of the countries most afflicted. Behavioral interventions are needed to increase maternal health service utilizations to improve outcomes. Hence, this trial aimed to evaluate effectiveness of trained religious leaders' engagement in maternal health education on maternal health service utilization.

Methods: The study employed a cluster-randomized controlled community trial that included baseline and end-line measurements. Data on end points were gathered from 593 pregnant mothers, comprising 292 and 301 individuals in the intervention and control groups, respectively. In the intervention group, the trained religious leaders delivered the behavioral change education on maternal health based on intervention protocol. Unlike the other group, the control group only received regular maternal health information and no additional training from religious leaders. Binary generalized estimating equation regression analysis adjusted for baseline factors were used to test effects of the intervention on maternal health service utilization.

Results: Following the trial's implementation, the proportion of optimal antenatal care in the intervention arm increased by 21.4% from the baseline (50.90 vs. 72.3, $p \leq 0.001$) and the proportion of institutional delivery in the intervention group increased by 20% from the baseline (46.1% vs. 66.1%, $p \leq 0.001$). Pregnant mothers in the intervention group significantly showed an increase of proportion of PNC by 22.3% from baseline (26% vs. 48.3%, $p \leq 0.001$). A statistically significant difference was observed between in ANC4 (AOR = 2.09, 95% CI: 1.69, 2.57), institutional delivery (AOR = 2.36, 95% CI: 1.94, 2.87) and postnatal care service utilization (AOR = 2.26, 95% CI: 1.79, 2.85) between the intervention and control groups.

Conclusion: This research indicated that involving religious leaders who have received training in maternal health education led to positive outcomes in enhancing the utilization of maternal health services. Leveraging the influential position of these religious leaders could be an effective strategy for improving maternal health service utilization. Consequently, promoting maternal health education through religious leaders is advisable to enhance maternal health service utilization

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Effect of group antenatal care versus individualized antenatal care on birth preparedness and complication readiness: a cluster randomized controlled study among pregnant women in Eastern Region of Ghana

[Vida A Kukula¹](#), [Elizabeth Awini¹](#), [Bidisha Ghosh²](#), [Veronica Apetorgbor¹](#), [Ruth Zielinski²](#), [Georgina Amankwah¹](#), [Winfred K Oforu³](#), [Katherine James³](#), [John E O Williams¹](#), [Jody R Lori¹](#), [Cheryl A Moyer⁴](#)

Abstract

Background: As utilization of individual antenatal care (I-ANC) has increased throughout sub-Saharan Africa, questions have arisen about whether individual versus group-based care might yield better outcomes. We implemented a trial of group-based antenatal care (G-ANC) to determine its impact on birth preparedness and complication readiness (BPCR) among pregnant women in Ghana.

Methods: We conducted a cluster randomized controlled trial comparing G-ANC to routine antenatal care in 14 health facilities in the Eastern Region of Ghana. We recruited women in their first trimester to participate in eight two-hour interactive group sessions throughout their pregnancies. Meetings were facilitated by midwives trained in G-ANC methods, and clinical assessments were conducted in addition to group discussions and activities. Data were collected at five timepoints, and results are presented comparing baseline (T0) to 34

weeks' gestation to 3 weeks post-delivery (T1) for danger sign recognition, an 11-point additive scale of BPCR, as well as individual items comprising the scale.

Results: 1285 participants completed T0 and T1 assessments (N = 668 I-ANC, N = 617, G-ANC). At T1, G-ANC participants were able to identify significantly more pregnancy danger signs than I-ANC participants (mean increase from 1.8 to 3.4 in G-ANC vs. 1.7 to 2.2 in I-ANC, $p < 0.0001$). Overall BPCR scores were significantly greater in the G-ANC group than the I-ANC group. The elements of BPCR that showed the greatest increases included arranging for emergency transport (I-ANC increased from 1.5 to 11.5% vs. G-ANC increasing from 2 to 41% ($p < 0.0001$)) and saving money for transportation (19-32% in the I-ANC group vs. 19-73% in the G-ANC group ($p < 0.0001$)). Identifying someone to accompany the woman to the facility rose from 1 to 3% in the I-ANC group vs. 2-20% in the G-ANC group ($p < 0.001$).

Conclusions: G-ANC significantly increased BPCR among women in rural Eastern Region of Ghana when compared to routine antenatal care. Given the success of this intervention, future efforts that prioritize the implementation of G-ANC are warranted.

BJOG. 2024 Aug;131(9):1259-1269.

doi: 10.1111/1471-0528.17775. Epub 2024 Feb 13.

Evaluating Chlamydia trachomatis and Neisseria gonorrhoeae screening and treatment among asymptomatic pregnant women to prevent preterm birth and low birthweight in Gaborone, Botswana: A secondary analysis from a non-randomised, cluster-controlled trial

[Adriane Wynn^{1,2}](#), [Aamirah Mussa^{2,3}](#), [Rebecca Ryan²](#), [Chibuzor M Babalola⁴](#), [Emily Hansman⁵](#), [Kehumile Ramontshonyana²](#), [Lefhela Tamuthiba²](#), [Neo Ndlovu²](#), [Melissa L Wilson⁴](#), [Doreen Ramogola-Masire⁶](#), [Jeffrey D Klausner⁴](#), [Chelsea Morroni^{2,7}](#)

Abstract

Objective: To evaluate the impact of screening and treating asymptomatic pregnant women for Chlamydia (C.) trachomatis and Neisseria (N.) gonorrhoeae infections on the frequency of preterm birth or low birthweight infants in Botswana.

Design: Non-randomised, cluster-controlled trial.

Setting: Four antenatal care clinics in Gaborone, Botswana.

Population: Pregnant women aged ≥ 15 years, attending a first antenatal care visit, ≤ 27 weeks of gestation and without urogenital symptoms were eligible.

Methods: Participants in the intervention clinics received screening (GeneXpert®, Cepheid) during pregnancy and at the postnatal visit. Participants in the standard-of-care clinics received screening at the postnatal visit only. We used multivariable logistic regression and post-estimation predictive margins analysis. Post-hoc analysis was conducted among sub-samples stratified by parity.

Main outcome measures: Preterm birth (< 37 weeks of gestation) and low birthweight (< 2500 g).

Results: After controlling for parity, hypertension, antenatal care visits and clinic site, the predicted prevalence of preterm birth or low birthweight was lower in the intervention arm (11%) compared with the standard-of-care arm (16%) (adjusted odds ratio [aOR] 0.59; 95% confidence interval [CI] 0.28-1.24). In post-hoc analysis, the intervention was more effective than the standard-of-care (aOR 0.20; 95% CI 0.07-0.64) among nulliparous participants.

Conclusion: A C. trachomatis and N. gonorrhoeae infection screening and treatment intervention among asymptomatic pregnant women may have reduced preterm birth or low birthweight outcomes, but results were not statistically significant. Post-hoc analysis found that the intervention reduced adverse outcomes among nulliparous participants.

BMC Res Notes. 2025 Jun 3;18(1):245.

doi: 10.1186/s13104-025-07309-w.

A single presumptive deworming may not suffice to reduce the burden of intestinal parasitic infections during pregnancy in rural Amhara, Ethiopia

[Kalkidan Yibeltal¹](#), [Firehiwot Workneh²](#), [Nebiyou Fasil³](#), [Estifanos Baye⁴](#), [Yunhee Kang⁵](#), [Workagegnhu Tarekegn Kidane⁶](#), [Sitota Tsegaye⁶](#), [Yoseph Yemane Berhane²](#), [Bethlehem Haymanot⁷](#), [Ingrid E Olson⁴](#), [Mulatu Melese Derebe⁸](#), [Rose L Molina^{9 10}](#), [Blair J Wylie¹¹](#), [Grace J Chan^{9 12 13}](#), [Parul Christian⁵](#), [Alemayehu Worku²](#), [Anne Cc Lee^{14 15}](#), [Yemane Berhane¹⁶](#)

Abstract

Objective: This study aimed to assess the prevalence of intestinal parasitic infections among pregnant women in the third trimester who received prior presumptive deworming in 12 health centers in the Amhara region, Ethiopia. This sub-study was part of the parent Enhancing Nutrition and Antenatal Infection Treatment (ENAT) study; a randomized clinical effectiveness study conducted to determine the effectiveness of packages of antenatal interventions to enhance maternal nutrition and infection management on birth outcomes.

Results: Three hundred fifty women provided a stool sample in their 3rd trimester for screening using wet mount microscopy. All women had previously received 500 mg of presumptive mebendazole in the 2nd trimester. One in three women (109/350, 31.0%) were found to have a parasitic stool infection after prior deworming and 15% of women reported gastrointestinal symptoms. The most common infections were Giardia lamblia (n = 43, 37.4%), Entamoeba histolytica (n = 40, 34.8%), and Hookworm (n = 25, 21.7%). Six mothers had co-infections with at least two parasites with trophozoites of Giardia lamblia and Entamoeba histolytica co-infection being dominant.

Community Health Equity Res Policy. 2024 Jul;44(4):377-389.

doi: 10.1177/0272684X221120481. Epub 2022 Oct 3.

Traditional Midwifery Contribution to Safe Birth in Cultural Safety: Narrative Evaluation of an Intervention in Guerrero, Mexico

[Iván Sarmiento^{1,2}](#), [Sergio Paredes-Solís³](#), [Abraham De Jesús-García³](#), [Nadia Maciel-Paulino³](#), [Alba Meneses-Rentería³](#), [Carolina Amaya²](#), [Anne Cockcroft¹](#), [Neil Andersson^{1,3}](#)

Abstract

A 2017 randomised controlled trial in Guerrero State, Mexico, showed supporting Indigenous traditional midwives on their own terms improved traditional childbirths without inferior maternal health outcomes. This narrative evaluation complements the trial to document participant experience of safer birth in cultural safety, transformative dynamics and implementation issues of the intervention. Stories came from 26 traditional midwives, 28

apprentices, 12 intercultural brokers and 20 Indigenous women who experienced the intervention. Their accounts indicate the intervention revitalised traditional midwifery and consolidated local skills through traditional midwife apprentices and intercultural brokers to support safe birth. According to the stories, communities reintroduced traditional perinatal care and reported positive health impacts for mothers, children, and other adults, which contributed to early collaboration with official health services. Challenges included remuneration and disinterest of younger apprentices and brokers. The intervention seems to have improved interaction between traditional and Western services, setting the stage for further intercultural dialogue.

Maternal mental health

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Effectiveness of psychosocial education program on postnatal depression, stress, and perceived maternal parenting self-efficacy among pregnant women in South India

[Savitha Prabhu¹](#), [Linu Sara George²](#), [Shyamala Guruvare³](#), [Judith Angelita Noronha⁴](#), [Tessy Treasa Jose¹](#), [Baby S Nayak⁵](#), [Anice George⁵](#), [Shreemathi Mayya⁶](#)

Abstract

Objective: This study aimed to evaluate the effect of a psychosocial education program on postnatal depression (PND), perceived stress, (PSS), and perceived maternal parenting self-efficacy (PMPSE).

Methods: A randomized controlled trial design was used with stratified block randomization. The sample size consisted of 128 pregnant women. The women in the experimental group were provided with a psychosocial education program along with standard care, and the control group received standard care with an information pamphlet. Post-test assessments (PND, PSS, and PMPSE) were performed at 1 week, 6 weeks, and 12 weeks after delivery in both groups.

Results: The result of the effect of the intervention on outcome variables on repeated measures ANOVA revealed that there was a positive statistically significant reduction in scores of postnatal depression [$F(1, 119) = 18.832, p = 0 < 0.001$] and perceived stress [$F(1, 119) = 22.488, p = < 0.001$] and no statistically significant change in perceived maternal parenting self-efficacy in the experimental group [$F(1, 119) = 0.036, p = 0.850$].

Conclusion: The psychosocial education program was found to be effective in reducing postnatal depression and stress related to pregnancy and childbirth to enable a smooth transition to motherhood.

Asian J Psychiatr. 2024 Dec:102:104290.

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Effectiveness of a package of community-based mental healthcare services to address perinatal mental disorders in Bangladesh: A cluster-randomized controlled trial

[Goutam Kumar Dutta¹](#), [Helal Uddin Ahmed²](#), [Md Quiume Talukder³](#), [Dipika Shankar Bhattacharyya⁴](#), [M Shamim Reza³](#), [Md Musfikur Rahman⁵](#), [Ratna Majumdar⁶](#), [Fahmida Tofail⁷](#), [Henry B Perry⁸](#), [Taposh Kumar Biswas⁹](#)

Abstract

Background: Perinatal mental disorders of women have an impact on their pregnancy and their child's brain development across low and middle-income countries. However, to address this issue, there are no specific guidelines for community-level service providers in Bangladesh. Therefore, we aimed to develop a community-based mental healthcare (CBMHC) service package and test its effectiveness in reducing depression, anxiety, and stress among mothers during the perinatal period.

Methods: A cluster-randomized controlled trial (cRCT) was applied to test the CBMHC package in 2017 and 2018. It was provided to one group of mothers along with routine maternal care while another group received only routine maternal care. Paired sample t-test was applied to assess mean changes at baseline and endline in the Depression, Anxiety, and Stress Scales-21 (DASS-21) and EuroQol-5 Dimension and 3 Level (EQ5D3L) scales. A linear mixed-effects model was used to assess the relationship between the DASS-21 score and EQ5D3L.

Results: 1215 participants were enrolled, including 605 in the intervention group and 610 in the control group. Measures of depression, anxiety, and stress were significantly decreased in both groups. Reduction in the levels of stress, as measured by changes in the stress score, were significantly greater in the intervention than in the control group (diff: 1.2, 95 % CI: 0.1, 2.2). The EQ5D3L index improved significantly, 0.02 units more at endline in the intervention group than in the control group (diff: 0.02, 95 % CI: 0.007, 0.03). The levels of mobility, usual activities, pain or discomfort, depression, and anxiety improved by 1.4 %, 7.6 %, 4.4 %, 2.6 %, and 0.4 % more, respectively, in the intervention group compared to the control groups. These improvements were statistically significant. The DASS-21 score was negatively and significantly correlated with both the EQ-5D3L index and the Visual Analogue Scale (VAS) score for the intervention group as well as for the usual care group, indicating that EQ5D3L improved when common mental disorders decreased.

Conclusion: Although the improvements were modest, a CBMHC service package was effective in reducing perinatal levels of stress among Bangladeshi rural women.

Lancet Psychiatry. 2024 Dec;11(12):965-974.

doi: 10.1016/S2215-0366(24)00256-6. Epub 2024 Nov 5.

Feasibility and acceptability of the Problem Management for Moms programme for improving maternal mental health in Zambia: an open-label trial

[Günther Fink¹](#), [Maria Melero-Dominguez²](#), [Mpela Chembe³](#), [Daniela de Vernisy-Romero⁴](#), [Thandiwe Tembo⁵](#), [Tamara Billima³](#), [Ravi Paul⁶](#), [Margarita Alegria⁷](#), [Doug Parkerson³](#), [Peter C Rockers⁸](#), [Zaliwe Banda⁹](#), [Gabriel Lungu⁹](#), [Dorothy Sikazwe¹⁰](#), [Irene Falgas-Bague¹¹](#)

Abstract

Background: Psychological distress is common among mothers in low-income and middle-income countries, limiting their capacity to care for themselves and their children. This study

aimed to test the feasibility and acceptability of an adapted psychosocial intervention for distressed mothers in low-resource settings.

Methods: In this open-label trial, we enrolled women living in Lusaka, Zambia, with high mental distress (>7 score on the 20-item Self-Reporting Questionnaire [SRQ-20]) and children younger than 2 years, who had previously enrolled in the ZamCharts early childhood nutrition trial. We randomly assigned participants (1:1) to the intervention or control group using a random number draw. The intervention was a newly developed Problem Management for Moms (PM4M) programme: a ten-session treatment adapted from Problem Management Plus, which was offered by phone or in person. After randomisation, participants in the intervention group underwent pre-intervention screening, a post-intervention assessment, and a final follow-up assessment 9 months after treatment initiation (ie, final follow-up visit). The control group was assessed at the baseline of ZamCharts and at the final follow-up assessment, and these participants did not receive any intervention. The primary study outcomes were feasibility, acceptability, and participant mental distress measured using the SRQ-20. All primary and secondary outcomes were estimated in the intention-to-treat population, which included all participants who were randomised to the intervention group and attended the final follow-up assessment. Data on ethnicity were not collected. The trial is registered at ClinicalTrials.gov, [NCT05627206](https://clinicaltrials.gov/ct2/show/study/NCT05627206), and has been completed. Women with lived experience of mental health symptoms were involved in this study.

Findings: Between April 26, and July 14, 2021, 790 women were interviewed in the ZamCharts trial, of whom 265 had high mental distress and were randomly assigned to treatment groups in this trial (134 to the intervention group and 131 to the control group). Of the 134 women in the intervention group, 61 (46%) received the PM4M intervention and 73 (55%) were excluded; 103 in the intervention group and 106 in the control group were successfully interviewed at the final follow-up assessment. The mean age of participants was 27·6 years (SD 7·6) at ZamCharts baseline. PM4M sessions were conducted between Dec 16, 2022, and May 6, 2023. The 61 participants deemed eligible after pre-intervention screening who started the intervention completed a mean of 7·9 (SD 2·9) of ten sessions. 55 (77%) of these 61 participants were somewhat or very satisfied with the intervention. In adjusted intention-to-treat models, the intervention reduced mean SRQ-20 scores by 2·11 points (95% CI -3·50 to -0·63) at the final follow-up, and the adjusted odds ratio of having an SRQ-20 of more than 7 was 0·50 (95% CI 0·27 to 0·93). No serious adverse events were reported.

Interpretation: The results presented here suggest that the PM4M mental health intervention is feasible and has high rates of acceptability. Further research is needed to assess the long-term efficacy of this intervention on women and their children, and its suitability for integration into routine care.

PLoS One. 2024 Aug 12;19(8):e0306887.

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[Effect of bitter orange blossom distillate on anxiety and sleep disorder in mothers with infants admitted to neonatal intensive care unit: A Randomized controlled clinical trial](#)

[Zahra Dehghan](#)¹, [Seyedeh Roghaye Jafarian Amiri](#)², [Seyyed Ali Mozaffarpur](#)³, [Hoda Shirafkan](#)⁴, [Afsaneh Arzani](#)⁵

Abstract

Objective: Mothers of neonates admitted to the intensive care unit are prone to sleep disorders due to stress and anxiety. Some herbs have anti-anxiety and sedative properties. This study aimed to investigate the effect of bitter orange blossom distillate on anxiety and sleep disorders in mothers with infants admitted to the neonatal intensive care unit.

Methods: This randomized controlled clinical trial was conducted from 2021 May 15 to 2022 February 2, on 60 mothers with NICU-admitted infants in one of the medical teaching centers affiliated with Babol University of Medical Sciences, Iran. Permuted block randomization was used to assign the mothers to the experimental (bitter orange blossom distillate syrup) and control groups (syrup prepared from water and sugar). Given the impossibility of blinding the participants, allocation concealment was used to prevent the researcher from predicting the future allocation of the samples to the groups. In addition, the statistical consultant received coded data pertaining to the type of intervention in each group. A demographic questionnaire, the Spielberger State and Trait Anxiety Inventory (STAI), and the General Sleep Disorder Scale were employed to collect data. We assessed the level of anxiety and sleep disorder (in both groups before the intervention and again after the last day of the intervention). Data were analyzed using SPSS V22 software. A P-value less than 0.05 were considered significant.

Results: The mean and standard deviation of the sleep disorder score in the intervention group from (50.26±5.81) to (44.70±6.94) and in the control group from (50.46±6.95) to (48.53±8.62) changed. The covariance test showed that bitter orange blossom distillate syrup has a significant effect on the improvement of sleep disorders ($P = 0.01$, Effect size = 0.09), but there was no significant difference in the State and Trait anxiety level of mothers ($P = 0.122$, 0.144 and Effect size = 0.04, 0.03) respectively.

Conclusions: Due to the positive effect of bitter orange blossom distillate syrup on sleep disorders of mothers with hospitalized babies, this low-cost and low-risk intervention is recommended.

Int J Community Based Nurs Midwifery. 2024 Oct 1;12(4):254-266.

doi: 10.30476/ijcbnm.2024.100522.2368. eCollection 2024 Oct.

The Effect of Applying Problem-solving Skills on Stress Coping Styles and Emotional Self-efficacy in Mothers of Preterm Neonates: A Randomized Clinical Trial

Mahbubeh Bagheri¹, Monir Ramezani², Saeed Vaghee³, Tahereh Sadeghi¹

Abstract

Background: Dysfunctional stress-coping styles may accelerate negative emotional self-efficacy in the mothers of preterm neonates. This study was conducted to determine the effect of applying problem-solving skills on stress-coping styles and emotional self-efficacy in mothers of preterm neonates.

Methods: This randomized clinical trial was conducted from January 2020 to February 2021 in 4 neonatal intensive care units (NICU) of Mashhad, Iran. 60 mothers were selected using convenience sampling method and randomly assigned to control and intervention groups. The intervention group was divided into groups of 3-5 people to attend 6 sessions of at least 60 minutes held 3 times a week for two weeks and received training on problem-solving skills. The control group received routine care. Data were collected using demographic characteristic forms, problem-solving inventory, ways of Coping Questionnaire, and the emotional self-efficacy scale. The tools were initially filled out by both groups and re-completed at the end of the second week after the intervention and four weeks later. Data

were analyzed using SPSS version 21 and the significance level of less than 0.05. Independent and paired t-test, Mann-Whitney, Chi-square, Fisher's exact test, repeated measures, and Bonferroni post hoc test were used.

Results: Analysis of variance with repeated measures showed that in the intervention group, there was an increase in the scores of problem-focused style (before: 37.9 ± 6.3 ; immediately: 46.2 ± 5.3 ; one month later: 47.5 ± 5.6) ($P < 0.001$), a decrease in scores of emotion-focused style (before: 44.0 ± 6.9 ; immediately: 38.6 ± 6.2 ; one month later: 38.0 ± 4.4) ($P < 0.001$), and an increase in mothers' emotional self-efficacy (before: 113.0 ± 14.9 ; immediately: 130.3 ± 10.6 ; one month later: 134.5 ± 8.3) ($P < 0.001$). Conclusion: Problem-solving skills are recommended to be used in NICU to empower mothers.

Conclusion: Problem-solving skills are recommended to be used in NICU to empower mothers to adopt appropriate strategies for dealing with the situational stress of having a preterm neonate and to increase emotional self-efficacy

J Affect Disord. 2024 Nov 1;364:41-47.

doi: 10.1016/j.jad.2024.08.021. Epub 2024 Aug 11.

Multiple mediation analysis of a task-shared psychosocial intervention for perinatal anxiety: Exploratory findings from a randomized controlled trial in Pakistan

[A Malik¹](#), [A Waqas²](#), [N Atif³](#), [J Perin⁴](#), [A Zaidi³](#), [M Sharif³](#), [A Rahman⁵](#), [P J Surkan⁶](#)

Abstract

Background: The "Healthy Mother Healthy Baby" (HMHB) study is a phase three, single-blind randomized clinical trial conducted at Holy Family Hospital (HFH) in association with Rawalpindi Medical University (RMU). We aimed to examine the mediators of a specialized psychosocial approach based on Cognitive Behavioural Therapy principles, targeting pregnant women experiencing anxiety. The HMHB intervention was effective in treating perinatal anxiety symptoms and preventing future depressive episodes.

Methods: The trial randomized participants into two arms: the HMHB intervention or Enhanced Usual Care (EUC), following World Health Organization guidelines. The HMHB intervention comprised strategies to strengthen social support networks, improving mother-baby bonding and strategies to deal with interpersonal conflicts, economic challenges, and societal gender preferences using cognitive and behavioural techniques and culturally resonant illustrations. Participants underwent rigorous data collection at three pivotal timepoints: baseline, third trimester, and 6-weeks postnatal. The primary outcome was anxiety symptom severity scores using the Hospital Anxiety and Depression Scale (HADS) at 6-weeks post-childbirth. Four potential mediators - social support, behavioural activation, perceived stress, and pregnancy experience - were assessed in the third trimester of pregnancy.

Results: A total of 1200 participants were randomized to the HMHB and EUC arms. In the six-week follow-up time point, 379 participants remained in the EUC group, and 387 continued in the HMHB group. Post-intervention, HMHB participants displayed significant improvements in postnatal anxiety and depression scores. Mediation analyses revealed social support and pregnancy hassles as significant mediators of the intervention's effect on postnatal anxiety outcomes, while only social support emerged as a significant mediator for depression outcomes.

Conclusion: The HMHB intervention showed promising results in improving anxiety and depression scores among pregnant women. Significant mediation effects suggest the importance of targeting social support and managing pregnancy-related hassles for optimal intervention effectiveness.

Acad Pediatr. 2024 Aug 1:S1876-2859(24)00286-9.

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Effects of a prenatal anxiety randomized controlled trial intervention on infant development in Pakistan

[Pamela J Surkan¹](#), [Soim Park²](#), [Ziyue Sheng³](#), [Ahmed Zaidi⁴](#), [Najia Atif⁵](#), [Lauren M Osborne⁶](#), [Atif Rahman⁷](#), [Abid Malik⁸](#)

Abstract

Objectives: Given that infant development is influenced by caregiver mental health, we tested whether an intervention to reduce antenatal anxiety could affect infant development. A secondary aim was to test depressive symptoms, maternal responsiveness, and maternal infant bonding as mediators of this relationship.

Methods: Between 2020 and 2022, pregnant women participated in a randomized controlled trial of the Happy Mother-Healthy Baby (HMHB) program based on cognitive behavioral therapy. We collected data on child development from 202 intervention and 198 control participants in a public hospital in Pakistan. Child development was measured using the Ages and Stages Questionnaires-Version 3 at six weeks postpartum. Using intent-to-treat analyses, we examined whether the intervention was associated with performance on the five ASQ-3 domains. Causal mediation analysis was used to assess depressive symptoms, bonding, and maternal-infant responsiveness as mediators.

Results: Socio-demographic characteristics were evenly distributed between study arms. Intervention arm infants showed a 2.1-point increase (95% CI: 0.12, 4.17) in communication scores compared to controls. Though not achieving statistical significance, intervention infants also showed a 2.0-point increase (95% CI: -0.06, 4.09) in gross motor development performance. Bonding, depression, and responsiveness were mediators between the intervention and infant communication ($B_{\text{indirect}}=1.94$ (95%CI: 0.86, 3.25) depression; $B_{\text{indirect}}=0.57$ (95% CI: 0.09, 1.16) bonding; $B_{\text{indirect}}=0.53$ (95% CI: 0.01, 1.21) responsiveness; and $B_{\text{indirect}}=1.94$ (95%CI: 0.86, 3.25). Bonding, responsiveness, and depression mediated 25%, 23%, and 87% of the total association, respectively.

Maternal malaria prevention

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Artemisinin combination therapy at delivery to prevent postpartum malaria: A randomised open-label controlled trial

[Paula Tesine¹](#), [Sze-Ann Woon²](#), [Moses Laman¹](#), [Gumul Yadi¹](#), [Phantica Yambo¹](#), [Bernadine Kasian¹](#), [Lina Lorry¹](#), [Leanne J Robinson³](#), [Sam Salman⁴](#), [Kevin T Batty⁵](#), [William Pomat¹](#), [Laurens Manning⁶](#), [Wendy A Davis²](#), [Timothy M E Davis²](#), [Brioni R Moore⁷](#)

Abstract

Objectives: Although the incidence of malaria is increased in women in endemic areas after delivery compared to non-pregnant women, no studies have assessed the benefit of presumptive antimalarial treatment given postpartum.

Methods: A randomised controlled trial investigating the efficacy of antimalarial treatment in preventing postpartum malaria was performed in healthy Papua New Guinea mothers immediately following delivery. Participants were randomised 1:1 to no treatment (n = 90) or artemisinin combination therapy (ACT), with further 1:1 ACT randomisation to artemether-lumefantrine (AL; n = 45) or dihydroartemisinin-piperaquine (DP; n = 45). Standardised reviews were conducted monthly for 6 months, including clinical assessment, malaria screening and haemoglobin measurement. The primary endpoint was incidence of slide-positive malaria within 6 months of delivery.

Results: Of 183 recruited participants, 151 completed study procedures and were included in per-protocol analyses (no treatment n = 71, AL n = 40, DP, n = 40). Those allocated to ACT were significantly less likely to develop slide-positive malaria during the 6-month follow-up period compared to those who were untreated (n = 17 (21%) vs n = 27 (38%); P = 0.016; hazard ratio 0.49 (95% confidence intervals 0.27-0.90). There was no significant difference in malaria incidence between the two ACT groups.

Conclusion: A treatment course of ACT at time of delivery halved the incidence of malaria infection during the first 6-month postpartum.

EBioMedicine. 2024 Oct 16:109:105397.

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Intermittent preventive treatment for malaria in pregnancy and infant growth: a mediation analysis of a randomised trial

[Yanwei Tong¹](#), [Kalani Ratnasiri²](#), [Suhi Hanif³](#), [Anna T Nguyen³](#), [Michelle E Roh⁴](#), [Grant Dorsey⁵](#), [Abel Kakuru⁶](#), [Prasanna Jagannathan⁷](#), [Jade Benjamin-Chung⁸](#)

Abstract

Background: Intermittent preventive treatment for malaria in pregnancy (IPTp) can improve birth outcomes, but whether it confers benefits to postnatal growth is unclear. We investigated the effect of IPTp on infant growth in Uganda and its pathways of effects using causal mediation analyses.

Methods: We analysed data from 633 infants born to mothers enrolled in a randomised trial of monthly IPTp with dihydroartemisinin-piperaquine (DP) vs. sulfadoxine-pyrimethamine (SP) ([NCT02793622](#)). Weight and length were measured from 0 to 12 months of age. Using generalised linear models, we estimated effects of DP vs. SP on gravidity-stratified mean length-for-age (LAZ) and weight-for-length Z-scores (WLZ). We investigated mediation by placental malaria, gestational weight change, maternal anaemia, maternal inflammation-related proteins, preterm birth, birth length, and birth weight. Mediation models adjusted for

infant sex, gravidity, gestational age at enrolment, maternal age, maternal parasitaemia at enrolment, education, and wealth.

Findings: SP increased mean LAZ by 0.18-0.28 Z from birth through age 4 months compared to DP, while DP increased mean WLZ by 0.11-0.28 Z from 2 to 8 months compared to SP among infants of multigravidae; at these ages, confidence intervals for mean differences excluded 0. We did not observe differences among primigravida. Mediators of SP included birth weight, birth length, maternal stem cell factor, and DNER. Mediators of DP included placental malaria and birth length, maternal IL-18, CDCP1, and CD6 at delivery.

Interpretation: In high malaria transmission settings, this exploratory study suggests different IPTp regimens may influence infant growth among multigravidae, potentially through distinct pathways, in the exclusive breastfeeding period, when few other interventions are available.

EClinicalMedicine. 2025 Apr 29;83:103202.

doi: 10.1016/j.eclim.2025.103202. eCollection 2025 May.

Dihydroartemisinin-piperaquine versus sulfadoxine-pyrimethamine for intermittent preventive treatment of malaria in pregnancy: a systematic review and individual participant data meta-analysis

[Michelle E Roh¹](#), [Julie R Gutman²](#), [Maxwell Murphy³](#), [Jenny Hill⁴](#), [Mywayiwawo Madanitsa⁵](#), [Abel Kakuru⁶](#), [Hellen C Barsosio^{4,7}](#), [Simon Kariuki⁷](#), [John P A Lusingu⁸](#), [Frank Mosha⁹](#), [Richard Kajubi⁶](#), [Moses R Kamya¹⁰](#), [Don Mathanga¹¹](#), [Jobiba Chinkhumba¹²](#), [Miriam K Laufer¹³](#), [Eulambius Mlugu¹⁴](#), [Appolinary A R Kamuhabwa¹⁵](#), [Eleni Aklillu¹⁶](#), [Omary Minzi¹⁵](#), [Roland Nnaemeka Okoro¹⁷](#), [Ado Danazumi Geidam¹⁸](#), [John David Ohieku¹⁷](#), [Meghna Desai²](#), [Prasanna Jagannathan¹⁹](#), [Grant Dorsey³](#), [Feiko O Ter Kuile⁴](#)

Abstract

Background: High-grade *Plasmodium falciparum* resistance to sulfadoxine-pyrimethamine in east and southern Africa has prompted trials evaluating intermittent preventive treatment in pregnancy (IPTp) with dihydroartemisinin-piperaquine as an alternative to sulfadoxine-pyrimethamine. We aimed to provide an updated and comprehensive review of trials conducted in areas of high *P. falciparum* resistance that compared the efficacy of two types of IPTp regimens on maternal, birth, and infant outcomes.

Methods: We conducted two-stage, individual participant data meta-analyses of randomised trials comparing IPTp with dihydroartemisinin-piperaquine to sulfadoxine-pyrimethamine on maternal, birth, and infant outcomes. We searched the WHO International Clinical Trials Registry Platform, ClinicalTrials.gov, PubMed, and the Malaria in Pregnancy Consortium Library, on July 30, 2020 (updated on September 24, 2024), without restrictions by publication date, peer-review status, or language. Eligible trials enrolled HIV-uninfected pregnant women, followed participants to delivery, included participants with no prior IPTp use during the current pregnancy, and were conducted in areas with high-level parasite resistance to sulfadoxine-pyrimethamine (i.e., PfDHPS 540E $\geq$ 90% and/or 581G > 0%). Only singleton pregnancies were analysed. The primary endpoint was a composite measure of any adverse pregnancy outcome defined as fetal or neonatal loss, small-for-gestational age, low birthweight, or preterm birth. Summary estimates were generated using a random-effects model. Gravidity subgroup analyses were performed. Causal mediation analyses were used

to investigate the maternal mechanisms underlying the effect of IPTp regimens on birth outcomes. The meta-analysis is registered in PROSPERO (CRD42020196127).

Findings: Of 85 screened records, six trials (one multi-country trial) from Kenya, Malawi, Uganda and Tanzania contributed data on 6646 pregnancies. Compared to sulfadoxine-pyrimethamine, dihydroartemisinin-piperaquine was associated with a 69% [95% CI: 45%-82%] lower incidence of clinical malaria during pregnancy, a 62% [37%-77%] lower risk of placental parasitaemia, and a 17% [0%-31%] lower incidence of moderate maternal anaemia. In contrast, sulfadoxine-pyrimethamine was associated with higher mean maternal weight gain (34 g/week [17-51]). There were no statistically significant differences in the composite adverse pregnancy outcome (RR = 1.05 [0.92-1.19]; $I^2 = 48\%$). Individual components of the primary outcome showed no statistically significant differences in the risks of fetal loss (RR = 0.94 [0.61-1.46]), preterm birth (RR = 0.93 [0.76-1.14]), low birthweight (RR = 1.09 [0.83-1.43]), or neonatal loss (RR = 0.73 [0.42-1.26]), though findings may have been underpowered. Small-for-gestational-age risk was 15% (3%-24%) lower in the sulfadoxine-pyrimethamine arm, particularly among multigravidae (a 22% reduction vs 9% in primigravidae). Among multigravidae, infant stunting and underweight by two months was 20% [8%-30%] and 35% [17%-49%] lower in the sulfadoxine-pyrimethamine arm compared to dihydroartemisinin-piperaquine. Compared to dihydroartemisinin-piperaquine, sulfadoxine-pyrimethamine was associated with higher mean newborn birthweight (mean difference (MD) = 50 g [95% CI: 13-88]; $p = 0.0090$, $I^2 = 61\%$) and BWGA z-scores (MD = 0.12 [95% CI: 0.05-0.20]; $p = 0.0012$, $I^2 = 51\%$), but not gestational age at birth (MD = 0 weeks [95% CI: -0.11 to 0.12]; $p = 0.94$; $I^2 = 42\%$). Infant wasting by two months was 13% [3%-22%] lower in the sulfadoxine-pyrimethamine arm, regardless of gravidity. Mediation analyses indicated that 15% [0%-19%] of sulfadoxine-pyrimethamine's superior effect on small-for-gestational-age risk was mediated by its greater impact on gestational weight gain.

Interpretation: In areas with high *P. falciparum* sulfadoxine-pyrimethamine resistance, dihydroartemisinin-piperaquine offers superior antimalarial efficacy than sulfadoxine-pyrimethamine. However, replacing sulfadoxine-pyrimethamine with dihydroartemisinin-piperaquine alone may not lead to improved maternal and infant health outcomes. Instead, it could result in slightly reduced gestational weight gain and a modest increase in the risk of small-for-gestational age births, and poor infant growth by two months of age. Future research evaluating alternative strategies for IPTp are needed.

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[Artemisinin combination therapy at delivery to prevent postpartum malaria: a randomized open-label controlled trial.: Preventing postpartum malaria](#)

[Paula Tesine¹](#), [Sze-Ann Woon²](#), [Moses Laman¹](#), [Gumul Yadi¹](#), [Phantica Yambo¹](#), [Bernadine Kasian¹](#), [Lina Lorry¹](#), [Leanne J Robinson³](#), [Sam Salman⁴](#), [Kevin T Batty⁵](#), [William Pomat¹](#), [Laurens Manning⁶](#), [Wendy A Davis²](#), [Timothy M E Davis²](#), [Brioni R Moore⁷](#)

Abstract

Objectives: Although the incidence of malaria is increased in women in endemic areas after delivery compared to non-pregnant women, no studies have assessed the benefit of presumptive antimalarial treatment given postpartum.

Methods: A randomised controlled trial investigating the efficacy of antimalarial treatment in preventing postpartum malaria was performed in healthy PNG mothers immediately following delivery. Participants were randomised 1:1 to no treatment (n=90) or artemisinin combination therapy (ACT), with further 1:1 ACT randomization to artemether-lumefantrine (AL; n=45) or dihydroartemisinin-piperaquine (DP; n=45). Standardised reviews were conducted monthly for six-months, including clinical assessment, malaria screening and haemoglobin measurement. The primary endpoint was incidence of slide-positive malaria within six-months of delivery.

Results: Of 183 recruited participants, 151 completed study procedures and were included in per protocol analyses (no treatment n=71, AL n=40, DP, n=40). Those allocated to ACT were significantly less likely to develop slide-positive malaria during the six-month follow-up period compared to those who were untreated (n=17 (21%) versus n=27 (38%); P=0.016; HR 0.49 (95% CI 0.27 to 0.90). There was no significant difference in malaria incidence between the two ACT groups.

Conclusions: A treatment course of ACT at time of delivery halved the incidence of malaria infection during the first 6-months postpartum.

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Delivery effectiveness of and adherence to intermittent preventive treatment for malaria in pregnancy with dihydroartemisinin-piperaquine with or without targeted information transfer or sulfadoxine-pyrimethamine in western Kenya: a three-armed, pragmatic, open-label, cluster-randomised trial

[Hellen C Barsosio¹](#), [Jayne Webster²](#), [Frederick Omiti³](#), [Alloys K'Oloo³](#), [Isdorah A Odero³](#), [Michael A Ojuok³](#), [Dawn Odiwa³](#), [Benson Omondi³](#), [Elizabeth Okello³](#), [James Dodd⁴](#), [Miriam Taegtmeier⁴](#), [Feiko O Ter Kuile⁵](#), [Maia Lesosky⁶](#), [Simon Kariuki³](#), [Jenny Hill⁴](#)

Abstract

Background: High-level resistance to sulfadoxine-pyrimethamine threatens the efficacy of WHO-recommended intermittent preventive treatment in pregnancy (IPTp) with single-dose sulfadoxine-pyrimethamine to prevent malaria. Monthly IPTp with dihydroartemisinin-piperaquine, a 3-day regimen, is an emerging alternative, but this regimen poses potential implementation and adherence challenges. We aimed to assess adherence to a multiday IPTp with dihydroartemisinin-piperaquine regimen and its delivery effectiveness in routine antenatal care settings in western Kenya.

Methods: We conducted a pragmatic, three-armed, open-label, cluster-randomised trial in antenatal clinics in 18 health-care facilities (six facilities per group) in Kisumu County and Homa Bay County in western Kenya. Clusters were facilities offering routine antenatal care services provided by trained Ministry of Health staff with 100 or more antenatal clinic attendances per month between July, 2018, and June, 2019. Private or mission hospitals, dispensaries, referral hospitals, and trial sites were excluded. Individuals in their first trimester, living with HIV, or who were not attending a scheduled antenatal clinic visit were excluded. The 18 antenatal clinics were grouped into matched triplets stratified by location and clinics in each matched triplet were randomly assigned to one of the three study groups

(1:1:1). Masking was not possible. Two groups were given IPTp with dihydroartemisinin-piperaquine (one group with a targeted information transfer intervention and one group without any additional interventions) and one group was given the standard of care (ie, IPTp with sulfadoxine-pyrimethamine). The primary endpoint, adherence, was defined as the proportion of participants completing their most recent 3-day IPTp with dihydroartemisinin-piperaquine regimen. This completion was verified by pill counts during home visits no more than 2 days after participants' 3-day regimens ended. The secondary endpoint, delivery effectiveness, was defined as the proportion of participants who received the correct number of IPTp tablets and correctly repeated dosing instructions (ie, correctly recalled the instructions they received about self-administered dihydroartemisinin-piperaquine doses and the number of sulfadoxine-pyrimethamine tablets they had received) at their exit from the antenatal clinic. Individuals receiving treatment for malaria, visiting a clinic for registration only, or interviewed during IPTp drug stock-outs were excluded from analyses. We used generalised linear mixed models to compare endpoints among the IPTp with dihydroartemisinin-piperaquine groups. This trial was registered with ClinicalTrials.gov, [NCT04160026](#), and is complete.

Findings: 15 facilities (five per group) completed the trial, with 1189 participants having exit interviews (377 in the IPTp with sulfadoxine-pyrimethamine group, 408 in the IPTp with dihydroartemisinin-piperaquine only group, and 404 in the IPTp with dihydroartemisinin-piperaquine plus targeted information transfer intervention group) and 586 participants having home visits (267 in the IPTp with dihydroartemisinin-piperaquine only group and 319 in the IPTp with dihydroartemisinin-piperaquine plus targeted information transfer intervention group) from Sept 8 to Dec 10, 2020. Relative to the IPTp with dihydroartemisinin-piperaquine only group, adherence was 16% higher in the IPTp with dihydroartemisinin-piperaquine plus targeted information transfer intervention group (266 [83%] of 319 participants vs 196 [73%] of 267 participants; adjusted relative risk [RR] 1.16, 95% CI 1.03-1.31; $p=0.0140$). Delivery effectiveness in the IPTp with dihydroartemisinin-piperaquine plus targeted information transfer intervention group was not significantly different from that in the IPTp with sulfadoxine-pyrimethamine group (352 [87%] of 403 participants vs 335 [89%] of 375 participants; adjusted RR 0.97, 95% CI 0.90-1.05; $p=0.4810$). However, delivery effectiveness in the IPTp with dihydroartemisinin-piperaquine only group was significantly lower than in the IPTp with sulfadoxine-pyrimethamine group (300 [74%] of 404 participants vs 335 [89%] of 375 participants; 0.84, 0.75-0.95; $p=0.0030$).

Interpretation: Targeted information transfer interventions to health-care providers and pregnant individuals boost antenatal care delivery adherence to a multiday regimen with dihydroartemisinin-piperaquine.

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[Effect of Antenatal Monthly Sulfadoxine-Pyrimethamine, Alone or with Azithromycin, on Gestational Weight Gain and Anemia during Pregnancy and One Month Postpartum in Malawi: A Randomized Controlled Trial Secondary Analysis](#)

[Mari Luntamo](#)¹, [Lotta Hallamaa](#)¹, [Teija Kulmala](#)¹, [Kenneth Maleta](#)², [Per Ashorn](#)^{1,3}

Abstract

Low gestational weight gain (GWG) and prenatal anemia are associated with adverse pregnancy, maternal and infant health outcomes. In a secondary analysis of a single-center, randomized, partially placebo-controlled, outcome assessor-blinded, controlled trial conducted in Malawi from 2003 to 2006, when antiretroviral treatment (ART) for HIV was not widely available, we studied whether GWG can be increased and the prevalence of maternal anemia decreased during pregnancy and at 1 month postpartum through the intermittent preventive treatment in pregnancy (IPTp) of maternal malaria and reproductive tract infections. The participants (≥ 15 -year-old women with uncomplicated second trimester single pregnancies) received either sulfadoxine (1,500 mg) and pyrimethamine (75 mg; SP) twice (control group, $n = 433$), monthly SP ($n = 439$), or monthly SP and azithromycin (1,000 mg) twice (AZI-SP, $n = 441$) during pregnancy. The mean weekly GWG in the sample was 256 g/week. The participants in the monthly SP group gained, on average (95% CI), 4 g (-13 to 20; $P = 0.671$), and those in the AZI-SP group gained 25 g (8-41; $P = 0.003$) more weight per week than control group participants. Among HIV-positive participants (12%), the differences were larger and also significant between the monthly SP group and control group. Mean hemoglobin and anemia prevalence did not differ between the groups during pregnancy or postnatally. The data support a hypothesis that IPTp with monthly SP and two doses of azithromycin can increase GWG, especially among HIV-positive women who are not on ART, possibly through the reduction of infections, inflammation, and effects on the maternal gut microbiome.

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Implementation of a Mobile Health Approach to a Long-Lasting Insecticidal Net Uptake Intervention for Malaria Prevention Among Pregnant Women in Tanzania: Process Evaluation of the Hati Salama (HASA) Randomized Controlled Trial Study

[Trinity Vey¹](#), [Eleonora Kinnicutt²](#), [Nicola West^{1,3}](#), [Jessica Sleeth¹](#), [Kenneth Bernard Nchimbi⁴](#), [Karen Yeates^{1,3}](#)

Abstract

Background: Malaria infection is associated with many adverse outcomes for pregnant women and neonates, yet pregnant women in East and Southern Africa remain frequently exposed to malaria. Long-lasting insecticidal nets (LLINs) can help prevent malarial infections and the associated adverse events. The Hati Salama (HASA) study was a cluster-randomized controlled trial implemented in 100 antenatal health facilities in urban and rural settings of Tanzania that provided pregnant women in both intervention and control groups with e-vouchers to redeem for LLINs for malaria prevention. The intervention group received behavior change communication mobile messages across a 14-day period while the e-voucher was active, and no significant difference between the rates of e-voucher redemption was found across the two groups.

Objective: This study was a process evaluation of the HASA randomized controlled trial to determine barriers and facilitators to e-voucher reception and LLIN acquisition for pregnant women enrolled in the trial, as well as challenges and lessons learned by nurses who worked at the antenatal health facilities supporting the trial.

Methods: Following the e-voucher's expiration at 14 days, voluntary phone follow-up surveys were conducted for nurses who supported the trial, as well as participants in both intervention and control groups of the trial who did not redeem their e-vouchers. Survey questions asked nurses about workflow, training sessions, network connectivity, proxy phone use, and more. Surveys asked participants about reasons for not redeeming e-vouchers. Both surveys provided lists of preset answers to questions, as well as the option to provide open-ended responses. Nurses and trial participants were contacted between January and June 2016 on up to three occasions.

Results: While nurses who supported the HASA trial seemed to recognize the value of the program in their communities, some barriers identified by nurses included network connectivity, workload increase, inadequate training and on-the-ground support, and difficulty following the workflow. Several barriers identified by trial participants included personal obligations preventing them from redeeming the e-voucher on time, network connectivity issues, losing the e-voucher number, no stock of LLINs at retailers when attended, inadequate explanation of where or how to redeem the e-voucher, or not receiving an SMS text message with the e-voucher number promptly or at all.

Conclusions: Large-scale e-voucher platforms for health-related commodity interventions, such as LLIN distribution in sub-Saharan Africa, are feasible, but challenges, including network connectivity, must be addressed. Nurses identified issues to be considered in a future scale-up, such that the number of nurses trained should be increased and the e-voucher issuance workflow should be simplified. To address some of the key barriers impacting e-voucher redemption for trial participants, the network of retailers could be expanded and the e-voucher expiration period should be extended.

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[Community-based strategies to increase coverage of intermittent preventive treatment of malaria in pregnancy with sulfadoxine-pyrimethamine in sub-Saharan Africa: a systematic review, meta-analysis, meta-ethnography, and economic assessment](#)

[Kadiatou Koita¹, Kassoum Kayentao², Eve Worrall³, Anna Maria Van Eijk³, Jenny Hill³](#)

Abstract

Background: Community-based approaches might increase uptake of intermittent preventive treatment of malaria in pregnancy with sulfadoxine-pyrimethamine (IPTp-SP). We assessed the effects of community-based approaches on IPTp-SP and antenatal care coverage, and barriers and facilitators to implementation in sub-Saharan Africa.

Methods: We did a systematic review, meta-analysis, meta-ethnography, and economic assessment. We searched the WHO International Clinical Trials Registry Platform, PubMed, the Malaria in Pregnancy Library database, Medline, Global Health and Global Health Archives, and the Cochrane Library for trials, mixed-methods, qualitative, and cost-effectiveness studies of community health worker promotion of antenatal care, IPTp-SP delivery, or both, with no language restrictions, published before March 21, 2024.

Information on interventions, number of IPTp-SP doses, antenatal care visits, and barriers and facilitators were extracted. We did a meta-analysis (random effects) comparing effects on two or more or three or more IPTp-SP doses and one or more or four or more antenatal care visits. We followed Noblit and Hare's method of meta-ethnography to synthesise

qualitative findings, using reciprocal translation and line-of-argument synthesis. We developed a theory for increased community IPTp-SP uptake. We also summarised cost and cost-effectiveness studies. This study is registered with PROSPERO, CRD42022364114.

Findings: Of 4753 records screened, we included 23 (0.5%) reporting on 15 studies. Community health worker involvement was associated with an increase in two or more IPTp-SP doses (pooled risk ratio 1.48, [95% CI 1.24-1.75]; 12 sub-studies; I^2 94.7%) and three or more IPTp-SP doses (1.73 [1.19-2.50]; ten sub-studies, I^2 97.5%), with no decrease in four or more antenatal care visits (1.17 [1.00-1.36]; 13 sub-studies; I^2 90.3%). Cluster-randomised controlled trials showed a lower increase in coverage of three or more IPTp-SP doses (1.08 [1.00-1.16]; I^2 0.0%; six studies) compared with before-and-after studies (2.86 [1.29-6.33]; I^2 98.9%; four studies; subgroup analysis $p=0.019$). Barriers to community health worker delivery of IPTp-SP included women's fear of side-effects, lack of knowledge, lack of trust in community health workers, and sociocultural factors. Community sensitisation, engagement of husbands, pre-established community health worker networks, and trained and supported community health workers facilitated IPTp-SP delivery by community health workers. Incremental cost-effectiveness ratios ranged from \$1.1 to \$543 per disability-adjusted life-year averted.

Interpretation: Community-based approaches increased IPTp-SP coverage and might have a positive effect on the number of antenatal care visits in addition to being cost-effective, although we found high heterogeneity among studies. Community sensitisation and engagement in addition to established, trained, and supported community health workers can facilitate acceptability, delivery, and uptake of IPTp-SP delivered by community health workers.

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Uptake and Effectiveness of Intermittent Preventive Treatment with Sulfadoxine-Pyrimethamine during Pregnancy in Africa: A Scoping Review

[Gifty Osei Berchie¹](#), [Patience Fakornam Doe²](#), [Theodora Dedo Azu¹](#), [Joyce Agyeiwaa¹](#), [Gifty Owusu¹](#), [Christian Makafui Boso³](#), [Naomi Kyeremaa Yeboa¹](#), [Dorcas Frempong Agyare³](#), [Irene Korkoi Aboh¹](#), [Bernard Nabe³](#), [Godson Obeng Ofori³](#), [Benjamin Anumel⁴](#), [Justice Enock Kagbo³](#), [Amidu Alhassan³](#), [Frank Odonkor Offei³](#), [Rita Opoku-Danso³](#), [Susanna Aba Abraham²](#), [Mustapha Amoadu⁵](#), [John Elvis Hagan Jr^{6,7}](#)

Abstract

Malaria poses a significant threat to pregnant women in sub-Saharan Africa, necessitating effective interventions like the intermittent preventive treatment of malaria in pregnancy with sulfadoxine-pyrimethamine (IPTp-SP). However, challenges persist in the uptake and effectiveness of this intervention. This scoping review aims to explore IPTp-SP uptake in African countries, identify influencing factors, and assess its effectiveness in preventing malaria and adverse outcomes in pregnancy. This scoping review follows Arksey and O'Malley's framework, employing the PRISMA-ScR guidelines for reporting. Searches were conducted in PubMed, Embase, Scopus, JSTOR, Web of Science, Google Scholar, and ProQuest, focusing on studies post-2000 published in the English language. The search produced 15,153 records, of which 104 full-text records were eligible and 101 papers were included in this review. The findings suggest varying IPTp-SP uptake rates, spanning from 5.3% to 98.9%, with their effectiveness supported by longitudinal studies, randomised

controlled-trials (RCTs), cross-sectional surveys, and mixed-method studies. IPTp-SP demonstrates efficacy in reducing malaria during pregnancy, placental parasitaemia, and anaemia episodes, alongside improved birth outcomes. Common adverse effects of IPTp-SP include prematurity and low birth weight. Facilitators of IPTp-SP uptake include education and ANC attendance, while commonly reported barriers included inadequate knowledge and healthcare system challenges. The findings also suggest adverse effects such as prematurity, low birth weight, and maternal and perinatal mortality associated with IPTp-SP uptake. It is vital to strengthen antenatal care services by integrating comprehensive counselling on IPTp-SP and address healthcare system challenges. Community engagement, women's empowerment, and context-specific interventions are necessary for promoting IPTp-SP uptake and improving maternal and neonatal health outcomes in Africa.

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Intermittent preventive treatment regimens for malaria in HIV-positive pregnant women

[Clara Pons-Duran^{1,2}](#), [Myrte J Wassenaar¹](#), [Koffi Emmanuel Yovo^{3,4}](#), [Clara Marín-Carballo¹](#), [Valérie Briand^{5,6}](#), [Raquel González^{1,7,8}](#)

Abstract

Background: Malaria and HIV infection overlap geographically in sub-Saharan Africa and share risk factors. HIV infection increases malaria's severity, especially in pregnant women. The World Health Organization (WHO) recommends intermittent preventive treatment in pregnancy (IPTp) with sulphadoxine-pyrimethamine (SP) for pregnant women living in areas of stable malaria transmission. However, HIV-positive women on daily cotrimoxazole prophylaxis (recommended for prevention of opportunistic infections in people with HIV) cannot receive SP due to adverse drug interactions, so malaria prevention in this vulnerable population currently relies on daily cotrimoxazole prophylaxis alone. This review is based on a new protocol and provides an update to the 2011 Cochrane Review that evaluated alternative drugs for IPTp to prevent malaria in HIV-positive women.

Objectives: To compare the safety and efficacy of intermittent preventive treatment regimens for malaria prevention in HIV-positive pregnant women.

Search methods: We searched CENTRAL, MEDLINE, Embase, three other databases, and two trial registries to 31 January 2024. To identify relevant additional studies or unpublished work, we checked references and contacted study authors and other researchers working on malaria and HIV.

Selection criteria: We included randomized controlled trials (RCTs) comparing any intermittent preventive treatment regimen for preventing malaria in HIV-positive pregnant women against daily cotrimoxazole prophylaxis alone, placebo, current or previous standard of care, or combinations of these options. By 'standard of care' we refer to the country's recommended drug regimen to prevent malaria in pregnancy among HIV-positive women, or the treatment that a trial's research team considered to be the standard of care.

Data collection and analysis: Review authors, in pairs, independently screened all records identified by the search strategy, applied inclusion criteria, assessed risk of bias in included trials, and extracted data. We contacted trial authors when additional information was required. We presented dichotomous outcomes using risk ratios (RRs), count outcomes as incidence rate ratios (IRRs), and continuous outcomes as mean differences (MDs). We

presented all measures of effect with 95% confidence intervals (CIs). We assessed the certainty of the evidence using the GRADE approach for what we considered to be the main comparisons and outcomes.

Main results: We included 14 RCTs, with a total of 4976 HIV-positive pregnant women initially randomized. All trials assessed the efficacy and safety of one antimalarial used as IPTp (mefloquine, dihydroartemisinin/piperaquine, SP, or azithromycin) with or without daily cotrimoxazole, compared to daily cotrimoxazole alone, placebo, or a standard of care regimen. We grouped the trials into nine comparisons. Our main comparison evaluated the current standard of care (daily cotrimoxazole) with another drug regimen (mefloquine or dihydroartemisinin/piperaquine) versus daily cotrimoxazole with or without placebo. In this comparison, two trials evaluated mefloquine and three evaluated dihydroartemisinin/piperaquine. We conducted meta-analyses that included trials evaluating dihydroartemisinin/piperaquine plus cotrimoxazole, and trials that evaluated mefloquine plus cotrimoxazole, as we considered there to be no qualitative or quantitative heterogeneity among trials for most outcomes. We considered drug-related adverse events and HIV-related outcomes to be drug-specific. Daily cotrimoxazole prophylaxis plus another drug regimen (mefloquine or dihydroartemisinin/piperaquine) probably results in lower risk of maternal peripheral parasitaemia at delivery (RR 0.62, 95% CI 0.41 to 0.95; 2406 participants, 5 trials; moderate-certainty evidence). It results in little or no difference in maternal anaemia cases at delivery (RR 0.98, 95% CI 0.90 to 1.07; 2417 participants, 3 trials; high-certainty evidence). It probably results in a decrease in placental malaria measured by blood smear (RR 0.54, 95% CI 0.31 to 0.93; 1337 participants, 3 trials; moderate-certainty evidence), and probably results in little or no difference in low birth weight (RR 1.16, 95% CI 0.95 to 1.41; 2915 participants, 5 trials; moderate-certainty evidence). There is insufficient evidence to ascertain whether daily cotrimoxazole prophylaxis plus another drug regimen affects the risk of cord blood parasitaemia (RR 0.27, 95% CI 0.04 to 1.64; 2696 participants, 5 trials; very low-certainty evidence). Daily cotrimoxazole prophylaxis plus another drug regimen probably results in little or no difference in foetal loss (RR 1.03, 95% CI 0.73 to 1.46; 2957 participants, 5 trials; moderate-certainty evidence), and may result in little or no difference in neonatal mortality (RR 1.21, 95% CI 0.68 to 2.14; 2706 participants, 4 trials; low-certainty evidence). Due to the probability of an increased risk of mother-to-child HIV transmission and some adverse drug effects noted with mefloquine, we also looked at the results for dihydroartemisinin/piperaquine specifically. Dihydroartemisinin/piperaquine plus daily cotrimoxazole probably results in little to no difference in maternal peripheral parasitaemia (RR 0.59, 95% CI 0.31 to 1.11; 1517 participants, 3 trials; moderate-certainty evidence) or anaemia at delivery (RR 0.95, 95% CI 0.82 to 1.10; 1454 participants, 2 trials; moderate-certainty evidence), but leads to fewer women having placental malaria when measured by histopathologic analysis (RR 0.67, 95% CI 0.50 to 0.90; 1570 participants, 3 trials; high-certainty evidence). The addition of dihydroartemisinin/piperaquine to daily cotrimoxazole probably made little to no difference to rates of low birth weight (RR 1.13, 95% CI 0.87 to 1.48; 1695 participants, 3 trials), foetal loss (RR 1.14, 95% CI 0.68 to 1.90; 1610 participants, 3 trials), or neonatal mortality (RR 1.03, 95% CI 0.39 to 2.72; 1467 participants, 2 trials) (all moderate-certainty evidence). We found low-certainty evidence of no increased risk of gastrointestinal drug-related adverse events (RR 1.42, 95% CI 0.51 to 3.98; 1447 participants, 2 trials) or mother-to-child HIV transmission (RR 1.54, 95% CI 0.26 to 9.19; 1063 participants, 2 trials).

Authors' conclusions: Dihydroartemisinin/piperaquine and mefloquine added to daily cotrimoxazole seem to be efficacious in preventing malaria infection in HIV-positive pregnant women compared to daily cotrimoxazole alone. However, increased risk of HIV transmission to the foetus and poor drug tolerability may be barriers to implementation of mefloquine in practice. In contrast, the evidence suggests that dihydroartemisinin/piperaquine does not increase the risk of HIV mother-to-child transmission and is well tolerated.

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Drug-Drug Interaction Between Dihydroartemisinin-Piperaquine and Sulfadoxine-Pyrimethamine During Malaria Chemoprevention in Pregnant Women

[Norah Mwebaza^{#1,2}](#), [Michelle E Roh^{#3}](#), [Yourong Z Geng⁴](#), [Leonard Opio¹](#), [Bishop Opira¹](#), [Florence Marzan⁴](#), [Moses W Mwima¹](#), [Timothy Ssemukuye¹](#), [Kevin Guo⁴](#), [David Gingrich⁴](#), [Nikoletta Fotaki⁵](#), [Abel Kakuru¹](#), [Jimmy Kizza¹](#), [Miriam Aguti¹](#), [Harriet Adrama¹](#), [Moses Kamya^{1,6}](#), [Grant Dorsey⁷](#), [Philip J Rosenthal⁷](#), [Francesca T Aweeka⁴](#), [Liusheng Huang⁴](#)

Abstract

Co-administration of dihydroartemisinin-piperaquine (DP) and sulfadoxine-pyrimethamine (SP) for intermittent preventive treatment of malaria in pregnancy (IPTp) may be superior in preventing adverse birth outcomes compared with either therapy alone, but potential drug-drug interactions require investigation. We conducted intensive and sparse pharmacokinetic (PK) studies in a subset of Ugandan women participating in a randomized controlled trial of monthly IPTp with SP vs. DP vs. DP + SP. Intensive PK sampling was performed from day 0 to 23 after dosing at 28 weeks gestation in 87 participants across treatment arms. Sparse sampling was performed on day 28 (trough) after dosing at 20 and 28 gestational weeks in additional 196 participants receiving SP vs. DP + SP. Intensive PK analysis demonstrated that compared with SP alone, co-administration of DP + SP was associated with lower maximal concentrations, the area under the concentration-time curves (AUC), and day 23 concentrations of sulfadoxine (25%, 25%, and 27%) and pyrimethamine (26%, 34%, and 32%) ($P < 0.05$ for all comparisons). Sparse PK results demonstrated participants co-administered DP + SP had lower trough concentrations after dosing at 20 and 28 gestational weeks for sulfadoxine (6%, $P = 0.68$ and 31%, $P = 0.023$, respectively) and pyrimethamine (18%, $P = 0.032$ and 33%, $P < 0.001$, respectively) compared with SP alone. Co-administration of DP + SP was associated with a 19% reduction in piperaquine AUC ($P = 0.046$), but no significant difference in other PK parameters compared with DP alone. In summary, co-administration of DP + SP was associated with significantly reduced SP exposure, with a greater magnitude during the third vs. second trimester. The clinical consequences of this interaction are yet unknown.

Obstetric care and delivery

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[Standards-based audit to improve quality of maternal and newborn care-A stepped-wedge cluster randomised trial in Malawi](#)

[Sarah Ann White¹](#), [Florence Mgawadere¹](#), [Somasundari Gopalakrishnan¹](#), [Nynke van den Broek¹](#)

Abstract

Background: Audit is a quality improvement approach used in maternal and newborn health. Our objective was to introduce the practice of standards-based audit at healthcare facility level, and to examine if this would improve quality of care assessed by compliance with standards developed and agreed with healthcare providers. Our focus was on emergency obstetric and newborn care (EmONC).

Methods: A multidimensional incomplete stepped-wedge cluster randomised trial with 8 steps was conducted in 44 healthcare facilities in Malawi. A total of 25 standards of care were developed. At each healthcare facility one (health centres) or two (hospitals) standards were audited per cycle with two consecutive audit cycles conducted. Each cycle consisted of five steps: (i) select standard to be audited, (ii) measure compliance with standard (measurement 1), (iii) review findings and identify what changes are required to increase compliance (iv) implement changes, (v) re-measure compliance (measurement 2). Each compliance measurement assessed 25 women. Multilevel mixed effects logistic regression models were used to analyse data for all standards.

Results: The crude overall compliance rate rose from 45% in the control phase (measurement 1) to 63% in the intervention phase (measurement 2) (from 51.6% to 70.6% at Basic and from 34.5% to 50.8% at Comprehensive EmONC healthcare facilities. When adjusted for standard, facility type, month, and healthcare facility by month, the adjusted OR (95% CI) was 2.80 (1.65, 4.76). Actions taken to improve compliance with standards included improving staff performance of clinical duties and general conduct through re-orientation and staff meetings as well as improved supervision, and, ensuring basic equipment and consumables were available on site (thermometers, rapid diagnostic tests, partograph).

Conclusion: The introduction of standards-based audit helped healthcare providers identify problems with service provision, which when addressed, resulted in a measurable and significant improvement in quality of care.

J Epidemiol Glob Health. 2024 Sep;14(3):690-698.

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[Maternal and Child Health Training of Traditional Birth Attendants and Pregnancy Outcomes: A Systematic Review and Meta-analysis](#)

[Rakhi Dwivedi^{#1}](#), [Muhammad Aaqib Shamim^{#2}](#), [Pradeep Dwivedi^{3,4}](#), [Anannya Ray Banerjee¹](#), [Akhil Dhanesh Goel⁵](#), [Varuna Vyas⁶](#), [Pratibha Singh⁷](#), [Shilpi Gupta Dixit⁸](#), [Kriti Mohan⁹](#), [Kuldeep Singh^{10,11}](#)

Abstract

Introduction: In remote communities, maternal and child health is often compromised due to limited access to healthcare. Simultaneously, these communities historically rely greatly on traditional birth attendants (TBAs). However, optimal integration of these traditional methods with modern healthcare practices remains a topic of debate. We assessed the effect of maternal and child health training of traditional birth attendants on adverse pregnancy outcomes.

Methods: We conducted a systematic review and meta-analysis to answer the above research question. We independently screened studies using databases like PubMed, Scopus, and CENTRAL, extracted data, and assessed the study quality. Due to fewer original studies in this field, we considered both pre-post and between-group differences to assess the effect of differences. These were synthesised separately, assessed against a p-value function, and subjected to sensitivity analyses.

Results: We included six interventional studies. Training TBAs reduced the risk of perinatal mortality [0.69, 0.61-0.78] and 7-day neonatal mortality [0.65, 0.53-0.80] but not stillbirth [0.70, 0.39-1.26]. In randomized controlled trials, there is a lower risk of perinatal mortality [0.73, 0.67-0.79] and neonatal mortality [0.70, 0.62-0.80] but not stillbirth [0.81, 0.56-1.18] with trained traditional birth attendants. There are methodological concerns with most existing studies, including domains like allocation concealment.

Discussion: There is some evidence of the benefit of training TBAs, though of a low to very low certainty. Due to fewer studies, inconsistent estimates for different critical outcomes, and concerns with the existing studies, further well-designed studies can give more insights. They can also help optimize the contents of TBA training interventions.

Midwifery. 2024 Nov;138:104153.

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Effect of health education provided to couples on maternal knowledge, attitude and use of maternity waiting homes in rural Ethiopia: A cluster-randomized trial

[Teklemariam Ergat Yarinbab¹](#), [Hailay Abrha Gesesew²](#), [Tefera Belachew³](#)

Abstract

Background: Maternity waiting home (MWH) has been advocated as an approach to improve women's access to obstetric services in low-resource settings; however, its use remains low. This study investigated the effectiveness of couple-based health education on maternal knowledge, attitudes, and use of MWHs in rural Ethiopia.

Methods: A total of 320 couples from 16 clusters were allocated to the intervention and control groups using restricted randomization. Participants in the intervention group received group health education, home visits, and information flyers along with usual care, whereas those in the control group received usual care. Statistical differences were estimated using the chi-squared test. The impact of the intervention was evaluated using generalized linear regression and difference-in-differences models.

Results: Baseline and endline data were collected from the 320 couples. The intervention increased knowledge by 37.5 % (95 % CI: 32.2 % - 42.8 %), attitude by 33.8 % (95 % CI: 28.8 %-39.2 %), and utilization of MWH by 32.9 % (95 % CI: 27.9 %-38.2 %) among women. In addition, compared to those in the control group, women in the intervention group were almost six times more likely to have increased knowledge of MWH (AOR 5.74, 95 % CI: 3.51-

9.38), four times more likely to have improved attitudes of MWH (AOR 4.45, 95 % CI: 2.78 - 7.13), and four times more likely to stay at MWH (AOR 4.45, 95 % CI: 2.78 -7.12).

Conclusion: Providing health education to couples can improve maternal knowledge, attitudes, and the use of MWHs. Policymakers and healthcare cadres can use the current intervention strategy to enhance maternal health services, particularly MWHs, in rural Ethiopia.

Am J Obstet Gynecol MFM. 2024 Sep;6(9):101450.

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Tranexamic acid in preventing postpartum blood loss in vaginal delivery: a double-blinded randomized controlled trial

[Pratibha Arya¹](#), [Garima Yadav²](#), [Pratibha Singh¹](#), [Navdeep Kaur Ghuman¹](#), [Charu Sharma¹](#), [Meenakshi Gothwal¹](#), [Priyanka Kathuria¹](#)

Abstract

Background: Postpartum hemorrhage (PPH) is an obstetrical emergency that occurs in 1% to 10% of all deliveries and contributes to nearly one-quarter of all maternal deaths worldwide. Tranexamic acid has been established as an adjunct in the treatment of PPH but its role in its prevention of PPH following vaginal delivery has not been widely studied.

Objective: This study aimed to assess the effect of prophylactic tranexamic acid (1 g) along with active management of the third stage of labor in reducing postpartum blood loss and the incidence of postpartum hemorrhage after vaginal delivery.

Study design: In this randomized controlled trial, 650 women with singleton pregnancies at ≥ 34 weeks of gestation who were undergoing vaginal delivery were included. Eligible women were randomly assigned to receive either 1 g of tranexamic acid or placebo intravenously along with active management of the third stage of labor. Calibrated blood collection bags were used to measure postpartum blood loss during the third and fourth stages of labor.

Results: Of 886 women approached for the study, 650 who met the inclusion criteria were enrolled, and 320 in group A and 321 in group B were analyzed. The maternal characteristics were similar between the groups. The mean blood loss did not differ significantly between the intervention and placebo groups (378.5 ± 261.2 mL vs 383.0 ± 258.9 mL; $P=.93$). The incidence of primary postpartum hemorrhage was comparable in both groups (15.9% in group A and 15.3% in group B; $P=.814$). The median quantitative decreases in hemoglobin levels within 12 to 24 hours after delivery were 0.60 g% (interquartile range, 0.40-0.90) in group A and 0.60 g% (interquartile range, 0.40-0.80) in group B, which were comparable in both groups ($P=.95$). The most common adverse effect reported was dizziness, and there was no thromboembolic event at 3 months follow-up in either group.

Conclusion: The use of tranexamic acid as a prophylactic measure along with active management of the third stage of labor does not provide additional benefit in reducing the postpartum blood loss and incidence of postpartum hemorrhage after vaginal delivery.

Eur J Obstet Gynecol Reprod Biol. 2024 Sep;300:337-344.

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Postpartum haemorrhage management: A randomized controlled trial comparing transvaginal uterine artery clamp, vacuum-assisted uterine contraction and condom tamponade

[Alisha Shajahan¹](#), [Vakkanal Paily Paily²](#), [Ajithakumari Sudhamma¹](#), [K Ambujam¹](#), [Joshy Joseph Neelankavil¹](#), [M G Usha¹](#), [G Raji Raj¹](#), [Raymond George¹](#), [Afshana Sidhik¹](#), [Sara Cheriyan¹](#), [Soumya Ramakrishnan¹](#), [Divya Vishnu¹](#), [Suhail K Shefeek¹](#), [Manu Pradeep¹](#)

Abstract

Objective: While there have been numerous innovations recently for the management of postpartum haemorrhage (PPH), a limited body of research supports their application during this critical complication, which contributes significantly to maternal mortality worldwide. This randomized controlled trial (RCT) aimed to evaluate the effectiveness of three interventions - transvaginal uterine artery clamp (TVUAC), vacuum-assisted uterine contraction using a suction cannula (SC), and condom tamponade (CT) - in the management of atonic PPH.

Methods: An open-label RCT was conducted among women who delivered vaginally and developed atonic PPH at a tertiary care obstetric facility. Block randomization with sealed envelopes was used to allocate eligible participants into three interventional arms with a 1:1:1 ratio. The exclusion criteria were twin deliveries, haemodynamically unstable patients, and individuals who did not provide informed consent. The primary outcome variables assessed were blood loss post-application, total blood loss, time taken for application, and time required to achieve haemostasis within each trial arm. The secondary outcomes were the need for a second instrument or surgical intervention to control bleeding, and requirement for blood transfusion. Effectiveness outcomes were analysed as intention-to-treat, whilst safety outcomes were analysed as as-treated.

Results: Sixteen participants were randomized to each intervention group (n = 48). TVUAC and SC demonstrated comparable outcomes, while CT lagged in all examined parameters. Following device application, blood loss was similar in both the TVUAC (235 ± 187 ml) and SC (246.5 ± 189 ml) groups. However, following the use of CT, there was blood loss of 431 ± 427 ml, although this difference was not significant (p = 0.113). When considering total blood loss, the TVUAC group (903 ± 234 ml) showed slightly higher values than the SC group (887 ± 184 ml). However, the CT group exhibited notably higher total blood loss (1068 ± 455 ml) than the TVUAC and SC groups. In terms of application time, both TVUAC (1.8 ± 1.1 min) and SC (1.6 ± 0.9 min) significantly outperformed CT (3 ± 1.3 min) (p = 0.002). Furthermore, the time interval from the diagnosis of PPH to achieving haemostasis (defined as the time taken for active haemostasis) was significantly shorter in the TVUAC group (6 ± 4 min) and the SC group (5.7 ± 1.6 min) compared with the CT group (9.7 ± 3.8 min) (p = 0.002).

Conclusions: TVUAC and SC are more effective for the management of PPH than CT. However, both TVUAC and SC have advantages and disadvantages. While these results suggest a potential preference for TVUAC and SC over CT for the management of PPH, further research is necessary to validate these findings.

Heat-Stable Carbetocin in the Management of Postpartum Haemorrhage in Low- and Middle-Income Countries: A Comprehensive Review of Clinical Evidence, Cost-Effectiveness, Implementation Challenges and Adoption Strategies

[Qorinah Estiningtyas Sakilah Adnani^{#1}](#), [Victor Abiola Adepoju^{#2,3}](#), [Safayet Jamil^{4,5}](#)

Abstract

Introduction: Postpartum haemorrhage (PPH) remains a leading global cause of maternal deaths, with over 70,000 annual deaths. Low- and middle-income countries disproportionately bear this burden, often due to compromised cold chains for oxytocin and insufficient staff training.

Methods: This review synthesized thirty publications on heat stable carbetocin (HSC) published from January 2018-March 2025. Eligible studies include randomized trials, systematic and narrative reviews, cost or economic evaluations, and implementation studies. Study findings were categorized into clinical efficacy and safety of HSC, cost-effectiveness, and adoption barriers and facilitators from field implementation, and sustainability strategies.

Results: Several large-scale trials, especially the CHAMPION trial, demonstrated that HSC is clinically non-inferior to oxytocin. In a pilot study from Nigeria (n = 18,364 deliveries), 56% of women received HSC for PPH prevention and PPH incidence dropped to 0.8%. Cost models from India estimated that HSC could prevent about 5,500 additional PPH cases and save five maternal lives per 100,000 births when priced comparably to oxytocin. Programs in Kenya and conflict-affected South Sudan achieved >90% coverage of HSC by implementing WHO policy updates, pooled procurement, simulation drills for frontline health workers, and appointing "PPH champions". Awareness of uterotonic and PPH danger signs among postpartum women increased from 48% to 81% after community-based intervention in Kenya. The thermostability of HSC (up to three years without refrigeration at a temperature of $\leq 30^{\circ}\text{C}$) addresses gaps in cold chain associated with oxytocin and reduces wastage from degradation. Integrating HSC with tranexamic acid and other postpartum haemorrhage bundle elements further improved maternal outcomes.

Conclusion: Heat-stable carbetocin offers a viable, cost-effective uterotonic strategy in LMIC settings. Consistent training, supportive supervision, regulatory oversight, and domestic funding, including private sector investment, are critical to achieving widespread adoption of HSC in LMIC. Expanding HSC across resource-limited settings could substantially reduce PPH-related deaths and accelerate maternal survival goals.

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A Perioperative Quality Improvement Program for Cesarean Delivery in Ethiopia: A Stepped-Wedge Cluster Randomized Clinical Trial

[Tihitena Negussie Mammo^{1,2}](#), [Mekdes Daba Feyssa^{3,4,5}](#), [Maia R Nofal^{2,6,7}](#), [Natnael Gebeyehu²](#), [Matiyas Asrat Shiferaw^{2,3}](#), [Assefa Tesfaye²](#), [Tefaneh Fikre⁴](#), [Habtamu Woldeamanuel²](#), [Senait Bitew Alemu²](#), [Kate Miller⁸](#), [Sara Taye Haile²](#), [Thomas G Weiser^{2,6}](#); [Checklist Expansion for Antisepsis and Infection Control in Cesarean Section \(CLEAN-CS\) Trial Group](#)

Abstract

Importance: Infections and complications following cesarean delivery are a significant source of maternal mortality in Ethiopia.

Objective: To study the effectiveness of a program to strengthen compliance with perioperative standards and reduce postoperative complications following cesarean delivery.

Design, setting, and participants: This stepped-wedge cluster randomized clinical trial included patients undergoing cesarean delivery from August 24, 2021, to January 31, 2023, at 9 hospitals organized into 5 clusters in Ethiopia.

Intervention: Clean Cut, a multimodal surgical quality improvement program that includes process-mapping 6 perioperative standards and creating site-specific, systems-level improvements. The control period was the period before implementation of the intervention.

Main outcomes and measures: The primary end point was surgical site infection rate, and secondary end points were maternal mortality and perinatal mortality and a composite outcome of infections and both mortality outcomes. All were assessed at 30 days postoperatively in the intervention and control groups, adjusting for clustering and demographics. Compliance with standards and the relationship between compliance and outcomes were also compared between the 2 arms.

Results: Among 9755 women undergoing cesarean delivery, 5099 deliveries (52.3%) occurred during the control period (2722 emergency cases [53.4%]) and 4656 (47.7%) during the intervention period (2346 emergency cases [50.4%]). Mean (SD) patient age was 27.04 (0.05) years. Thirty-day follow-up was completed for 5153 patients (52.8%). No significant reduction in infection rates was detected after the intervention (OR, 0.84; 95% CI, 0.55-1.27; $P = .40$). Intraoperative infection prevention standards improved significantly in the intervention arm vs control arm for compliance with at least 5 of the 6 standards (odds ratio [OR], 2.95; 95% CI, 2.40-3.62; $P < .001$). Regardless of trial arm, high compliance was associated with reduced odds of maternal (OR, 0.32; 95% CI, 0.11-0.93; $P = .04$) and perinatal (OR, 0.64; 95% CI, 0.47-0.89; $P = .008$) mortality.

Conclusions and relevance: In this stepped-wedge cluster randomized clinical trial of patients undergoing cesarean delivery, no significant reductions in surgical site infections were observed. However, compliance with perioperative standards improved following the intervention.

Maternal nutrition and micronutrient supplementation

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[Context-Tailored Food-Based Nutrition Education and Counseling for Pregnant Women to Improve Birth Outcomes: A Cluster-Randomized Controlled Trial in Rural Malawi](#)

[Penjani Rhoda Kamudoni¹](#), [Lillian Kaunda²](#), [Marion Tharrey^{3,4}](#), [Maggie Mphande⁵](#), [Shyreen Chithambo⁶](#), [Elaine Ferguson⁷](#), [Zumin Shi⁸](#), [Ibrahimu Mdala⁹](#), [Kenneth Maleta¹⁰](#), [Alistair Munthali¹¹](#), [Gerd Holmboe-Ottesen¹](#), [Per Ole Iversen^{2,12,13}](#)

Abstract

Background: Inadequate maternal dietary intakes remain a public health challenge in low-income countries like Malawi and can cause adverse birth outcomes.

Objectives: To improve maternal dietary intakes and thus reduce the prevalence of adverse birth outcomes in rural Malawi.

Methods: We performed a 2-armed (1:1) cluster-randomized controlled trial in Southern Malawi, enrolling pregnant women at gestational age 12-18 wk. Twenty villages (clusters) were randomly assigned to an intervention or a control group. A nutrition education and counseling (NEC) intervention consisted of education sessions followed by cooking demonstrations and counseling sessions. The women were encouraged to use locally available nutrient-dense foods to enhance dietary adequacy and -diversity. We applied linear programming to identify food combinations that could increase micronutrient intakes. The control group received standard antenatal health education.

Results: Among the 311 women recruited, 187 (60%) completed the trial. We found no significant difference in mean birth weights recorded within 1 or 24 h of birth between the intervention and control groups. Intervention infants had greater birth length ($P = 0.043$) and abdominal circumference ($P = 0.007$) compared to controls, whereas other birth outcomes did not differ significantly. Notably, a quantile analysis revealed that the NEC intervention favored birth weight among mothers with a height below the mean height of the participant sample (156 cm) (P -interaction = 0.043).

Conclusions: Tailoring NEC in food-insecure communities did not result in a significant difference in birth weight among infants of the participating mothers, but mean birth length and abdominal circumference were greater in the intervention group compared to controls. We noted that the NEC intervention favored birth weight among mothers with a lower height than the mean sample height. Our results warrant further investigation into offering tailored NEC early in pregnancy and on a larger scale

Lancet Glob Health. 2025 Feb;13(2):e298-e308.

doi: 10.1016/S2214-109X(24)00449-2.

The effects of prenatal multiple micronutrient supplementation and small-quantity lipid-based nutrient supplementation on small vulnerable newborn types in low-income and middle-income countries: a meta-analysis of individual participant data

Dongqing Wang¹, Enju Liu², Nandita Perumal³, Uttara Partap⁴, Ilana R Cliffer⁴, Janaína Calu Costa⁴, Molin Wang⁵, Wafaie W Fawzi⁶; Gestational Weight Gain Pooling Project Consortium

Abstract

Background: Small vulnerable newborn types, defined by combinations of being born too soon or too small, have distinct determinants and health consequences. We aimed to assess the effects of prenatal multiple micronutrient supplementation (MMS) and small-quantity lipid-based nutrient supplementation (SQ-LNS) on small vulnerable newborn types, which are currently unknown.

Methods: In this meta-analysis, individual participant data from randomised controlled trials of MMS and randomised controlled trials of SQ-LNS in low-income and middle-income countries were used. We systematically searched the literature using PubMed, Embase, and Web of Science to identify randomised controlled trials of prenatal nutritional supplementation using MMS or SQ-LNS among pregnant people published between Jan 1, 2000, and Dec 31, 2021. Studies were excluded if they were conducted exclusively among participants selected by pre-existing health conditions, such as anaemia status, HIV infection, or diabetes. We contacted the corresponding authors of all identified studies to

seek data contribution. As individual participant data became available, we mapped relevant variables and harmonised the data across studies. Iron and folic acid supplementation was the control group in most studies. Newborns were classified into ten groups through the combinations of preterm or term birth, small, appropriate, and large for gestational age, and low birthweight (LBW) or non-LBW. Newborns were also analysed using a four-group categorisation of preterm or term and LBW or non-LBW. Log-binomial models were used to estimate study-specific risk ratios (RRs), which were pooled using meta-analyses.

Findings: 14 randomised controlled trials of MMS (n=42 618; the mean maternal age at study enrolment was 24.3 years [SD 5.6]; 22 086 [51.8%] male neonates and 20 532 [48.2%] female neonates) and four randomised controlled trials of SQ-LNS (n=6246; the mean maternal age at study enrolment was 23.3 years [SD 5.3]; 3137 [50.2%] male neonates and 3109 [49.8%] female neonates) were used. In the ten-group categorisation of small vulnerable newborns, prenatal MMS reduced the risk of preterm-small for gestational age (SGA)-LBW (RR 0.73, 95% CI 0.64-0.84; p=0.0003); preterm-appropriate for gestational age (AGA)-LBW (0.82, 0.74-0.91; p=0.0010); preterm-AGA-non-LBW (0.89, 0.80-0.98; p=0.019); term-SGA-LBW (0.91, 0.85-0.96; p=0.0046); and term-SGA-non-LBW (0.95, 0.90-1.00; p=0.050). In the four-group categorisation, prenatal MMS reduced the risk of preterm-SGA (0.71, 0.62-0.82; p=0.0002) and term-SGA (0.93, 0.89-0.98; p=0.0066). Prenatal SQ-LNS had no significant effects on the risk of giving birth to small vulnerable newborns except for preterm-large for gestational age-non-LBW in the ten-group categorisation (0.78, 0.65-0.94; p=0.023).

Interpretation: Prenatal MMS and SQ-LNS reduce the risk of giving birth to small vulnerable newborns to varying extents, with the greatest magnitude of effects observed for small vulnerable newborn types that confer the greatest neonatal mortality risk. This study underscores the importance of nutritional supplements in prenatal care.

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[**Efficacy of a Personalized mHealth App in Improving Micronutrient Supplement Use Among Pregnant Women in Karachi, Pakistan: Parallel-Group Randomized Controlled Trial**](#)

[Khadija Vadsaria¹](#), [Rozina Nuruddin²](#), [Nuruddin Mohammed³](#), [Iqbal Azam²](#), [Saleem Sayani⁴](#)

Abstract

Background: Micronutrient deficiencies in folate, ferritin, calcium, and vitamin D are common during pregnancy in low- and middle-income countries, often due to inadequate diets. Micronutrient supplementation can address this need, whereas innovative awareness strategies in antenatal practices could enhance supplement use compliance.

Objective: We evaluated the efficacy of a personalized mobile health (mHealth) intervention, hypothesizing a 30% improvement in supplement use in the intervention group compared to a conventional face-to-face counseling group.

Methods: In an unblinded randomized controlled trial, we enrolled 306 first-trimester pregnant women from Aga Khan University Hospital between January 2020 and September 2021 who owned smartphones with internet connection. Women on regular medications or with dietary restrictions or critical illnesses were excluded. The intervention group received personalized micronutrient supplement use coaching through an mHealth app (PurUmeed Aaghaz) as thrice-a-week push messages and tailored recommendations over a 24-week period. The comparison group received standard face-to-face counseling at 6, 12, 18, and 24

weeks after enrollment. Baseline sociodemographic, obstetrics, anthropometric, dietary, and lifestyle data were collected through face-to-face interviews. At each follow-up, participants reported their weekly use of folic acid, iron, calcium, and vitamin D supplements, scored as 0 (daily), 1.5 (4-6 times weekly), and 3 (≤ 3 times weekly). Scores were summed to calculate the cumulative supplement use score (CSUS; 0-12), with higher scores indicating greater inadequacy. Every fourth woman was invited for biochemical micronutrient assessment. Data were analyzed using Stata (version 14), with random-effects linear and logistic panel regression to compare CSUS and supplement use between the 2 groups from baseline to endline.

Results: Of 153 participants per group, 107 (69.9%) in the intervention and 125 (81.7%) in the nonintervention group completed the study. After 24 weeks, the intervention group showed a greater but insignificant reduction in mean CSUS compared to the nonintervention group ($\beta = -.27$, 95% CI -0.65 to 0.12; $P = .17$). Daily supplement use improved by 20% versus 22.4% for folic acid, 11.2 times versus 2.1 times for iron, 1.2 times versus 14.2 times for calcium, and 3 times versus 1.3 times for vitamin D in the intervention versus nonintervention group, respectively. Multivariable analysis showed higher, though insignificant, odds of sufficient folic acid (adjusted odds ratio [aOR] 1.26, 95% CI 0.68-2.36; $P = .46$) and iron (aOR 1.31, 95% CI 0.95-1.81; $P = .10$) use in the intervention group, whereas vitamin D use was significantly higher (aOR 1.88, 95% CI 1.43-2.47; $P < .001$). Calcium intake improved in the nonintervention group (aOR 0.59, 95% CI 0.44-0.79; $P < .001$). Anemia decreased in the intervention group, whereas ferritin, calcium, and vitamin D deficiencies persisted or worsened, particularly in the nonintervention group.

Conclusions: An appropriately implemented mHealth intervention can improve antenatal vitamin D supplementation. Affordable, accessible, and personalized counseling through mHealth could ameliorate micronutrient status during pregnancy.

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doi: 10.1016/j.ajcnut.2024.08.008. Epub 2024 Aug 16.

Effects of prenatal small-quantity lipid-based nutrient supplements on pregnancy, birth, and infant outcomes: a systematic review and meta-analysis of individual participant data from randomized controlled trials in low- and middle-income countries

Kathryn G Dewey¹, K Ryan Wessells², Charles D Arnold², Seth Adu-Afarwuah³, Benjamin F Arnold⁴, Per Ashorn⁵, Ulla Ashorn⁶, Ana Garcés⁷, Lieven Huybregts⁸, Nancy F Krebs⁹, Anna Lartey³, Jef L Leroy⁸, Kenneth Maleta¹⁰, Susana L Matias¹¹, Sophie E Moore¹², Malay K Mridha¹³, Harriet Okronipa¹⁴, Christine P Stewart²

Abstract

Background: Undernutrition during pregnancy increases the risk of giving birth to a small vulnerable newborn. Small-quantity lipid-based nutrient supplements (SQ-LNSs) contain both macro- and micronutrients and can help prevent multiple nutritional deficiencies.

Objectives: We examined the effects of SQ-LNSs provided during pregnancy compared with 1) iron and folic acid or standard of care (IFA/SOC) or 2) multiple micronutrient supplements (MMSs) and identified characteristics that modified the estimates of effects of SQ-LNSs on birth outcomes.

Methods: We conducted a 2-stage meta-analysis of individual participant data from 4 randomized controlled trials of SQ-LNSs provided during pregnancy (n = 5273). We generated study-specific and subgroup estimates of SQ-LNS compared with IFA/SOC or MMS and pooled the estimates. In sensitivity analyses, we examined whether the results differed depending on methods for gestational age dating, birth anthropometry, or study design.

Results: SQ-LNSs (compared with IFA/SOC) increased birth weight [mean difference: +49 g; 95% confidence interval (CI): 26, 71 g] and all birth anthropometric z-scores (+0.10-0.13 standard deviation); they reduced risk of low birth weight by 11%, newborn stunting by 17%, newborn wasting by 11%, and small head size by 15%. Only 2 trials compared SQ-LNSs and MMSs; P values for birth outcomes were >0.10 except for head circumference (e.g., z-score for gestational age: +0.11; 95% CI: -0.01, 0.23). Effect estimates for SQ-LNSs compared with IFA/SOC were greater among female infants and, for certain outcomes, among mothers with body mass index <20 kg/m², inflammation, malaria, or household food insecurity. Effect estimates for SQ-LNSs compared with MMSs were greater for certain outcomes among female infants, first-born infants, and mothers <25 y.

Conclusions: SQ-LNSs had positive impacts on multiple outcomes compared to IFA/SOC, but further research directly comparing SQ-LNSs and MMSs is needed. Targeting SQ-LNSs to vulnerable subgroups may be worth considering.

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Effects of Vitamin D-3 Supplementation During Pregnancy and Lactation on Maternal and Infant Biomarkers of Environmental Enteric Dysfunction, Systemic Inflammation, and Growth: A Secondary Analysis of a Randomized Controlled Trial

[Jacqueline M Lauer¹](#), [Miles A Kirby²](#), [Alfa Muhihi³](#), [Nzovu Ulenga⁴](#), [Said Aboud⁵](#), [Enju Liu⁶](#), [Robert Km Choy⁷](#), [Michael B Arndt⁸](#), [Jianqun Kou⁹](#), [Wafaie W Fawzi²](#), [Andrew T Gewirtz⁹](#), [Christopher R Sudfeld¹⁰](#), [Karim P Manji¹¹](#), [Christopher P Duggan¹²](#)

Abstract

Background: Environmental enteric dysfunction (EED) is an acquired, subclinical state of intestinal inflammation common in children and adults in low-income and middle-income countries. Although vitamin D-3 supplementation has purported anti-inflammatory properties, its ability to ameliorate biomarkers of EED remains unclear.

Objectives: This study aimed to examine the effects of maternal vitamin D-3 supplementation during pregnancy and lactation on biomarkers of EED, systemic inflammation, and growth in women living with HIV and their infants in Dar es Salaam, Tanzania.

Methods: We conducted subgroup analyses among randomly selected mothers (n = 720) and infants (n = 365 at 6 wk of age, and n = 266 at 6 mo of age) who participated in a randomized, triple-blind, placebo-controlled trial of daily maternal 3000 IU vitamin D-3 supplementation from the second trimester of pregnancy until 1 y postpartum. Biomarkers of EED (soluble CD14 and intestinal fatty acid-binding protein), systemic inflammation (C-reactive protein and α 1-acid glycoprotein), and growth factors (insulin-like growth factor 1 and fibroblast growth factor 21) were measured via the Micronutrient and Environmental Enteric Dysfunction Assessment Tool. Anti-flagellin and anti-lipopolysaccharide immunoglobulins were measured via enzyme-linked immunosorbent assay. Comparisons by randomized

treatment arm were performed using ordinary least squares regression models with log₂-transformed biomarkers.

Results: At 32 wk of gestation, intestinal fatty acid-binding protein (β : -0.19; $P = 0.03$) and α 1-acid glycoprotein (β : -0.11; $P = 0.04$) were significantly lower in mothers in the vitamin D-3 group than those in mothers in the placebo group. At 6 wk of age, insulin-like growth factor 1 (β : -0.31; $P = 0.03$) was significantly lower in infants whose mothers were in the vitamin D-3 group than that in infants whose mothers were in the placebo group.

Conclusions: Vitamin D-3 supplementation during pregnancy and lactation reduced selected EED and systemic inflammation biomarkers among women living with HIV. While the effects of maternal vitamin D-3 supplementation do not appear to extend to infants, there may be an effect on growth factors.

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Effect of maternal postnatal balanced energy protein supplementation and infant azithromycin on infant growth outcomes: an open-label randomized controlled trial

Ameer Muhammad¹, Yasir Shafiq², Muhammad Imran Nisar³, Benazir Baloch³, Aneela Pasha³, Nida Salman Yazdani¹, Arjumand Rizvi⁴, Sajid Muhammad⁴, Fyezah Jehan⁵

Abstract

Background: Maternal undernutrition is a direct risk factor for infant growth faltering.

Objectives: We evaluated the effect of postnatal balanced energy protein (BEP) supplementation in lactating women and azithromycin (AZ) in infants on infant growth outcomes.

Methods: A randomized controlled superiority trial of lactating mother-newborn dyads was conducted in Karachi, Pakistan. Mothers intending to breastfeed their newborns with mid-upper arm circumference of <23 cm and live infants between 0 and 6 d of life were randomly assigned to 1 of 3 arms in a 1:1:1 ratio. Lactating mothers in the control arm received standard-of-care counseling on exclusive breastfeeding, nutrition, infant immunization, and health promotion plus iron-folate supplementation until the infant was 6 mo old. In intervention arm 1, mothers additionally received two 75-g sachets of BEP per day. In intervention arm 2, along with the standard-of-care and BEP to the mother, the infant also received 1 dose of azithromycin (20 mg/kg) at the age of 42 d. The primary outcome was infant length velocity at 6 mo. The total sample size was 957 (319 in each arm).

Results: From 1 August, 2018 to 19 May, 2020, 319 lactating mother-newborn dyads were randomly assigned in each arm, and the last follow-up was completed on 20 November, 2020. The mean difference in length velocity (cm/mo) between BEP alone and control was 0.01 (95% confidence interval [CI]: -0.03, 0.06), BEP plus AZ and control was 0.08 (95% CI: 0.03, 0.13), and between BEP + AZ and BEP alone was 0.06 (95% CI: 0.01, 0.11). There were 1.46% (14/957) infant deaths in the trial, and 17.9% (171/957) nonfatal events (injectable treatment and/or hospitalizations) were recorded.

Conclusions: Postnatal maternal BEP supplementation and infant AZ administration could modestly improve infant growth outcomes at 6 mo, suggesting potential benefits in simultaneously addressing maternal and infant undernutrition. This trial was registered at clinicaltrials.gov as [NCT03564652](https://clinicaltrials.gov/ct2/show/study/NCT03564652).

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Management of undernutrition during preconception and pregnancy in an urban setting in North India

[Neeta Dhabhai¹](#), [Ranadip Chowdhury¹](#), [Sunita Taneja¹](#), [Medha Shekhar¹](#), [Jasmine Kaur¹](#), [Pratima Mittal²](#), [Rupali Dewan²](#), [Nita Bhandari¹](#)

Abstract

Introduction: The prevalence of underweight in women of reproductive age (WRA) in South Asia remains unacceptably high. Underweight women suffer from lowered immunity, infertility, and a risk of developing non-communicable diseases. In pregnancy, undernutrition results in poor neonatal and maternal outcomes. We present the findings and the management strategy of undernutrition in the preconception and pregnancy phase intervention group in the WING study in low- to lower-middle-income neighborhoods of North India.

Methods: We analyzed data from the Women and Infants Integrated Interventions for Growth Study (WINGS) intervention group. In this individually randomized factorial design trial, 13,500 women were enrolled from low to middle-income neighborhoods of Delhi: 6,722 women in the preconception group and 2,640 from the pregnancy group. Food supplements in the form of locally prepared snacks were given to provide necessary calories and protein requirements as per the Body mass index (BMI) during the preconception period and each trimester of pregnancy. The snacks (sweet or savory) and milk or egg as a source of high-quality protein were delivered at home, and intakes were observed. Individual tracking and close monthly monitoring were done for compliance, besides screening and treatment of infections.

Results: The enrolled women's mean (SD) age was 24.2 (3.1) years. Approximately 35% of women had a height of < 150 cm, and 50% had schooling >12 years. 17% of women in preconception and 14 % in pregnancy intervention groups were Underweight. Approximately two-thirds of underweight women improved 9-12 months after management in the preconception group, and the same proportion improved 4 weeks after management during pregnancy. The proportion of women with inadequate weight gain (IWG) during pregnancy was higher in women who were underweight during preconception.

Discussion: A comprehensive approach to managing undernutrition with high-quality energy-dense food supplementation substantially improved weight gain in women during preconception and pregnancy.

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Effect of nutrition education integrating the health belief model and theory of planned behavior during pregnancy on gestational weight gain and birth weight in Southeast Ethiopia using complex analyses

[Girma Beressa^{1,2}](#), [Susan J Whiting³](#), [Tefera Belachew⁴](#)

Abstract

Background: The incidence of inadequate or excessive gestational weight gain (GWG) is an indicator of reproductive health problems. However, scientific evidence for the effect of

nutrition education during pregnancy on GWG and neonatal birth weight (BW) in urban settings in Ethiopia is sparse. This study aimed to assess the effect of nutrition education during pregnancy on GWG and neonatal birth weight (BW) in urban settings in Southeast Ethiopia.

Methods: A community-based two-arm parallel cluster randomized controlled trial was conducted among 447 randomly selected pregnant women attending antenatal care (224 intervention and 223 control) from February to December 2021. Study participants were selected by multistage cluster sampling followed by systematic sampling. Women receiving the intervention received six nutrition education sessions, while women in the control group received standard care. GWG was the difference between the last recorded weight before delivery and the weight recorded during the first trimester. BW was measured within the first hour of delivery. The generalized structural equations model (GSEM) and structural equations model (SEM) were used to examine the direct, indirect, and total effects of nutrition education on GWG and BW via the dietary diversity score (DDS), food security (FS), and knowledge.

Results: The GSEM revealed that receiving intervention during pregnancy had a total effect on GWG [(AOR = 2.056, 95% CI: 1.705, 2.695)]. Having dietary diversity had direct and total effects on GWG [(AOR = 1.105, 95% CI: 1.022, 1.196)]. Having food security had a total effect on GWG [(AOR = 1.928, 95% CI: 1.817, 2.052)]. Having fruit and vegetable knowledge had a total effect on GWG [(AOR = 1.971, 95% CI: 1.856, 2.105)]. The SEM revealed that receiving intervention during pregnancy had a direct effect on BW (unstandardized β = 0.144, 95% CI: 0.034, 0.252). Similarly, it revealed that receiving intervention during pregnancy had a direct effect on DDS (β = 0.580, 95% CI: 0.024, 1.038). Likewise, it indicated that receiving intervention during pregnancy had a total effect on increasing BW (β = 0.137, 95% CI: 0.029, 0.243). Nevertheless, there was no statistically observed indirect effect of nutrition education during pregnancy on GWG and BW via mediators.

Conclusion: The SEM revealed that receiving nutrition education interventions during pregnancy had a total effect on GWG and direct and total effects on BW. The generalized structural equation modelling (GSEM) and structural equation modelling (SEM) findings show that integrating theory-based nutrition education during pregnancy will improve gestational weight gain (GWG) and birth weight (BW) in Ethiopia.

Maternal anaemia and iron

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[Daily oral iron supplementation during pregnancy](#)

[Julia L Finkelstein¹](#), [Anna Cuthbert²](#), [Jo Weeks²](#), [Sudha Venkatramanan¹](#), [Doreen Y Larvie¹](#), [Luz Maria De-Regil³](#), [Maria Nieves Garcia-Casal⁴](#)

Abstract

Background: Iron and folic acid supplementation have been recommended in pregnancy for anaemia prevention, and may improve other maternal, pregnancy, and infant outcomes.

Objectives: To examine the effects of daily oral iron supplementation during pregnancy, either alone or in combination with folic acid or with other vitamins and minerals, as an intervention in antenatal care.

Search methods: We searched the Cochrane Pregnancy and Childbirth Trials Registry on 18 January 2024 (including CENTRAL, MEDLINE, Embase, CINAHL, ClinicalTrials.gov, WHO's International Clinical Trials Registry Platform, conference proceedings), and searched reference lists of retrieved studies.

Selection criteria: Randomised or quasi-randomised trials that evaluated the effects of oral supplementation with daily iron, iron + folic acid, or iron + other vitamins and minerals during pregnancy were included.

Data collection and analysis: Review authors independently assessed trial eligibility, ascertained trustworthiness based on pre-defined criteria, assessed risk of bias, extracted data, and conducted checks for accuracy. We used the GRADE approach to assess the certainty of the evidence for primary outcomes. We anticipated high heterogeneity amongst trials; we pooled trial results using a random-effects model (average treatment effect).

Main results: We included 57 trials involving 48,971 women. A total of 40 trials compared the effects of daily oral supplements with iron to placebo or no iron; eight trials evaluated the effects of iron + folic acid compared to placebo or no iron + folic acid. Iron supplementation compared to placebo or no iron Maternal outcomes: Iron supplementation during pregnancy may reduce maternal anaemia (4.0% versus 7.4%; risk ratio (RR) 0.30, 95% confidence interval (CI) 0.20 to 0.47; 14 trials, 13,543 women; low-certainty evidence) and iron deficiency at term (44.0% versus 66.0%; RR 0.51, 95% CI 0.38 to 0.68; 8 trials, 2873 women; low-certainty evidence), and probably reduces maternal iron-deficiency anaemia at term (5.0% versus 18.4%; RR 0.41, 95% CI 0.26 to 0.63; 7 trials, 2704 women; moderate-certainty evidence), compared to placebo or no iron supplementation. There is probably little to no difference in maternal death (2 versus 4 events, RR 0.57, 95% CI 0.12 to 2.69; 3 trials, 14,060 women; moderate-certainty evidence). The evidence is very uncertain for adverse effects (21.6% versus 18.0%; RR 1.29, 95% CI 0.83 to 2.02; 12 trials, 2423 women; very low-certainty evidence) and severe anaemia (Hb < 70 g/L) in the second/third trimester (< 1% versus 3.6%; RR 0.22, 95% CI 0.01 to 3.20; 8 trials, 1398 women; very low-certainty evidence). No trials reported clinical malaria or infection during pregnancy. Infant outcomes: Women taking iron supplements are probably less likely to have infants with low birthweight (5.2% versus 6.1%; RR 0.84, 95% CI 0.72 to 0.99; 12 trials, 18,290 infants; moderate-certainty evidence), compared to placebo or no iron supplementation. However, the evidence is very uncertain for infant birthweight (MD 24.9 g, 95% CI -125.81 to 175.60; 16 trials, 18,554 infants; very low-certainty evidence). There is probably little to no difference in preterm birth (7.6% versus 8.2%; RR 0.93, 95% CI 0.84 to 1.02; 11 trials, 18,827 infants; moderate-certainty evidence) and there may be little to no difference in neonatal death (1.4% versus 1.5%, RR 0.98, 95% CI 0.77 to 1.24; 4 trials, 17,243 infants; low-certainty evidence) or congenital anomalies, including neural tube defects (41 versus 48 events; RR 0.88, 95% CI 0.58 to 1.33; 4 trials, 14,377 infants; low-certainty evidence). Iron + folic supplementation compared to placebo or no iron + folic acid Maternal outcomes: Daily oral supplementation with iron + folic acid probably reduces maternal anaemia at term (12.1% versus 25.5%; RR 0.44, 95% CI 0.30 to 0.64; 4 trials, 1962 women; moderate-certainty evidence), and may reduce maternal iron deficiency at term (3.6% versus 15%; RR 0.24, 95% CI 0.06 to 0.99; 1 trial, 131 women; low-certainty evidence), compared to placebo or no iron + folic acid. The evidence is very uncertain about the effects of iron + folic acid on maternal iron-deficiency anaemia (10.8% versus 25%; RR 0.43, 95% CI

0.17 to 1.09; 1 trial, 131 women; very low-certainty evidence), or maternal deaths (no events; 1 trial; very low-certainty evidence). The evidence is uncertain for adverse effects (21.0% versus 0.0%; RR 44.32, 95% CI 2.77 to 709.09; 1 trial, 456 women; low-certainty evidence), and the evidence is very uncertain for severe anaemia in the second or third trimester (< 1% versus 5.6%; RR 0.12, 95% CI 0.02 to 0.63; 4 trials, 506 women; very low-certainty evidence), compared to placebo or no iron + folic acid. Infant outcomes: There may be little to no difference in infant low birthweight (33.4% versus 40.2%; RR 1.07, 95% CI 0.31 to 3.74; 2 trials, 1311 infants; low-certainty evidence), comparing iron + folic acid supplementation to placebo or no iron + folic acid. Infants born to women who received iron + folic acid during pregnancy probably had higher birthweight (MD 57.73 g, 95% CI 7.66 to 107.79; 2 trials, 1365 infants; moderate-certainty evidence), compared to placebo or no iron + folic acid. There may be little to no difference in other infant outcomes, including preterm birth (19.4% versus 19.2%; RR 1.55, 95% CI 0.40 to 6.00; 3 trials, 1497 infants; low-certainty evidence), neonatal death (3.4% versus 4.2%; RR 0.81, 95% CI 0.51 to 1.30; 1 trial, 1793 infants; low-certainty evidence), or congenital anomalies (1.7% versus 2.4; RR 0.70, 95% CI 0.35 to 1.40; 1 trial, 1652 infants; low-certainty evidence), comparing iron + folic acid supplementation to placebo or no iron + folic acid. A total of 19 trials were conducted in malaria-endemic countries, or in settings with some malaria risk. No studies reported maternal clinical malaria; one study reported data on placental malaria.

Authors' conclusions: Daily oral iron supplementation during pregnancy may reduce maternal anaemia and iron deficiency at term. For other maternal and infant outcomes, there was little to no difference between groups or the evidence was uncertain. Future research is needed to examine the effects of iron supplementation on other maternal and infant health outcomes, including infant iron status, growth, and development.

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[Using an experience-based co-design approach to develop strategies for implementing an intravenous iron intervention to treat moderate and severe anemia in pregnancy in Malawi](#)

[Elisabeth Mamani-Mategula](#)¹, [Naomi Von-Dinklage](#)², [Hana Sabanovic](#)³, [Ebony Verbunt](#)³, [Khic-Houy Prang](#)³, [Effie Chipeta](#)⁴, [Lucinda Manda-Taylor](#)⁴

Abstract

Background: In low- and middle-income countries, women experiencing anemia during pregnancy are recommended to take 30 mg to 60 mg of oral iron daily throughout pregnancy. However, oral iron tablets are often poorly tolerated and slow in correcting anemia, resulting in low adherence, prolonged anemia, and increased risk of adverse maternal and fetal outcomes. An alternative to oral iron is intravenous (IV) iron, commonly used in high-income countries to restore the body's iron stores rapidly. A randomized controlled trial was conducted to investigate the effectiveness and safety of IV iron compared to standard-of-care oral iron supplementation for pregnant women with moderate and severe anemia in the third trimester in Malawi (REVAMP-TT). Using an experience-based co-design approach, our study aimed to identify barriers and facilitators to IV iron use to treat anemia in pregnancy in the primary healthcare system of Malawi, and develop mitigating strategies for the successful implementation of REVAMP-TT.

Methodology: The co-design process involved two phases: i) We conducted an information-gathering exercise to identify barriers and facilitators to IV iron use to treat anemia in pregnancy in the primary healthcare system of Malawi. We interviewed key informants (n = 53) including the policymakers, government partners, healthcare managers, and healthcare providers. We also gathered previous research findings from a formative qualitative study on the perceptions and experiences of IV iron treatment for pregnant women experiencing anemia in Malawi (n = 29). ii) We conducted two co-design workshops with end-users (n = 20) and healthcare providers (n = 20) to confirm and identify the key barriers and facilitators and developed mitigating strategies to inform the successful implementation of the REVAMP-TT trial. We mapped the emerging barriers to the Consolidated Framework for Implementation Research 2.0 (CFIR 2.0) and matched the mitigating strategies to the corresponding Expert Recommendations for Implementing Change (ERIC) compilation.

Results: The following were identified as key barriers to IV iron use to treat anemia in pregnancy in the primary healthcare system of Malawi: the cost of IV iron, the lack of available resources and knowledge, local attitudes including myths and misconceptions about IV iron and keeping pregnancy a secret, local conditions, the lack of political will and buy-in from high-level leaders, the lack of capability of healthcare providers to deliver IV iron, and the lack of male involvement to support pregnant women's access to antenatal care. The proposed strategies to mitigate the barriers for the successful implementation of the REVAMP TT trial included providing financial strategy, developing stakeholder relationships, training and educating stakeholders, supporting clinicians, and engaging end-users.

Conclusion: The use of the experience-based co-design approach in our study provided a valuable method to expose the potential barriers and facilitators to IV iron use and develop mitigating strategies to successfully implement the REVAMP-TT trial. Engaging both the key informants and end users promoted ownership and consensus among stakeholders and ensured a collaborative environment for sharing deeply rooted real-world experiences and insights. Not only do these findings address the needs of this study, but they also, lay a groundwork for the possible integration of IV iron into routine care in Malawi and provide knowledge for policymakers to make informed decisions on the management of anemia in the primary healthcare systems of Malawi.

Lancet Glob Health. 2024 Dec;12(12):e2049-e2058.

doi: 10.1016/S2214-109X(24)00380-2.

Postpartum maternal and infant haematological effects of second-trimester ferric carboxymaltose versus standard-of-care oral iron in Malawi: longitudinal follow-up of a randomised controlled trial

[Glory Mzembe¹](#), [Ernest Moya¹](#), [Martin N Mwangi²](#), [Ricardo Ataide³](#), [Rebecca Harding⁴](#), [Justina Kaunda¹](#), [Truwah Zinenani¹](#), [Gomezgani Mhango¹](#), [William Stones⁵](#), [Owen Mtambo¹](#), [Ayse Y Demir⁶](#), [Hans Verhoef⁷](#), [Sabine Braat³](#), [Sant-Rayn Pasricha⁸](#), [Kamija S Phiri⁹](#)

Abstract

Background: Anaemia is common in mothers and infants in the first year postpartum, especially in sub-Saharan Africa. We evaluated whether treating anaemia in the second trimester of pregnancy with a single dose of intravenous iron, ferric carboxymaltose, compared with standard-of-care oral iron could alleviate anaemia in postpartum women and their infants.

Methods: REVAMP (ACTRN12618001268235), an open-label, individually randomised, controlled trial done across nine urban and five rural health centres in Malawi, recruited women if they were in the second trimester of singleton pregnancy, had a capillary haemoglobin concentration of less than 10.0 g/dL, and had a negative malaria rapid diagnostic test. Once enrolled, women were randomly assigned (1:1) to receive intravenous ferric carboxymaltose (20 mg/kg up to 1000 mg) or standard of care (60 mg oral elemental iron twice daily for 90 days); all women received preventive malaria treatment. The primary endpoint of REVAMP was anaemia prevalence at 36 weeks of gestation, with follow-up of mothers and infants until 1 month postpartum. In REVAMP-EXTENDED, women from REVAMP who gave consent, and their infants, were followed up at 3, 6, 9, and 12 months postpartum, and venous blood was collected for haemoglobin, ferritin, and C-reactive protein measurement. Maternal postpartum outcomes comprised prevalence of anaemia (venous haemoglobin concentration <11 g/dL up to and including delivery and <12.0 g/dL postpartum) and haemoglobin concentration, as well as iron status (iron deficiency, defined as serum ferritin <15 µg/L, or <30 µg/L if C-reactive protein >5 mg/L, and iron deficiency anaemia [both iron deficiency and anaemia]). Infant outcomes comprised cord ferritin concentration, and haemoglobin and ferritin concentrations at 1, 3, 6, 9, and 12 months of age.

Findings: Between Nov 12, 2018, and March 2, 2021, 862 women were randomly assigned in REVAMP, of whom 793 (393 in the ferric carboxymaltose group [376 liveborn infants] and 400 [379 liveborn infants] in the standard-of-care group) provided consent for REVAMP-EXTENDED. At 12 months postpartum, ferritin concentrations were higher (geometric mean ratio 1.47 [95% CI 1.29-1.66], $p<0.0001$), and prevalence of iron deficiency was lower (prevalence ratio 0.65 [0.48-0.88], $p=0.0050$), in mothers receiving ferric carboxymaltose than in those receiving standard of care. Anaemia was less common in women who received ferric carboxymaltose than in those who received standard of care at 1 month (prevalence ratio 0.84 [95% CI 0.71-0.98], $p=0.027$), 3 months (0.75 [0.62-0.91], $p=0.0029$), and 6 months (0.78 [0.63-0.96], $p=0.018$) postpartum but not thereafter. There was no evidence of a difference between groups regarding cord ferritin, infant ferritin, or infant haemoglobin concentrations at any timepoint. Benefits on postpartum anaemia were restricted to mothers with baseline iron deficiency.

Interpretation: Ferric carboxymaltose treatment in the second trimester protected women from postpartum anaemia and iron deficiency but did not affect infant haematological or iron status.

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Efficacy of different doses of daily prophylactic iron supplementation in pregnant women: A systematic review and meta-analysis

Indar Kumar Sharawat¹, Prateek Kumar Panda¹, Surbhi Choudhary², Pranita Pradhan³, Vivek Singh Malik⁴, Meenu Singh⁵

Abstract

Introduction: Several randomized controlled trials (RCT) have been conducted in the past to determine the optimum dose of iron supplementation during pregnancy, but there is a lack

of consensus among different guidelines regarding the appropriate dosage of iron for prophylaxis during pregnancy.

Methods: Relevant electronic databases were searched to identify publications describing RCTs comparing different daily dosages of iron supplementation during pregnancy. Meta-analysis for various efficacy and safety outcomes such as changes in blood hemoglobin, serum ferritin, serum iron, and serum transferrin saturation, as well as the frequency of adverse effects, was performed using random and fixed effect models suitably depending on the degree of heterogeneity. Two groups were compared: those receiving 60 mg elemental iron or less and those receiving more than 60 mg elemental iron per day. Additionally, the efficacy of those receiving 30 mg elemental iron per day and those receiving 60 mg elemental iron per day were also compared.

Results: A total of 15 RCTs comprising 2726 participants were included in the meta-analysis. Change in blood hemoglobin levels was comparable between the ≤ 60 mg/day and >60 mg/day group (pooled estimate for mean difference, 0.01 [-0.11, 0.09], $p = 0.86$, $I^2 = 96\%$), but serum ferritin, iron level, and serum transferrin saturation change were higher in the >60 mg group ($p < 0.0001$, 0.008, and 0.02, respectively). Change in blood hemoglobin level was better in the 60 mg/day group compared to the 30 mg/day group (pooled estimate for mean difference, -0.11 [-0.21, 0.00], $p = 0.04$, $I^2 = 90\%$), as well as changes in serum ferritin and serum transferrin saturations ($p = 0.004$ and 0.0004, respectively).

Conclusion: Daily supplementation of 60 mg elemental iron is more efficacious than daily supplementation of 30 mg elemental iron for the prophylaxis of anemia in pregnant women (certainty of evidence-moderate), and daily supplementation of ≤ 60 mg elemental iron is equally efficacious compared to daily supplementation of >60 mg elemental iron for the prophylaxis of anemia in pregnant women (certainty of evidence-moderate).

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Intravenous versus oral iron for anaemia among pregnant women in Nigeria (IVON): an open-label, randomised controlled trial

[Bosede B Afolabi¹](#), [Ochuwa A Babah²](#), [Titilope A Adeyemo³](#), [Mobolanle Balogun⁴](#), [Aduragbemi Banke-Thomas⁵](#), [Ajibola I Abioye⁶](#), [Opeyemi R Akinajo²](#), [Hadiza S Galadanci⁷](#), [Rachel A Quao⁸](#), [Hameed Adelabu⁸](#), [Nadia A Sam-Agudu⁹](#), [Victoria O Adaramoye¹⁰](#), [Abdulazeez Abubakar⁷](#), [Bolanle Banigbe¹¹](#), [Gbenga Olorunfemi¹²](#), [Lenka Beňová¹³](#), [Elin C Larsson²](#), [Kristi S Annerstedt²](#), [Claudia Hanson²](#), [Jim Thornton¹⁴](#); [IVON Trial Investigators](#)

Abstract

Background: Oral iron for anaemia in pregnancy is often not well tolerated, with poor adherence. Iron administered intravenously might address these tolerance and adherence issues. We investigated the effectiveness and safety of intravenous ferric carboxymaltose versus oral ferrous sulphate on anaemia and iron deficiency among pregnant women in Nigeria.

Methods: We did a multicentre, open-label, parallel, randomised controlled trial of pregnant women (aged 15-49 years) with haemoglobin (Hb) concentrations of less than 10 g/dL at 20-32 weeks' gestation from 11 primary, secondary, or tertiary health facilities in Nigeria (five in Lagos and six in Kano). Exclusion criteria included vaginal bleeding, blood transfusion or

major surgery within the past 3 months, symptomatic anaemia, anaemia known to be unrelated to iron deficiency, clinically confirmed malabsorption syndrome, previous hypersensitivity to any form of iron, pre-existing maternal depression or other major psychiatric illness, immune-related diseases, such as systemic lupus erythematosus or rheumatoid arthritis, or severe allergic reactions. Participants were randomly assigned (1:1) by nurses and doctors using a web-based randomisation service to either receive a single dose of intravenous ferric carboxymaltose (20 mg/kg to a maximum of 1000 mg) or oral ferrous sulphate (200 mg; 65 mg elemental iron) three times daily until 6 weeks postpartum. The study was primarily unmasked. Primary outcomes were maternal anaemia (Hb <11 g/dL) at 36 weeks' gestation and preterm birth at before 37 weeks' gestation, with analysis by intention to treat in participants with available data. This study was registered at the ISRCTN registry on Dec 10, 2020 (ISRCTN63484804) and on ClinicalTrials.gov ([NCT04976179](https://clinicaltrials.gov/ct2/show/study/NCT04976179)) on April 7, 2021.

Findings: Between Aug 10, 2021, and Dec 15, 2022, 13 724 pregnant women were screened for eligibility. 12 668 were excluded due to ineligibility for inclusion, and 1056 provided consent to participate and were randomly assigned to either the intravenous or oral administration groups. 527 were assigned to the intravenous ferric carboxymaltose group and 529 were assigned to the oral ferrous sulphate group. 518 in the intravenous group were assessed at 36 weeks' gestational age and after 518 deliveries, and 511 completed the 6 weeks postpartum visit. 513 in the oral ferrous sulphate group were assessed at 36 weeks' gestational age and after 512 deliveries, and 501 completed the 6 weeks postpartum visit. No significant difference was found in anaemia at 36 weeks (299 [58%] of 517 in the intravenous group vs 305 [61%] of 503 in the oral group; risk ratio 0.95, 95% CI 0.85-1.06; $p=0.36$), nor in preterm birth (73 [14%] of 518 vs 77 [15%] of 513; 0.94, 0.70-1.26; $p=0.66$). There were no significant differences in adverse events. The most common adverse events were diarrhoea (in six participants) and vomiting (in three participants) in the oral group and fatigue (in two participants) and headache (in two participants) in the intravenous group.

Interpretation: Although the effect on overall anaemia did not differ, intravenous iron reduced the prevalence of iron deficiency to a greater extent than oral iron and was considered to be safe. We recommend that intravenous iron be considered for anaemic pregnant women in Nigeria and similar settings.

Post-natal care

Bull World Health Organ. 2025 Apr 1;103(4):255-265.

doi: 10.2471/BLT.24.292145. Epub 2025 Feb 13.

[A mobile messaging service for families on postnatal knowledge and practices: a cluster randomized trial, India](#)

[Jamie Sewan Johnston](#)¹, [Pooja Suri](#)², [Shirley Yan](#)³, [Adithi Chandrasekar](#)⁴, [Saumya Singla](#)¹, [Victoria C Ward](#)⁵, [Seema Murthy](#)⁶

Abstract

Objective: To evaluate the impact of a mobile messaging service that delivers World Health Organization recommendations on postnatal care to families from birth through six weeks postpartum via a messaging platform.

Methods: We randomized tertiary hospitals in four Indian states into two groups. In the treatment group, 15 hospitals promoted the messaging service to families in maternity wards before discharge following a recent birth. Nine control hospitals provided standard in-hospital information. From mid-March 2021 to mid-January 2022, we recruited mothers to participate in the study. Consenting mothers completed a face-to-face baseline survey before hospital discharge after birth and a follow-up phone survey roughly 6 weeks postpartum. Using logistic regression controlling for state-fixed effects and baseline covariates, we examine intent-to-treat estimates and report risk differences.

Findings: A total of 21 937 participants met the inclusion criteria. We observed significant positive impacts in 7 out of 11 neonatal and maternal care practices examined (P -values < 0.05). Breastfeeding increased by 3.1 percentage points, recommended cord care practices by 4.1 percentage points, skin-to-skin care with mothers by 9.2 percentage points, and skin-to-skin care by fathers by 2.2 percentage points. For recommended maternal dietary practices, we observed significant increases in adherence to guidelines advising no reduction of food intake (7.1 percentage points), no reduction of water intake (7.9 percentage points) and no restrictions on food items (10.8 percentage point; P -values < 0.01).

Conclusion: This study demonstrates that concise yet comprehensive digital messaging delivered to families during the postpartum period can effectively encourage recommended postnatal care practices.

BMC Pregnancy Childbirth. 2024 Dec 31;24(1):886.

doi: 10.1186/s12884-024-07109-3.

Effect of postpartum clinical guideline on maternal outcomes in iranian women: a randomized controlled clinical trial

Leila Abdoli Najmi¹, Sakineh Mohammad-Alizadeh-Charandabi¹, Shayesteh Jahanfar², Fatemeh Abbasalizadeh³, Haniyeh Salehi Poormehr⁴, Mojgan Mirghafourvand⁵

Abstract

Background: The postpartum period is a vital time for women, infants, spouses, parents, caregivers and families. Considering the importance of postpartum care and the necessity of using comprehensive and up-to-date clinical guidelines in Iran, this study was designed to implement a indigenized clinical guideline in Iran on maternal outcomes, including maternal functioning, postpartum depression and postpartum specific anxiety (primary outcomes) as well as infant care, maternal health problems, experiencing violence, feeding method and contraception use (secondary outcomes).

Methods: This randomized controlled trial was conducted with 272 postpartum women in Taleghani and Alzahra hospitals in Tabriz in 2023. Participants were randomly allocated to intervention and control groups. The intervention group received care and training based on clinical guideline while the control group received routine care and training. Both groups were followed up by telephone at the second and sixth week after delivery. Questionnaires assessing maternal health problems and postpartum depression were completed in the second and sixth weeks and while assessments of maternal functioning, postpartum depression, postpartum specific anxiety, infant care behavior, and experiences of violence

were conducted in the sixth week after delivery. ANCOVA, independent-t tests, and Mann-Whitney U tests were used for data analysis.

Results: There was no significant difference between the two groups regarding of socio-demographic characteristics ($P < 0.05$). Additionally, there were no significant differences in the mean score of maternal functioning, anxiety, depression, infant care behavior or experiences of violence after the intervention between the intervention and control groups based on ANCOVA or Mann-Whitney U tests ($P < 0.05$). However, the rate of infant formula use was significantly lower in the intervention group (12.9%) compared to the control group (23.4%) ($P = 0.027$). In terms of contraceptive methods used, 24.3% of the intervention group and 22.2% of the control group reported using reliable contraceptive methods ($P = 0.035$). Furthermore, 98.5% of participants in the intervention group expressed satisfaction with the education and recommendations provided, compared to 88.2% in the control group ($P = 0.002$).

Conclusion: Providing clinical guideline-based care was associated with increased breastfeeding rates, greater use of reliable contraception methods, and higher levels of maternal satisfaction. However, it did not have a significant impact on other maternal outcomes.

Nurs Res. 2025 May-Jun;74(3):171-178.

doi: 10.1097/NNR.0000000000000814. Epub 2025 Feb 13.

[Randomized Trial of Group Postpartum Care Model Improves Knowledge and Clinical Outcomes](#)

[Yenupini Joyce Adams](#), [John Stephen Agbenyo](#), [Elizabeth Lau](#), [Jessica Young](#), [David Haas](#)

Abstract

Background: In sub-Saharan Africa, the risk of obstetric complications remains high throughout the postpartum period.

Objective: We developed and tested a novel, integrated model of group postpartum care titled Focused-Postpartum Care (Focused-PPC) to improve outcomes. In this paper, we report clinical outcomes of participants in the intervention arm and differences in knowledge of postbirth warning signs among those in the intervention and control arms.

Methods: Focused-PPC encompassed recommended clinical assessments, targeted education, and peer support up to 1 year after birth. Focused-PPC was implemented as a parallel randomized controlled trial involving 192 postpartum women across four health centers in Tamale, Ghana, from February 2022 to August 2023. Eligible participants 18 years or older with a live birth were randomly assigned to either the Focused-PPC intervention arm or the control arm at a 1:1 allocation and were not blinded to their allocation. At each health center, 48 participants were allocated to either an intervention or control arm. Focused-PPC groups in the intervention arm consisted of eight participants per group. Participants in the intervention arm received the Focused-PPC integrated group model of care. Participants in the control arm received the standard of postnatal care already administered at each health center.

Results: Baseline analysis included 96 participants from the control arm and 91 participants from the intervention arm. We found that vital signs and clinical outcomes were relatively stable; however, incidences of hypertension substantially decreased among participants in the intervention arm. By 3 months postbirth, most participants in the intervention arm were able to identify all postbirth warning signs and retain this knowledge compared to the

control arm. Those in the intervention arm were also knowledgeable of more warning signs at each time point compared to the control arm.

Discussion: An integrated, evidence-based approach to postpartum care, such as Focused-PPC, has potential to increase knowledge and improve clinical outcomes among mothers in Ghana.

Family planning and birth spacing

Meningitis and encephalitis

Pediatrics. 2024 Aug 1;154(Suppl 1):e2024066588H.

doi: 10.1542/peds.2024-066588H.

Efficacy of Antibiotic Regimens for Meningitis in Young Infants Aged 0-59 Days: A Systematic Review

[Sitarah Mathias^{1,2}](#), [Krysten North^{2,3}](#), [Alexandra Santana^{2,4}](#), [Carl Britto^{2,5}](#), [Alastair Fung⁶](#), [Roger Chou⁷](#), [Carrie G Wade⁸](#), [Karen M Edmond⁹](#), [Anne Cc Lee^{2,3}](#)

Abstract

Context: Meningitis is associated with high mortality risk in young infants, yet the optimal treatment regimen is unclear.

Objectives: To systematically evaluate the efficacy of antibiotic regimens to treat meningitis in young infants aged 0 to 59 days on critical clinical outcomes.

Data sources: MEDLINE, Embase, CINAHL, WHO Global Index Medicus, and Cochrane Central Registry of Trials.

Study selection: We included randomized controlled trials (RCTs) of young infants with meningitis (population) comparing the efficacy of antibiotic regimens (interventions) with alternate regimens (control) on clinical outcomes.

Data extraction: We extracted data on study characteristics and assessed risk of bias in duplicate. Grading of Recommendations Assessment, Development, and Evaluation was used to assess certainty of evidence.

Results: Of 1088 studies screened, only 2 RCTs were identified. They included 168 infants from 5 countries and were conducted between 1976 and 2015. Neither study compared current World Health Organization-recommended regimens. One multisite trial from 4 countries compared intrathecal gentamicin plus systemic ampicillin/gentamicin to systemic ampicillin/gentamicin and found no difference in mortality (relative risk, 0.88; 95% confidence interval, 0.41-1.53; 1 trial, n = 98, very low certainty of evidence) or adverse events (no events in either trial arm). Another trial in India compared a 10-day versus 14-day course of antibiotics and found no difference in mortality (relative risk, 0.88; 95% confidence interval, 0.41-1.53; 1 trial, n = 98, very low certainty of evidence) or other outcomes.

Conclusions: Trial data on the efficacy of antibiotic regimens in young infant meningitis are scarce. Rigorous RCTs are needed to inform recommendations for optimal antibiotic

regimens for meningitis treatment in this vulnerable population, particularly within the context of changing epidemiology and increasing antimicrobial resistance.

Mental health and child psychiatry

J Adolesc Health. 2024 Dec 16:S1054-139X(24)00548-2.

doi: 10.1016/j.jadohealth.2024.10.030. Online ahead of print.

[Pathways From Poverty to Child Mental Health in Burkina Faso: Longitudinal Mediation Analyses in a Cluster-Randomized Clinical Trial](#)

[Leyla Karimli¹](#), [Leyla Ismayilova²](#), [Christine R Wells³](#)

Abstract

Purpose: The study applies the Family Stress Model to examine the impact of an integrated intervention on the mental health of children facing chronic adversity in Burkina Faso. Its primary goal is to enhance understanding of individual and relational factors at the family level as mediators and specific mechanisms through which poverty reduction can impact child well-being.

Methods: Cross-lagged autoregressive longitudinal mediation analyses tested the intervention effect on child mental health, examining maternal depression, maternal anxiety, harsh parenting, and child exposure to abuse as potential mediators. Longitudinal data were collected over the course of 24 months in a cluster-randomized controlled trial conducted among 360 dyads (children aged 10-15 and their female caregivers) in Burkina Faso. Participants were randomized into a control arm, economic intervention using the Graduation approach (Treatment Arm 1), or a combination of economic strengthening and family coaching (Treatment Arm 2).

Results: In Treatment Arm 1, maternal depression fully mediated the intervention effect on child's depression ($B = -0.09$, 95% confidence interval [CI] from -0.26 to -0.003) and child's self-esteem ($B = 0.05$, 95% CI from 0.001 to 0.18). In Treatment Arm 2, violent parenting practices partially mediated the intervention effect on child's depression ($B = -0.08$, 95% CI from -0.29 to -0.01).

Discussion: Our study underscores the importance of multifaceted interventions merging economic empowerment with family-focused child protection strategies. This approach fosters a supportive family environment, reducing children's vulnerability to mental health issues in resource-poor communities. It enriches our understanding of how parental economic and behavioral interventions impact child mental health outcomes.

Psychiatry Res. 2025 Jul;349:116498.

doi: 10.1016/j.psychres.2025.116498. Epub 2025 Apr 14.

[The effectiveness of combining interactive media based cognitive behaviour therapy with art and music therapies for ameliorating the generalised anxiety disorder of children exposed to abduction](#)

[Jiaqi Xu¹](#), [Shamim Akhter²](#), [Oberiri Destiny Apuke³](#)

Abstract

The researchers examined the efficacy of integrating interactive media-based cognitive behaviour in conjunction with art and music therapy for treating generalised anxiety disorder (GAD) in children abducted in Nigeria. A randomised control trial was carried out using three randomly selected secondary schools in Northern part of Nigeria. The study sample comprised 450 students randomly divided into a control group of (n = 225) and an experimental group of (n = 225). The treatment group was randomly selected into (n = 56) each for cognitive behaviour, art, and music therapy. While CBT + art and music had (n = 57) participants. This study's finding shows that cognitive behaviour therapy combined with art and music delivered through interactive media may be superior for treating paediatric GAD, than using only either CBT, art or music therapy. Participants who were assigned to a combined therapy that involved integrating CBT, music and art therapies reported a lower level of GAD, compared to those who were assigned to either CBT, art, or music alone. However, a cost benefit analysis points to the adopting of CBT in treating the GAD of children kidnapped. This study concluded with some implication for theory and health promotion.

Autism Res. 2024 Aug;17(8):1705-1720.

doi: 10.1002/aur.3213.

A preliminary randomized controlled study of the PEERS® program for Taiwanese autistic adolescents: The effectiveness on reducing school bullying and enhancing social function

Mei-Ni Hsiao^{1,2}, Yi-Ling Chien^{1,3}, Yueh-Ming Tai⁴, Heng-Man Chen⁵, Hsien-Hsueh Shih⁶, Li-Wei Chen⁷, Yu-Ying Chen⁵, Wei-Tsuen Soong^{1,3}, Yen-Nan Chiu^{1,3}, Wen-Che Tsai^{1,3}, Elizabeth Laugeson⁸, Mei-Hui Tseng², Susan Shur-Fen Gau^{1,2,3}

Abstract

Individuals with autism spectrum disorder (ASD) often experience lifelong social communication challenges and are more vulnerable to school bullying. Addressing their social difficulties and school bullying requires evidence-based interventions. PEERS® (Program for the Education and Enrichment of Relational Skills) was adapted and translated for Taiwanese adolescents. This randomized controlled study aimed to examine the effectiveness of the Taiwanese version of PEERS® in reducing school bullying and enhancing social function among autistic adolescents. Twenty-one autistic adolescents (mean age 14.29 ± 1.67 years; female n = 733.33%) were randomized to a treatment group (TG, n = 10) or a delayed treatment control group (DTG, n = 11). The outcome measures (school bullying, social challenges, social skills knowledge, and social skills performance) were assessed at baseline, post-treatment, and follow-up. The group and time interaction analyses revealed greater magnitudes of reduction in general school bullying (p < 0.001), victimization (p < 0.001), perpetration (p = 0.012), social challenges (p = 0.001), and peer conflicts (p < 0.001), and improvement in social knowledge (p < 0.001) in the TG group than the DTG group. The findings suggest that the PEERS® program tailored for Taiwanese adolescents is effective in reducing school bullying, decreasing social challenges, and enhancing social skills among autistic adolescents, with very large effect sizes (Cohen's d ranging from 1.19 to 2.88). Consequently, participation in the PEERS® program is recommended for adolescents with social difficulties to improve their social communication and interactions to offset school bullying and other social challenges related to adverse outcomes.

BMC Psychol. 2024 Dec 24;12(1):780.

doi: 10.1186/s40359-024-02300-9.

Reframe-IT+, an indicated preventive school-based intervention, reduces suicidal ideation among adolescents in vulnerable contexts in Chile

Daniel Nuñez^{1,2,3}, Daniela Meza^{1,2}, Javiera Andaur¹, Jo Robinson^{4,5}, Jorge Gaete^{6,7}

Abstract

Background: Suicide prevention programs delivered in school settings have been shown to reduce suicide attempts and ideation among adolescents. School-based digital interventions targeting at-risk youth are a promising avenue for suicide prevention, and some evidence has shown that blending digital and face-to-face components may improve the effectiveness. However, further evidence is needed, especially in Latin America, where mental health support is limited. We tested the effectiveness of the Reframe-IT+, a blended cognitive behavioral indicated intervention to reduce suicidal ideation, designed to be delivered in school settings. It includes 13 sessions, combining eight internet-based sessions and five face-to-face sessions.

Methods: We conducted a cluster RCT and delivered the Reframe-IT + among secondary students attending Years 9-11. We recruited 21 schools that were randomized into two groups: (1) Intervention Reframe-IT + Group (IG) (n = 863) and (2) Control Group (CG) (n = 683). All consented students completed online screening self-reported questionnaires at baseline. The primary outcome was suicidal ideation . Additionally, we tested the impact of the intervention on depressive and anxiety symptoms, hopelessness, and emotion regulatory strategies, including social solving-problems skills, behavioral activation, cognitive reappraisal, and emotion suppression. A total of 303 students (IG, n = 164; CG, n = 139) were identified as at risk and eligible for inclusion in the study. From those, 224 students (IG, n = 123; CG, n = 101) and their caregivers were interviewed to confirm inclusion and exclusion criteria. Finally, 48 and 47 students were allocated to control and intervention groups, respectively, and answered the online questionnaires at post-intervention. We performed an intention-to-treat analysis using repetitive measures and multilevel regression analyses.

Results: We found a significant reduction in suicidal ideation ($b=-6.7$, $p = 0.015$, Cohen ´s $d = 0.49$), depressive ($b=-3.1$, $p = 0.002$, Cohen ´s $d = 0.81$) and anxiety ($b=-2.60$, $p < 0.001$, Cohen ´s $d = 0.72$) symptoms, and hopelessness ($b=-3.7$, $p < 0.001$, Cohen ´s $d = 0.70$) in the intervention group compared to the control group at post-intervention. We also found improvement in solving-problems skills ($b=-1.6$, $p = 0.002$, Cohen ´s $d = 0.58$), behavioral activation ($b = 2.8$, $p = 0.019$, Cohen ´s $d = 0.47$), and cognitive reappraisal ($b = 2.2$, $p = 0.029$, Cohen ´s $d = 0.53$). In the exploration of the intervention mechanisms concerning suicidal ideation, the total indirect effect of the intervention ($b = -5.727923$; $p = 0.008$) was significant, whereas the direct effect ($b = -0.03195473$, $p = 0.903$) was not significant (Suppl 2, Table 1). Problem-solving skill ($b=-2.84$, $p = 0.016$) was a significant mediator of intervention effects on suicidal ideation (Path a*b).

Conclusions: This is the first clustered RCT evaluation of the effectiveness of a blended indicated intervention to prevent suicidality in school settings in Latin America. This is the first step to informing policymakers to scale up an effective intervention for an important public health problem.

Mobile phones and Apps

JMIR Mhealth Uhealth. 2025 May 5;13:e63527.

doi: 10.2196/63527.

[SEARCH Study: Text Messages and Automated Phone Reminders for HPV Vaccination in Uganda: Randomized Controlled Trial](#)

[Sabrina B Kitaka^{#1}](#), [Joseph Rujumba¹](#), [Sarah K Zalwango^{2,3}](#), [Betsy Pfeffer⁴](#), [Lubega Kizza¹](#), [Juliane P Nattimba¹](#), [Ashley B Stephens⁴](#), [Nicolette Nabukeera-Barungi¹](#), [Chelsea S Wynn⁴](#), [Juliet N Babirye³](#), [John Mukisa⁵](#), [Ezekiel Mupere¹](#), [Melissa S Stockwell^{#4,6}](#)

Abstract

Background: Cervical cancer is currently the leading female cancer in Uganda. Most women are diagnosed with late-stage disease. Human papillomavirus (HPV) vaccination is the single most important primary preventive measure. While research regarding text message vaccine reminder use is strong in the United States, their use has not yet been demonstrated in a preteen and adolescent population in subSaharan Africa or other low- and middle-income countries.

Objective: The objective of this pilot randomized controlled trial was to assess the impact of vaccine reminders with embedded interactive educational information on timeliness of HPV vaccination in Kampala, Uganda.

Methods: In this randomized controlled trial conducted in 2022, caregivers of adolescents needing a first or second HPV vaccine dose were recruited from an adolescent clinic and three community health centres in Kampala, Uganda. Families (n=154) were randomized 1:1 into intervention versus usual care, stratified by dose (ie, initiation, completion) and language (ie, English, Luganda) within each site. Intervention caregivers received a series of automated, personalized text messages or automated phone calls based on family preference. Five messages were sent before the due date, including both static and interactive educational information, with five follow-up messages for those unvaccinated. Receipt of the needed dose by 24 weeks postenrollment was assessed by χ^2 , regression, and Kaplan-Meier with log-rank test. All analyses were conducted using intention-to-treat principles.

Results: Overall, 154 caregivers were enrolled (51.3% for dose 1; 48.7% for dose 2) and 64.3% (n=99) spoke Luganda. Among individuals in the intervention arm, 62% (48/78) requested SMS text message reminders and 38% (n=30) requested automated phone reminders. There was no significant difference in requested mode by HPV vaccine dose or language. Intervention adolescents were more likely to receive the needed dose by 24 weeks (51/78, 65.4% vs 27/76, 35.5%; $P<.001$; RR 1.8; 95% CI 1.3-2.6). There was no interaction by dose or language. There was no difference in vaccination between those requesting SMS text message versus phone reminders (32/49, 65.3% vs 19/30, 63.3%; $P=.86$). The number needed to message for one additional vaccination was 3.4 (95% CI 2.2-6.8). Kaplan-Meier curves demonstrated more timely vaccination in the intervention arm ($P<.001$).

Conclusions: In this novel trial, SMS text message and automated phone reminders were effective in promoting more timely HPV vaccination in this population.

Mortality – post-discharge

Neurological disease and neurodevelopmental conditions

Lancet Glob Health. 2024 Jul;12(7):e1149-e1158.

doi: 10.1016/S2214-109X(24)00102-5. Epub 2024 May 13.

[Doxycycline for the treatment of nodding syndrome: a randomised, placebo-controlled, phase 2 trial](#)

[Richard Idro¹](#), [Rodney Ogwang²](#), [Ronald Anguzu²](#), [Pamela Akun²](#), [Albert Ningwa²](#), [Catherine Abbo³](#), [Maria P Giannoccaro⁴](#), [Joseph Kubofcik⁵](#), [Amos D Mwaka³](#), [Phellister Nakamya⁶](#), [Bernard Opar⁶](#), [Mark Taylor⁷](#), [Thomas B Nutman⁵](#), [Alison Elliott⁸](#), [Angela Vincent⁹](#), [Charles R Newton¹⁰](#), [Kevin Marsh¹¹](#)

Abstract

Background: Nodding syndrome is a poorly understood neurological disorder that predominantly occurs in Africa. We hypothesised that nodding syndrome is a neuroinflammatory disorder, induced by antibodies to *Onchocerca volvulus* or its *Wolbachia* symbiont, cross-reacting with host neuronal proteins (HNPs), and that doxycycline can be used as treatment.

Methods: In this randomised, double-blind, placebo-controlled, phase 2 trial, we recruited participants from districts affected by nodding syndrome in northern Uganda. We included children and adolescents aged 8-18 years with nodding syndrome, as defined by WHO consensus criteria. Participants were randomly assigned (1:1) to receive either 100 mg doxycycline daily or placebo for 6 weeks via a computer-generated schedule stratified by skin microscopy results, and all parties were masked to group assignment. Diagnoses of *O. volvulus* and antibodies to HNPs were made using luciferase immunoprecipitation system assays and immunohistochemistry. The primary outcome was change in the proportion with antibodies to HNPs, assessed at 24 months. All participants were included in safety analyses, and surviving participants (those with samples at 24 months) were included in primary analyses. Secondary outcomes were: change in concentrations of antibodies to HNPs at 24 months compared with baseline; proportion of participants testing positive for antibodies to *O. volvulus*-specific proteins and concentrations of Ov16 or OVOC3261 antibodies at 24 months compared with baseline; change in seizure burden, proportion achieving seizure freedom, and the proportions with interictal epileptiform discharges on the diagnostic EEG; overall quality of life; disease severity at 24 months; and incidence of all-cause adverse events, serious adverse events, and seizure-related mortality by 24 months. This trial is registered with ClinicalTrials.gov, [NCT02850913](#).

Findings: Between Sept 1, 2016, and Aug 31, 2018, 329 children and adolescents were screened, of whom 240 were included in the study. 140 (58%) participants were boys and 100 (42%) were girls. 120 (50%) participants were allocated to receive doxycycline and 120 (50%) to receive placebo. At recruitment, the median duration of symptoms was 9 years (IQR 6-10); 232 (97%) participants had *O. volvulus*-specific antibodies and 157 (65%) had autoantibodies to HNPs. The most common plasma autoantibodies were to human protein deglycase DJ-1 (85 [35%] participants) and leiomodin-1 (77 [32%] participants) and, in cerebrospinal fluid (CSF), to human DJ-1 (27 [11%] participants) and leiomodin-1 (14 [6%] participants). On immunohistochemistry, 46 (19%) participants had CSF autoantibodies to HNPs, including

leiomodrin-1 (26 [11%]), γ -aminobutyric acid B receptors (two [$<1\%$]), CASPR2 (one [$<1\%$]), or unknown targets (28 [12%]). At 24 months, 161 (72%) of 225 participants had antibodies to HNPs compared with 157 (65%) of 240 at baseline. 6 weeks of doxycycline did not affect the concentration of autoantibodies to HNPs, seizure control, disease severity, or quality of life at the 24-month follow-up but substantially decreased Ov16 antibody concentrations; the median plasma signal-to-noise Ov16 ratio was 16.4 (95% CI 6.4-38.4), compared with 27.9 (8.2-65.8; $p=0.033$) for placebo. 14 (6%) participants died and, other than one traffic death, all deaths were seizure-related. Acute seizure-related hospitalisations (rate ratio [RR] 0.43 [95% CI 0.20-0.94], $p=0.028$) and deaths (RR 0.46 [0.24-0.89], $p=0.028$) were significantly lower in the doxycycline group. At 24 months, 96 (84%) of 114 participants who received doxycycline tested positive for antibodies to Ov16, compared with 97 (87%) of 111 on placebo ($p=0.50$), and 74 (65%) participants on doxycycline tested positive for antibodies to OVOC3261, compared with 57 (51%) on placebo ($p=0.039$). Doxycycline was safe; there was no difference in the incidence of grade 3-5 adverse events across the two groups.

Interpretation: Nodding syndrome is strongly associated with O volvulus and the pathogenesis is probably mediated through an O volvulus induced autoantibody response to multiple proteins. Although it did not reverse disease symptoms, doxycycline or another prophylactic antibiotic could be considered as adjunct therapy to antiseizure medication, as it might reduce fatal complications from acute seizures and status epilepticus induced by febrile infections.

Autism

BMJ Paediatr Open. 2025 Mar 4;9(1):e003045.

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[Impact of probiotic supplements on behavioural and gastrointestinal symptoms in children with autism spectrum disorder: A randomised controlled trial](#)

[Himani Narula Khanna](#)^{1,2}, [Sushovan Roy](#)³, [Aqsa Shaikh](#)³, [Rajiv Chhabra](#)⁴, [Azhar Uddin](#)³

Abstract

Objective: To investigate whether probiotic supplementation can improve behavioural and gastrointestinal (GI) symptoms in children with autism spectrum disorder (ASD) aged 2-9 years and further explore the correlation between these symptoms.

Design: Single-blinded, randomised, placebo-controlled study.

Setting: Five developmental paediatric outpatient clinics of 'Continua Kids'.

Patients: Children aged 2-9 years diagnosed with ASD along with their caregivers.

Interventions: Probiotic or placebo sachet reconstituted in 50 mL of lukewarm milk/water, taken two times per day for 3 months.

Main outcome measures: Change in behavioural (measured by Social Responsiveness Scale-2 (SRS-2) and Aberrant Behaviour Checklist-2 (ABC-2) tools) and GI (measured by GI Severity Index (GSI) score) symptoms after receiving intervention for 3 months.

Results: A total of 180 children with ASD were enrolled in the study (probiotic group: 90 and placebo group: 90). All children completed the study. The probiotic group showed a significant reduction in behavioural symptom severity as measured by the SRS-2 tool

(47.77% vs 23.33%; $p=0.000$) compared with the placebo. Probiotic-treated children demonstrated significant reductions in severe symptoms, including social withdrawal/lethargy (40%), stereotypic behaviour (37.77%), hyperactivity (34.44%) and inappropriate speech (32.22%) post-intervention ($p=0.000$). They also had marked improvements in constipation ($p=0.003$) and diarrhoea ($p=0.043$) compared with the placebo group. Both groups exhibited a statistically significant correlation between behavioural and GI symptoms.

Conclusions: Probiotic supplementation improved behavioural and GI symptoms in children with ASD with no adverse effects. Both symptoms were significantly correlated. However, these results need to be validated in a larger sample size.

Eur J Pediatr. 2024 Nov;183(11):4827-4835.

doi: 10.1007/s00431-024-05762-6. Epub 2024 Sep 7.

Efficacy of oral folinic acid supplementation in children with autism spectrum disorder: a randomized double-blind, placebo-controlled trial

[Prateek Kumar Panda](#)^{#1}, [Indar Kumar Sharawat](#)^{#2}, [Sarama Saha](#)³, [Diksha Gupta](#)¹, [Achanya Palayullakandi](#)¹, [Kiran Meena](#)³

Abstract

Oral folinic acid has shown potential to improve symptoms in children with autism spectrum disorder (ASD). However, randomized controlled trials (RCTs) are limited. This double-blind, placebo-controlled RCT aimed to compare changes in Childhood Autism Rating Scale (CARS) scores in children with ASD aged 2-10 years, among folinic acid (2 mg/kg/day, maximum of 50 mg/day) and placebo groups at 24 weeks, in comparison with baseline. Both the groups received standard care (ABA and sensory integration therapy). Secondary objectives included changes in behavioral problems measured by the Child Behavior Checklist (CBCL) and serum levels of anti-folate receptor autoantibodies and folic acid, correlated with changes in autism symptom severity. Out of the 40 participants recruited in each group, 39 and 38 participants completed the 24-week follow-up in the folinic acid and placebo groups, respectively. The change in CARS score was higher in the folinic acid group (3.6 ± 0.8) compared to the placebo group (2.4 ± 0.7 , $p < 0.001$). Changes in CBCL total score and CBCL internalizing score were also better in the folinic acid group (19.7 ± 9.5 vs. 12.6 ± 8.4 and 15.4 ± 7.8 vs. 8.5 ± 5.7 , $p < 0.001$ for both). High-titer anti-folate receptor autoantibodies were positive in 32/40 and 33/40 cases in the folinic acid and placebo groups, respectively ($p = 0.78$). In the placebo group, improvement in CARS score was comparable regardless of autoantibody status ($p = 0.11$), but in the folinic acid group, improvement was more pronounced in the high-titer autoantibody group ($p = 0.03$). No adverse reactions were reported in either group.

Conclusions: Oral folinic acid supplementation is effective and safe in improving ASD symptoms, with more pronounced benefits in children with high titers of folate receptor autoantibodies.

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Metformin efficacy and safety as an adjunctive treatment for irritability in children with autism spectrum disorder: A randomized, double-blind, placebo-controlled trial

[Zahra Bazrafshan¹](#), [Parsa Mohammadi¹](#), [Alireza Hasanzadeh¹](#), [Mohammad Sanjari Moghaddam²](#), [Maryam Kabiri^{1,2}](#), [Hossein Sanjari Moghaddam¹](#), [Amir Hossein Abdolghaffari³](#), [Mohammad-Reza Mohammadi¹](#), [Shahin Akhondzadeh¹](#)

Abstract

Background: Antidiabetic medications have shown efficacy in alleviating autism symptoms. However, there is a lack of clinical research on the impact of metformin on irritability associated with autism. This study aimed to assess the efficacy and safety of metformin as an adjuvant therapy with risperidone for managing irritability in children diagnosed with Autism Spectrum Disorder (ASD).

Methods: This is a randomized, 10-week, double-blind, placebo-controlled trial conducted at the children's autism clinic of Roozbeh Hospital (Tehran, Iran) from March 2024 to May 2024. Participants were divided into two groups of risperidone plus metformin (500 mg per day) and risperidone plus placebo and were assessed at baseline, weeks 5 and 10 with the aberrant behavior checklist-community scale (ABC-C).

Results: A total of 55 patients were included in the final analysis. Irritability (primary outcome measure) sharply decreased in the metformin compared to the placebo group ($p = 0.008$). Among the other four subscales of ABC-C, the hyperactivity/noncompliance score showed a significant drop during the baseline-to-week-5 period ($p = 0.021$). In addition, inappropriate speech subscales decreased significantly from baseline-to-week 5 in the metformin compared to the placebo group ($p = 0.045$). No other significant finding was observed among ABC-C scores for lethargy/social withdrawal or stereotypic behavior subscales.

Conclusion: Metformin demonstrated promising results in reducing irritability in ASD patients, which is in concordance with previous studies. However, further studies are required before any broad clinical recommendation.

Cerebral palsy

JAMA Pediatr. 2025 Jun 1;179(6):621-629.

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Sustainable Model of Early Intervention and Telerehabilitation for Children With Cerebral Palsy in Rural Bangladesh: The SMART-CP Randomized Clinical Trial

[Mahmudul Hassan Al Imam^{1,2,3,4}](#), [Israt Jahan^{1,2,3,4}](#), [Nuruzzaman Khan⁵](#), [Delwar Akbar⁶](#), [Shafiul Islam^{3,4}](#), [Mohammad Muhit^{3,4}](#), [Nadia Badawi^{7,8}](#), [Gulam Khandaker^{2,9,10}](#)

Abstract

Importance: Access to early intervention and rehabilitation services among children with cerebral palsy (CP) remains limited in Bangladesh, which demands an innovative and sustainable service delivery model.

Objective: To evaluate the effectiveness of the Sustainable Model of Early Intervention and Telerehabilitation for Children With CP (SMART-CP) model compared with usual care in

improving access to and utilization of early diagnosis, early intervention, and rehabilitation services in rural Bangladesh.

Design, setting, and participants: This was a 2-arm cluster randomized clinical trial, with 8 clusters (ie, subdistricts) randomly allocated to the intervention (SMART-CP model) or control arm. The setting was in Sirajganj, Bangladesh, and included children with CP 18 years or younger. Outcomes were measured at 0 and 12 months, and an intention-to-treat analysis was conducted. Data were analyzed from December 2023 to May 2024.

Interventions: The SMART-CP model comprised (1) a rural referral network involving key informants and caregiver peer groups (called mPower or mothers' power), (2) subdistrict level SMART-CP centers, and (3) telerehabilitation services. Children in the intervention arm received weekly goal-directed therapy, mPower group meetings every 2 weeks, and monthly telerehabilitation sessions.

Main outcomes and measures: The primary outcome was whether a child with CP accessed any form of rehabilitation services, with secondary outcomes analyzed as hypothesis generating.

Results: Overall, 968 children with CP (mean [SD] age, 7.9 [4.9] years; 581 male [60.0%]) were enrolled, with 500 in the intervention arm and 468 in the control arm. Between baseline and endline, rehabilitation services uptake significantly increased in the intervention arm (70.2% [351 of 500] vs 99.4% [497 of 500]), compared with the control arm (63.9% [299 of 468] vs 68.2% [319 of 468]; $P < .001$). Children in the intervention arm were 1.5 times more likely to access rehabilitation than the control arm. Secondary analyses suggested that the intervention arm also facilitated early CP diagnosis (mean [SD] diagnosis time, 2.0 [2.0] years vs 3.8 [3.3] years; Cohen $d = -0.7$) and initiation of rehabilitation (mean [SD] rehabilitation time, 1.8 [1.8] years vs 3.6 [2.4] years; Cohen $d = -0.9$). Additionally, higher therapy session counts (mean [SD] session counts, 23.4 [31.7] vs 4.3 [20.8]; Cohen $d = 0.7$), increased assistive device utilization (20.8% [104 of 500] vs 3.0% [14 of 468]; risk ratio, 0.82; 95% CI, 0.78-0.86; $P < .001$), and lower out-of-pocket expenditure per month (mean [SD] expenditure, \$1.5 [\$1.6] vs \$2.9 [\$5.1]; Cohen $d = -0.4$) were found in the intervention arm. No significant difference in clinical outcomes and mortality rates was observed between the intervention and control groups.

Conclusions and relevance: Results of this cluster randomized clinical trial reveal that the SMART-CP model improved access to and utilization of early diagnosis and intervention services for children with CP in rural Bangladesh. This model holds promise for global scalability.

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[Functioning and activity outcomes of the Akwenda Intervention Program for children and young adults with cerebral palsy in Uganda: A cluster-randomized trial](#)

[Elizabeth Asige¹](#), [Gillian Saloojee²](#), [Carin Andrews^{3,4}](#), [Lukia H Namaganda⁵](#), [Angelina Kakooza-Mwesige^{1,3}](#), [Diane L Damiano⁶](#), [Hans Forssberg^{3,7}](#)

Abstract

Aim: To evaluate the efficacy of the Akwenda Intervention Program on motor, self-care, and social function of children and young people with cerebral palsy (CP).

Method: This was a cluster-randomized, controlled, single-blinded, intervention study of 100 participants with CP (2-23 years; 52 males) in rural eastern Uganda. Half were allocated to

the intervention program, the remainder served as waitlist controls. Gross Motor Function Measure-66 (GMFM-66) and the Ugandan version of Pediatric Evaluation of Disability Inventory (PEDI-UG) were collected before group allocation and after intervention. General linear models and t-tests were used to compare changes within and between groups. Cohen's d estimated the effect size of group differences. Change scores were evaluated by age and mobility subgroups.

Results: Significant group by time interactions were found for GMFM-66 ($p = 0.003$) and PEDI-UG outcomes ($p < 0.001$), except mobility, with the intervention group demonstrating greater changes. Both groups increased their scores on the GMFM-66 and child PEDI-UG, while only the intervention group had significant increases in caregiver assistance scores and across all age and mobility subgroups. Cohen's d showed large effect sizes ($d > 0.8$) of differences for PEDI-UG outcomes except mobility.

Interpretation: The Akwenda Intervention Program had a large positive impact on functioning and activity across age and mobility levels.

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Participation in activities of daily living after the Akwenda Intervention Program for children and young people with cerebral palsy in Uganda: A cluster-randomized trial

Elizabeth Asige^{1,2}, Gillian Saloojee^{2,3}, Godfrey Wanjala², Carin Andrews^{2,4,5}, Lukia H Namaganda^{2,6}, Angelina Kakooza-Mwesige^{1,2}, Diane L Damiano^{2,7}, Hans Forssberg^{2,4,8}

Abstract

Aim: To evaluate the efficacy of the Akwenda Intervention Program on participation attendance and involvement of children and young people with cerebral palsy (CP) in rural Uganda.

Method: This was a cluster-randomized, controlled, single-blind, interventional study of 100 participants with CP (aged 2-23 years; 48 females; allocated to the intervention or waiting list control group). Picture My Participation interviews assessed participation attendance and involvement in 20 home and community activities. Group differences were analysed using a Mann-Whitney U test and effect sizes were calculated. Change in attendance was related to age and functional level, and to improvements in child functioning, which was published in a previous report from the same study.

Results: Attendance increased more in the intervention compared to the control group ($p < 0.001$; $r = 0.48$; $z = -4.62$) and across both Gross Motor Function Classification System (GMFCS) subgroups and two age subgroups (2-5 years and 13-23 years). Positive correlations were found between increases in attendance and higher GMFCS levels ($p = 0.25$, $p = 0.03$) and with all three caregiver assistance scales and the social function child scale of the Ugandan version of the Pediatric Evaluation of Disability Inventory. The intervention group had larger increases in involvement than the controls ($p < 0.001$; $r = 0.41$; $z = -3.95$), although positive changes were seen in both groups.

Interpretation: The Akwenda Intervention Program, which intervened at the level of the child, family, and community, was successful in enhancing participation for children with CP.

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Hand-arm bimanual intensive therapy versus modified constraint-induced movement therapy in children with hemiparetic cerebral palsy: A randomized controlled trial

[Prateek Kumar Panda¹](#), [Indar Kumar Sharawat²](#), [Diksha Gupta¹](#), [Achanya Palayullakandi¹](#), [S Senthil Kumaran³](#), [Poonam Sherwani⁴](#), [Suthiraj Sopanam¹](#), [Osama Neyaz⁵](#)

Abstract

Introduction: Modified Constraint-Induced Movement Therapy (mCIMT) and Hand-Arm Bimanual Intensive Therapy (HABIT) are widely used for treating hemiparetic cerebral palsy (CP). Prior randomized controlled trials (RCTs) comparing these approaches yielded mixed outcomes.

Methods: This RCT evaluated the efficacy of 12 weeks of mCIMT versus HABIT in children aged 5-18 years with hemiparetic CP. Primary objective was to compare improvements in upper limb function (quality of upper extremity skills test [QUEST] total score) in both groups. Secondary objectives were to compare speed of upper limb movements (nine-hole peg board test), muscle strength (thumb strength and hand grip strength), quality of life (CPQoL), compliance to advised therapy in both groups, sustenance of improvement 4 weeks after stopping supervised treatment, and to describe and compare diffusion tensor imaging (DTI) and resting functional magnetic resonance imaging (fMRI) changes. Both groups received 2-h supervised sessions, 8 sessions over 4 weeks, followed by weekly sessions for 8 more weeks. Participants practiced 2 h daily at home, monitored by activity logs and videos when feasible.

Results: Each group had 30 participants. Changes in QUEST total scores after 12 weeks were comparable between HABIT and mCIMT (12.00 ± 7.52 vs. 11.35 ± 7.10 , $p = 0.48$). Individual QUEST domain scores, nine-hole peg test times, thumb and grip strength, and CPQoL improvements were also similar between groups ($p > 0.05$ for all). Both groups showed significant improvements across all outcomes at 12 weeks ($p < 0.05$), maintained at 16 weeks. DTI revealed comparable changes in apparent diffusion co-efficient and fractional anisotropy values in the contralateral corticospinal tract ($p = 0.63$ and 0.71 , respectively). fMRI showed increased activation in the contralateral sensorimotor cortex in both groups at 12 weeks.

Conclusion: HABIT and mCIMT demonstrate similar efficacy for upper limb function improvement in children with hemiparetic CP.

JMIR Rehabil Assist Technol. 2025 Feb 18;12:e65358.

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Evaluation of a Game-Based Mechatronic Device for Rehabilitation of Hand-Arm Function in Children With Cerebral Palsy: Feasibility Randomized Controlled Trial

[Mrudula Kanakapura Peramalaiah¹](#), [Sanjay Tejraj Parmar¹](#), [Nariman Sepehri²](#), [Saman Muthukumarana³](#), [Anuprita Kanitkar⁴](#), [Cherry Kit-Fong Hin⁴](#), [Tony Joseph Szturm⁴](#)

Abstract

Background: Children with neurodevelopmental disorders, such as cerebral palsy (CP), often experience motor impairments in manual dexterity, which hinder daily tasks and social interactions. Traditional rehabilitation methods require repetitive task practice, which can be difficult for children to sustain due to low engagement. Game-based rehabilitation devices and robots offer a promising alternative by combining therapy with digital play, improving motivation and compliance. However, many systems fail to incorporate actual

object manipulation, which is essential for motor learning through sensory feedback. To address this limitation, a low-cost, easy-to-use robotic manipulandum device (RMD) was developed. The RMD enables real-time object manipulation during gameplay while providing assistive force, allowing the practice of a wide range of manual dexterity skills beyond gross reaching. This system offers an engaging and effective rehabilitation approach to enhance hand function in children with CP.

Objective: This study aimed to provide evidence for the feasibility and therapeutic value of the RMD game-based exercise program for children with CP.

Methods: In total, 34 children with CP, aged 4 to 10 years, were randomly assigned to the experimental group (XG) or the control group (CG). The XG received a computer game-based exercise program using the RMD, focusing on object manipulation tasks, while the CG received task-specific training similar to constraint-induced movement therapy. Both groups received their respective therapy programs 3 times per week for 8 weeks. Semistructured interviews with parents and children, along with qualitative analysis, were conducted to evaluate their experiences with the exercise program. The following outcome measures were used: (1) the Peabody Developmental Motor Scale-2 (PDMS-2) grasping and visual-motor integration subtests and (2) the computer game-based upper extremity (CUE) assessment of manual dexterity.

Results: No dropouts occurred during the 8-week program. Both groups showed significant improvements in the PDMS-2 subtests ($P < .001$) and the CUE assessment of manual dexterity, including success rates (tennis ball: $P = .001$; cone: $P < .001$; medicine ball: $P = .001$; and peanut ball: $P < .001$) and movement errors (tennis ball: $P = .01$; cone: $P < .001$; medicine ball: $P = .04$; and peanut ball: $P < .001$). The XG outperformed the CG, showing greater improvements in PDMS-2 grasping ($P = .002$) and visual-motor integration ($P = .01$). In the CUE assessment, the XG demonstrated higher success rates (medicine ball: $P = .001$ and peanut ball: $P = .02$) and fewer movement errors (cone: $P < .001$). Parents reported an increase in the children's independence in daily tasks.

Conclusions: This study demonstrates the feasibility, acceptability, and positive outcomes of the RMD game-based exercise program for improving hand function in children with CP. The findings support further research and development of computer game-assisted rehabilitation technologies.

Pediatr Neurol. 2024 Sep;158:35-40.

doi: 10.1016/j.pediatrneurol.2024.06.004. Epub 2024 Jun 14.

Efficacy of Oral Trihexyphenidyl Plus Clonazepam Versus Trihexyphenidyl for the Treatment of Dystonia in Children With Dystonic Cerebral Palsy: An Open-Label Randomized Controlled Trial

[Prateek Kumar Panda¹](#), [Vetoni Moirangthem¹](#), [Apurva Tomar¹](#), [Osama Neyaz²](#), [Indar Kumar Sharawat³](#)

Abstract

Background: Trihexyphenidyl and clonazepam are commonly used to treat dystonia in children with cerebral palsy (CP). However, there is a notable gap in the literature when it comes to studies that combine these first-line agents for the management of dystonia.

Methods: This open-label, randomized controlled trial aimed to compare the efficacy of adding oral clonazepam to trihexyphenidyl (THP + CLZ) versus using trihexyphenidyl alone (THP) in reducing the severity of dystonia, as measured by the Barry-Albright Dystonia (BAD) score. The study was conducted over a 12-week therapy period in children with dystonic CP aged two to 14 years.

Results: Each group enrolled 51 participants. The THP + CLZ group showed significantly better improvement in dystonia severity at 12 weeks compared with the THP group alone (-4.5 ± 2.9 vs -3.4 ± 1.7 , $P = 0.02$). Furthermore, the THP + CLZ group exhibited superior improvement in the severity of choreoathetosis, upper limb function, pain perception by the child, and quality of life, with P values of 0.02, 0.009, 0.01, and 0.01, respectively. The number of participants experiencing treatment-emergent adverse events was comparable in both groups ($P = 0.67$). Importantly, none of the participants in any of the groups reported any serious adverse events.

Conclusion: A combination of oral THP + CLZ proves to be more efficacious than using THP alone for the treatment of dystonic CP in children aged two to 14 years in terms of reducing the severity of dystonia.

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Efficacy of virtual reality on balance impairment in ataxic cerebral palsy children: randomized controlled trial

[Hanady A Mouhamed](#)¹, [Nehad A Abo-Zaid](#)^{2,3}, [Heba A Khalifa](#)^{4,5}, [Mohammed E Ali](#)⁶, [Noha S Elserty](#)⁷, [Mohamed A Behiry](#)⁸, [Walaa E Heneidy](#)⁹

Abstract

Background: Children with ataxic cerebral palsy have unsteady movements and poor balance. Many therapeutic interventions are used to improve their upper and lower functioning.

Aim: To assess the effectiveness of virtual reality (VR) on balance impairment in ataxic cerebral palsy children.

Design: RCT.

Population: Sixty-four children with ataxic cerebral palsy.

Methods: Children were randomly assigned into two equal groups with 32 patients in each group. The control group received a specially developed physical therapy program and the VR group received VR training on a Wii balance board in addition to the control group's program. For three successive months the intervention program was implemented three times a week for both groups. Stability indices (overall, anteroposterior, and mediolateral) were measured using the Biodex balance system and Pediatric Balance Scale (PBS) at baseline and after three months of intervention for both groups.

Results: At the beginning of the intervention, there were no statistically significant differences between the two groups ($P > 0.05$). However, following three months of the intervention, there was a statistically significant decline in the stability index scores, as well as a statistically significant improvement in the score of the PBS in both groups with a notable advancement in favor of the VR group ($P \leq 0.05$).

Conclusions: Adding VR training on a Wii balance board to a designed physical therapy program has a significant impact on improving balance deficits in ataxic cerebral palsy children.

Clinical rehabilitation impact: VR has a therapeutic effect on improving balance that may result in better and more efficient rehabilitation program of children with ataxic cerebral palsy.

Spina bifida

Neuro-rehabilitation medicine

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Consensus Guidelines of the Indian Academy of Pediatrics (IAP)-Neurodevelopmental Pediatrics Chapter on Developmentally Supportive Follow-Up for High-Risk Infants

[Zafar Mahmood Meenai¹](#), [M K C Nair²](#), [Samir Dalwai³](#), [Lal D V Nair⁴](#), [Sheffali Gulati⁵](#), [Sharmila B Mukherjee⁶](#), [Naveen Jain⁷](#), [Deepak Dwivedi⁸](#), [Kawaljit S Multani⁹](#), [Shambhavi Seth¹⁰](#), [Vivek V Singh¹¹](#), [Atanu Bhadra¹²](#), [Vasant Khalatkar¹³](#), [Santhosh K Kraleti¹⁴](#), [Monica Juneja¹⁵](#), [Leena Deshpande¹⁶](#), [Anjan Bhattacharya¹⁷](#), [Lallan Kumar Bharti¹⁸](#), [Yogesh Parikh¹⁹](#), [Leena Srivastava²⁰](#), [Sitaraman Sadasivan²¹](#), [Jeeson C Unni²²](#), [Manmeet K Sodhi²³](#), [Shyamal Kumar²⁴](#), [Deepa Bhaskaran²⁵](#), [Adarsh Eregowda²⁶](#), [Indu Surana²⁷](#), [Abraham K Paul²⁸](#), [Ashok Raj²⁹](#), [Sanjay Shivanna³⁰](#), [Khurshid Wani³¹](#), [Lata Bhat³²](#), [Shabina Ahmed³³](#), [Nimmy K Joseph³⁴](#)

Abstract

Justification: With increasing neonatal survival, there is a need for trained staff for timely identification and intervention for high-risk infants. Since the foundation of neurodevelopment is laid in the first three years of life, addressing the lacunae of a robust guidelines for extended follow-up of high-risk infants needs to be formulated to avoid remediation or rehabilitation later on.

Objectives: To develop comprehensive evidence-based consensus guidelines for developmentally supportive care and follow-up of high-risk infants in the Indian context with the aim of reducing the need for future rehabilitative services.

Process: Scientific literature over the last 10 years was searched using database-specific controlled vocabularies like Emtree for Embase, MeSH terms for PubMed, Scopus, CINAHL headings for CINAHL databases, and the Cochrane Library. The available studies were analyzed based on their scientific credibility and strength of evidence. Data from meta-analysis, systematic reviews, and randomized controlled trials was extracted, and relevant statements were prepared. These were deliberated in two onsite Delphi rounds of discussion (February 19, 2023 and January 11, 2025) and one hybrid (online and onsite) Delphi round (February 6, 2025). The final draft was made under different headings and was circulated, followed by recommendations made with Grading of Recommendations Assessment, Development and Evaluation (GRADE) analysis. The final draft after incorporating all suggestions was circulated and accepted online on March 2, 2025.

Statement: The recommendations propose using a color-coded system to monitor high-risk infants, risk stratification, promoting early stimulation, structured interventions, and parental involvement. Routine care should align with the infant's behavioral state and use

validated screening tools and growth charts. Comprehensive follow-ups, including screening for retinopathy of prematurity, thyroid disorders, developmental dysplasia of hip, and hearing impairments, are essential, with specialized therapies provided as needed. Structured follow-up guidelines are likely to improve the selection of high-risk infants, plan follow-up, and guide pediatricians on screening, evaluation, early stimulation, intervention, and plan-specific definitive therapies with rehabilitation therapists which would ultimately decrease the childhood disability.

Newborn care

Essential newborn care

N Engl J Med. 2025 Mar 13;392(11):1100-1110.

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[Outcomes of a Program to Reduce Birth-Related Mortality in Tanzania](#)

[Benjamin A Kamala^{1,2}](#), [Hege L Ersdal^{3,4}](#), [Robert D Moshiro^{5,6}](#), [Godfrey Guga¹](#), [Ingvild Dalen⁷](#), [Jan T Kvaløy^{7,8}](#), [Felix A Bundala^{2,9}](#), [Ahmad Makuwani⁹](#), [Ntuli A Kapologwe⁹](#), [Rashid S Mfaume¹⁰](#), [Esto R Mduma¹](#), [Paschal Mdoe¹](#); [Safer Births Bundle of Care Study Group](#)

Abstract

Background: Birth-related mortality is a major contributor to the burden of deaths worldwide, especially in low-income countries. The Safer Births Bundle of Care program is a combination of interventions developed to improve the quality of care for mother and baby with the goal of reducing birth-related mortality.

Methods: We performed a 3-year stepped-wedge cluster-randomized study of the Safer Births program at 30 high-burden facilities in five regions in Tanzania. The bundle of interventions in the program was aimed at continuous quality improvement through regular onsite simulation-based training, the collection and use of local clinical data, the assistance of trained local facilitators, and the use of innovative tools for perinatal care. The primary outcome was perinatal death, which included intrapartum stillbirth (suspected death during labor) and neonatal death within the first 24 hours after birth.

Results: A total of 281,165 mothers and 277,734 babies were included in the final analysis. The estimated incidence of perinatal death decreased from 15.3 deaths per 1000 births in the baseline period of the program to 12.5 deaths per 1000 births after implementation (adjusted relative risk, 0.82; 95% confidence interval [CI], 0.73 to 0.92; $P = 0.001$), with substantial heterogeneity among regions. The incidence of intrapartum stillbirths was 8.6 deaths per 1000 births in the baseline period and 8.7 deaths per 1000 births after implementation (adjusted relative risk, 1.01; 95% CI, 0.87 to 1.17), and the incidence of neonatal deaths within the first 24 hours after birth was 6.4 and 3.9 deaths per 1000 births, respectively (adjusted relative risk, 0.61; 95% CI, 0.49 to 0.77). No serious adverse events were reported.

Conclusions: Implementation of the Safer Births Bundle of Care program showed the feasibility of integrating quality-improvement efforts targeting birth-related emergencies in

resource-limited settings and was associated with a significant reduction in perinatal mortality.

Reprod Health. 2024 Dec 17;21(1):183.

doi: 10.1186/s12978-024-01932-9.

Effect of early essential newborn care on breastfeeding and outcomes of mothers/newborns post-cesarean section: a randomized controlled trial in China

Min Zhou^{#1}, Jin-Yi Guo^{#2}, Tai-Yang Li¹, Chun-Hua Zhou¹, Xiao-Qin Zhang¹, Wei Wei¹, Jie Zhou², Sharon R Redding³, Yan-Qiong Ouyang⁴, Hui-Jun Chen⁵

Abstract

Background: The implementation of early essential newborn care (EENC) is important to maternal and neonatal health. However, few studies have conducted a complete procedure of EENC in cesarean section. This study aimed to systematically evaluate the effects of EENC during and after cesarean section.

Methods: A randomized controlled trial was conducted at a tertiary hospital in Wuhan, China. Full-term pregnant women who had no comorbidities and underwent elective cesarean section were recruited and received EENC intervention or routine health care. The Infant Breastfeeding Assessment Tool (IBFAT), the Breastfeeding Self-Efficacy Scale-Short Form (BSES-SF), a questionnaire of the breastfeeding behavior, the Maternal Postnatal Attachment Scale (MPAS) and the Edinburgh Postnatal Depression Scale (EPDS) were used to collect data. The correlation between EENC implementation and breastfeeding, maternal-infant attachment, postpartum depression, and other maternal and neonatal outcomes was analyzed.

Results: Mother-newborn pairs (N = 157) were enrolled in this study, 78 in the EENC group and 79 in the control group. A total of 155 (98.8%) were followed up at 14 days, 144 (91.7%) at 42 days, and 123 (78.3%) at 3 months. For the primary outcomes, generalized linear mixed model analysis showed that implementing EENC during cesarean section was beneficial for initiating breastfeeding (OR = 0.021), shortening the breastfeeding initiation time ($\beta = -45.321$), improving the IBFAT scores ($\beta = 2.740$), and enhancing breastfeeding self-efficacy ($\beta = 4.880$). These effects were not influenced by time interaction. However, no difference was observed in the rate of exclusive breastfeeding between these two groups ($P > 0.05$).

Implementing EENC during cesarean section significantly improved maternal-infant attachment ($\beta = 9.668$). Moreover, univariate analysis showed benefits of EENC in improving postpartum depression ($P < 0.001$) and decreasing maternal perinatal blood loss ($P < 0.05$).

Conclusions: According to our small sample study, there is a trend of improvement in breastfeeding related behavior and maternal infant attachment in women who received EENC during cesarean deliveries. The effects of EENC on exclusive breastfeeding should be further explored in the future.

Indian Pediatr. 2025 Feb 15;62(2):116-120.

doi: 10.1007/s13312-025-3374-6.

One Milligram Versus Two Milligram Intramuscular Vitamin K to Prevent Late-Onset Hemorrhagic Disease in Young Infants: A Randomized Controlled Trial

[Amala Srilatha Natarajan¹](#), [C G Delhikumar²](#), [G P Senthil Kumar³](#), [Nivedita Mondal¹](#), [R Sasirekha⁴](#)

Abstract

Objective: To compare the efficacy of a standard dose (1 mg) with 2 mg vitamin K administered by intramuscular (IM) route in reducing subclinical late-onset vitamin K deficiency bleeding (VKDB) assessed using serum protein induced by vitamin K absence (PIVKA II) levels.

Methods: This was an open-labeled randomized controlled trial that enrolled healthy term neonates delivered vaginally. Neonates delivered to mothers receiving antiepileptics, anti-tuberculous drugs, or warfarin, and those with a family history of bleeding disorder were excluded. Participants were randomized to receive either 1 or 2 mg of vitamin K1 (Phytomenadione) IM at birth. PIVKA II was measured in the cord blood and at 30 and 72 days after birth by ELISA method. PIVKA II level >100 ng/mL was labeled as subclinical VKDB.

Results: Forty-one neonates were recruited in each arm. On the 30 days follow-up visit 9 infants (4 in 1 mg group; 5 in 2 mg group) were lost to follow-up. All babies had PIVKA II levels >100 ng/mL at birth. The median PIVKA II values (ng/mL) in the 1 mg group were 827.68 (cord blood), 678.80 (30 days), and 644.10 (72 days). The corresponding levels (ng/mL) in the 2 mg group were higher, viz., 770.55, 726.35, and 693.14 ng/mL; $P > 0.05$ for all comparisons. PIVKA II level in the 1 mg group reduced significantly on 72 days of life compared to that observed at birth (cord blood) ($P = 0.012$). However, the fall in 2 mg group was not statistically significant.

Conclusion: There was no difference in PIVKA II levels between neonates receiving 1 mg or 2 mg vitamin K IM suggesting a similar risk for late-onset VKDB in both groups.

Avoiding hypothermia

Pediatr Res. 2024 Jul;96(1):190-198.

doi: 10.1038/s41390-024-03115-5. Epub 2024 Mar 5.

[Temperature probe placement in very preterm infants during delivery room stabilization: an open-label randomized trial](#)

[Pranav R Jani^{#12}](#), [Rajesh Maheshwari^{#34}](#), [Hannah Skelton³⁵](#), [Patricia Viola³](#), [Sheela Thomas³](#), [Lynette Ryder⁶](#), [Mihaela Culcer³⁴](#), [Umesh Mishra³⁴](#), [Swapnil Shah³⁴](#), [Jane Baird³](#), [James Elhindi⁴⁷](#), [Ann-Maree Padernia³](#), [Traci-Anne Goyen³](#), [Daphne D'Cruz³](#), [Melissa Luig³](#), [Dharmesh Shah³⁴](#)

Abstract

Background: Variation in practice exists for temperature probe positioning during stabilization of very preterm infants (<32 weeks gestation). We explored the influence of temperature probe sites on thermoregulation.

Methods: An open-label, stratified, balanced, parallel, randomized trial was conducted. Inborn infants were randomly assigned temperature probe to the axilla or to the upper back. The primary outcome was normothermia (local range: 36.8-37.3 °C and World Health Organization (WHO) range: 36.5-37.5 °C) at admission to the neonatal intensive care unit.

Results: Between 1 November 2018 and 4 July 2022, 178 infants were randomly assigned to one of the two sites (n = 89 each), 175 included in the final analysis. Normothermia (local

range) was achieved for 39/87 infants (44.8%) assigned to the upper back compared to 28/88 infants (31.8%) assigned to the axilla [risk difference:13%; 95% CI -1.3-27.3]. Normothermia (WHO range) was achieved for 78/87 infants (89.7%) assigned to the upper back compared to 70/88 infants (79.6%) assigned to the axilla [risk difference:10.1%; 95% CI -0.5-20.7]. No infant recorded temperatures >38 °C or developed skin injury.

Conclusions: In very preterm infants, upper back site was equally effective as the axilla in maintaining normothermia, with no increase in adverse events.

Clinical trial registration: The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12620000293965).

Impact: Substantial variation in practice exists for the site of securing a temperature probe during delivery room stabilization of very preterm infants and the influence of temperature probe site on thermoregulation remains unknown. In this study, upper back site was equally effective as the axilla in maintaining normothermia, with no increase in adverse events. Clinicians could adopt upper back site for maintaining normothermia. This study may contribute data to future international participant data prospective meta analysis of randomized controlled trials worldwide on temperature probe positioning in very preterm infants, increasing translation of research findings to optimize thermoregulation and clinical outcomes.

Avoiding hypoglycaemia

Cord management

Zhonghua Yi Xue Za Zhi. 2024 Aug 20;104(32):3042-3049.

doi: 10.3760/cma.j.cn112137-20240621-01378.

[The application of cut-umbilical cord milking in term cesarean deliveries for preventing anemia and iron deficiency of newborns](#)

[Q F Song¹](#), [Y Xiong²](#), [K Y Si³](#), [Q Y Du⁴](#), [H H Zhou⁵](#), [Y B Zhou¹](#), [H T Li⁶](#), [J M Liu⁶](#)

Abstract

Objective: To analyse the efficacy and safety of cut-umbilical cord milking (C-UCM) compared with immediate cord clamping in preventing anemia and iron deficiency among term cesarean-delivered newborns. **Methods:** A total of 485 pregnant women planning to deliver by cesarean section were recruited in this randomized controlled trial in Hunan Maternal and Child Health Hospital and Liuyang Maternal and Child Health Care Hospital from July 2016 to April 2019. A block randomization was conducted to evenly allocate them to the controlled group and the C-UCM group. In the controlled group, the cord was clamped within 30 seconds as routine. In the C-UCM group, the cord was first clamped at 25 cm from the newborn's navel, and then the blood in the cord was gently squeezed into the newborn's body until the cord became white and shriveled. The cord was clamped twice at 2-3 cm from the newborn's navel subsequently. Neonatal jaundice, hyperbilirubinemia and polycythemia were monitored before discharge. After the newborns discharged, their hemoglobin, red blood cell count, hematocrit (at the age of 1, 6 and 12 months) and serum ferritin (at the age of 6 and 12 months) were followed up; body length and weight were measured; and information about their feeding and iron supplementation were collected (at the age of 1, 6, 12 and 18 months). The two groups were compared by *t* test, Mann-Whitney *U* test, χ^2 test, or

Fisher exact probability method. The hospital was set as a random item, and the mixed effects regression model was used to evaluate the effect of C-UCM on relevant indicators of cesarean-delivered newborns. **Results:** There were 244 women in the C-UCM group with an average age of (31.9±4.4) years, and 241 in the control group with an average age of (31.8±4.2) years ($P>0.05$). There was no statistically significant difference between the C-UCM group and the control group at 1, 6 and 12 months of age in hemoglobin [(123.6±14.5) vs (122.2±14.5) g/L, (115.3±9.4) vs (114.1±8.5) g/L, (115.6±9.6) vs (116.1±12.6) g/L] or anemia incidence rate [15.2% (17/112) vs 18.4% (19/103), 22.7% (34/150) vs 26.8% (44/164), 22.3% (25/112) vs 19.5% (22/113)] (all $P>0.05$). There was no statistically significant difference between the two groups at 6 and 12 months of age in serum ferritin [$M(Q_1, Q_3)$, 39.9 (24.9, 61.8) vs 43.6 (25.2, 100.9) µg/L, 40.3 (25.4, 259.2) vs 40.3 (26.4, 167.6) µg/L] or iron deficiency incidence rate [6.1% (5/82) vs 4.2% (3/72), 6.7% (5/75) vs 3.8% (3/80)] (all $P>0.05$). There were also no significant difference between the two groups in other indicators, such as the Z-score of weight-for-length, the incidence of neonatal jaundice, and the incidence of neonatal hyperbilirubinemia (all $P>0.05$). After adjusting for the relevant covariates, there were still no significant effects of C-UCM on these outcomes above. **Conclusions:** Compared to immediate cord clamping, the intervention of gently squeezing 25 cm of the cord does not significantly reduce the risk of anemia or iron deficiency in term cesarean-delivered newborns, nor does it have a significant impact on infant growth and development. Yet this intervention does not increase the risk of jaundice or hyperbilirubinemia in newborns as well.

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"Serum ferritin levels in newborns at 3 months of life after intact umbilical cord milking versus delayed cord clamping"-a randomized controlled trial

[Bhavana Koppad¹](#), [Charkala Rajkumar²](#), [Anita Nyamagoudar³](#), [Manjunath Hukkeri⁴](#), [Kanchibhotla Meghana⁴](#), [Mrutyunjaya B Bellad⁴](#)

Abstract

The objective of the study was to compare the serum ferritin levels (by chemiluminescence immunoassay) among two groups of newborns with intact umbilical cord milking (UCM) versus delayed cord clamping (DCC) at the 3rd month of life. Randomized controlled trial, unblinded, parallel group was conducted at tertiary care referral unit in South India after obtaining informed consent from eligible mothers in late preterm gestation and beyond, and the newborn babies were randomized into two groups by computer-generated sequence (SNOSE method) with two modes of umbilical cord management UCM and DCC. A total of 190 mothers were enrolled, and they were randomized into two arms: DCC group (n = 95) and UCM group (n = 95). Of these 190 mothers who were enrolled, the intervention was done for 180 babies, i.e., DCC (n = 92) and UCM (n = 88). Follow-up with serum ferritin was done for 108 babies. DCC-63 and UCM-45. Ferritin levels measured at 3 months of life showed comparable results, i.e., mean ferritin levels in the DCC group was 258.07 ng/ml and in the UCM group was 248.44 ng/ml, with a mean difference of - 9.63 (p 0.72).

Conclusion: Both UCM and DCC resulted in comparable levels of serum ferritin at 3 months of life, implying that a similar amount of placental transfusion occurs in both the groups. UCM is a feasible alternative to prevent anemia during infancy as compared to DCC when the latter cannot be done due to undue limitation.

Analgesia in newborn care

Neonatal sepsis

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[Efficacy of short-course antibiotics for culture-positive neonatal sepsis: A systematic review and meta-analysis](#)

[Poonam Singh](#)¹, [Mayank Priyadarshi](#)¹, [Suman Chaurasia](#)¹, [Sriparna Basu](#)¹

Abstract

Sepsis is a common cause of neonatal mortality and morbidity. Though antibiotics are the mainstay of treatment in culture-positive neonatal sepsis, the dilemma persists for the optimum duration of antimicrobial therapy. The present study aimed to evaluate the efficacy of short-course antibiotics for uncomplicated culture-positive neonatal sepsis. This systematic review and meta-analysis (PROSPERO: CRD42023444899) identified, appraised, and synthesised the available evidence from randomised and quasi-randomised controlled trials related to the efficacy of short-course (7-10 days) versus standard-course (14 days) antibiotics for uncomplicated culture-positive neonatal sepsis on the rate of treatment failure, mortality, duration of hospitalisation, morbidities including antibiotics-related adverse events, long-term neurodevelopmental outcomes and cost analysis. Data were pooled using RevMan 5.4 software. Certainty of evidence (COE) for predefined outcomes was analysed by GRADE. Available evidence showed no significant difference in the rate of treatment failure between 7- to 10-day versus 14-day antibiotics courses [risk ratio (95% confidence interval, CI), 2.45 (0.93-6.47), $I^2 = 0\%$, six studies, $n = 573$, very low COE]. No incidence of death was reported in either treatment arm in the two included studies. Duration of hospitalisation was significantly shorter with the short-course antibiotics arm compared to standard-course [mean difference (95% CI), -3.88 (-4.22 to -3.54) days, $I^2 = 0\%$, five studies, $n = 507$, low COE]. Morbidities reported in the three studies were similar. Other outcomes were not reported. To conclude the evidence is very uncertain about the effect of short-course antibiotic regimen, compared to a standard-course, on the treatment failure rate in uncomplicated culture-positive neonatal sepsis. Adequately powered trials with outcomes including death and long-term neurodevelopmental impairment are needed.

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[Antiseptic efficacy and plasma chlorhexidine levels following two different methods of application of 1% aqueous chlorhexidine gluconate for skin disinfection in preterm newborns: a randomized controlled trial](#)

[Richie Dalai](#)¹, [Sarita Mohapatra](#)², [Thirumurthy Velpandian](#)³, [Jeeva Sankar](#)¹, [Anu Thukral](#)¹, [Ankit Verma](#)¹, [Minu Bajpai](#)⁴, [R Dhinakaran](#)¹, [Mohammad Tousifullah](#)¹, [Ramesh Agarwal](#)⁵

Abstract

Objective: Many neonatal units have started using Chlorhexidine gluconate for neonatal skin antisepsis. However, there is in-vitro evidence of inhibition of neurite growth. The current

study aimed to compare two methods of its local application, for the extent of systemic absorption and antiseptic efficacy.

Study design: Parallel group, blinded, randomised trial, at a Level III, neonatal intensive care unit. Between December 2020 to July 2022, neonates from 28 to 34 weeks gestation, were randomized to local skin antiseptics by either- (a) 1% aqueous chlorhexidine (CHG aq) followed by cleansing off the residual agent with sterile water swab (Cleansing group) or (b) 1% CHG aq followed by air drying (No cleansing group). The outcome measures were the proportion of post antiseptics skin swabs with no/insignificant growth, and the plasma chlorhexidine levels.

Results: Of the total of 457 enrollments (Cleansing: n = 230; No Cleansing: n = 227), 216 (93.91%) in "Cleansing" vs. 221 (97.36%) in "No cleansing" (risk difference -3.45%, 95% CI -7.2 to 0.28%; p = 0.072) had no/insignificant growth post-antiseptics. The lower bound of the confidence interval crossed the pre-specified non-inferiority limit of 5%. The median (IQR) plasma chlorhexidine levels were not significantly different between the two groups (7.9 (5.6, 17.9)) ng/mL in Cleansing vs. 6.5 (4.6, 17.7) in No cleansing groups (p = 0.437).

Conclusion: Cleansing with sterile water after application of chlorhexidine in preterm neonates was not shown to be non-inferior compared to no cleansing, for skin antiseptics efficacy. Systemic absorption occurred to a similar extent despite cleansing off the residual agent.

Ital J Pediatr. 2025 Feb 27;51(1):61.

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Micafungin versus Amphotericin B in treatment of invasive fungal infection in preterm neonates: a randomized control trial

[Mariam John Amin Ibrahim¹](#), [Marwa Saad Mohammed Fathy²](#), [Mertte Ashraf Thabet Ghobrial³](#), [Maha Hassan Mohamed⁴](#)

Abstract

Background: Micafungin, Amphotericin B, and Fluconazole are the primary therapeutic agents employed to address invasive fungal candidiasis in neonates. Resistance to fluconazole is gradually developing in neonatal intensive care units. We aimed to conduct a comparative analysis of Micafungin and Amphotericin B in terms of their effectiveness and safety in the treatment of invasive fungal infections in neonates.

Methods: Fifty-six preterm neonates with invasive fungal infection proven by fungal culture and who had received fluconazole for at least one week were included in our study and were divided randomly into two groups. Micafungin group: twenty-eight preterms received Micafungin at a dose of 8 mg/kg/day for 14 days. Amphotericin B group: twenty-eight preterms received amphotericin B at a dose of 1 mg /kg/day for 14 days. Clinical and laboratory follow up by fungal culture were performed after 14 days.

Results: Neonates in the Micafungin group showed significant increased percentage for complete cure of the fungal infection compared to Amphotericin B group 18(64.3%) vs. 10(35.7%) respectively and decreased percentage of incomplete cure 10(35.7%) vs. 18(64.3%) respectively with p-value 0.030. A higher percentage of neonates were completely cured for both candida albicans (65.2%) and non-albicans (60%) in the micafungin group. Duration of respiratory and circulatory support was significantly shorter also. No additional drug side effects were observed with Micafungin except for mild hypomagnesemia. There was an increase in blood urea nitrogen with Amphotericin B.

Conclusion: Micafungin is effective and well tolerated for the treatment of invasive fungal infections in preterm neonates.

Low birth weight and prematurity

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[Safety and efficacy of extended expectant management in preterm premature rupture of membrane between 32 and 34 weeks of pregnancy-A randomization control trial](#)

[Deepti Ghosh¹](#), [Pramila Jena²](#), [Partha Sarathi Sahu³](#), [Deepti Damayanty Pradhan⁴](#), [Jyochnamayi Panda⁵](#), [Bandita Panda⁶](#)

Abstract

Background: Cases of preterm premature rupture of membranes (PPROM) occur in approximately 3 % of pregnancies and are a significant contributor to preterm birth and its associated complications. Traditionally expectant management followed by delivery at 34 weeks is the recommended standard for treatment of PPRM but recent evidence suggests that extended expectant management in selected cases improves the pregnancy outcome. Thus the study aims to compare the fetomaternal outcome in PPRM cases between traditional management (delivery at 34 weeks) and extended expectant management (delivery at 36 weeks) **METHODOLOGY:** Women presenting to labor emergency with leakage due to membrane rupture at 32 to 34 weeks of gestation were randomly assigned as per CONSORT guidelines into two groups, group A (n = 72) with traditional treatment and group B (n = 72) with extended expectant management. The pregnancy outcomes and fetomaternal outcomes of both groups were analyzed by appropriate statistical tools.

Results: Out of a total of 144 cases with comparable baseline characteristics, 72 patients in group A had the mean gestational age at delivery was 34.02 weeks and in group B it was 35.02 weeks. There is no significant increase in chorioamnionitis and other maternal morbidity in group B. The mean birth weight was significantly higher in group B patients. The median duration of NICU stay, need for mechanical ventilation and complications like neonatal jaundice and necrotizing enterocolitis were significantly lower (p-value < 0.05) in Group B as compared to Group A reflecting a better perinatal outcome.

Conclusion: Extended expectant management can safely be considered in PPRM cases till 36 weeks based on the timing of onset of PPRM without the fear of increased risk of maternal chorioamnionitis and adverse neonatal outcomes.

Ultrasound Obstet Gynecol. 2025 Jun 2.

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[Aspirin delays preterm birth in pregnancies at high risk for preterm pre-eclampsia: evidence from randomized clinical trial in Asia](#)

[H H Y Leung¹](#), [I Papastefanou²](#), [Y Chen¹](#), [L Nguyen-Hoang^{1,3}](#), [D-A Nguyen⁴](#), [L T Dinh⁴](#), [R K Pooh⁵](#), [A Shiozaki⁶](#), [M Zheng⁷](#), [Y Hu⁸](#), [Y Wu⁹](#), [A Kusuma¹⁰](#), [P Yapan¹¹](#), [A Gosavi¹²](#), [A Sekizawa¹³](#), [S Luewan¹⁴](#), [T-Y Chang¹⁵](#), [N Chaayasit¹⁶](#), [T Nanthakomon¹⁷](#), [H Liu¹⁸](#), [S W Shaw¹⁹](#), [W](#)

[C Leung²⁰](#), [A S Mohamad²¹](#), [A Aguilar²²](#), [S L Lau¹](#), [N M W Lee¹](#), [J Lin¹](#), [D S Sahota¹](#), [M K C Chong²³](#), [L C Poon¹](#)

Abstract

Objectives: To investigate the impact of aspirin administration on the incidence of preterm birth, according to the type of delivery and gestational age at preterm birth, and to examine the hypothesis that aspirin delays preterm delivery.

Methods: This was a secondary analysis of a multicenter stepped-wedge cluster randomized trial of a first-trimester screen-and-prevent strategy for preterm pre-eclampsia (PE), which included 18 maternity/diagnostic units in 10 regions across Asia between 1 August 2019 and 28 February 2022. Women deemed to be at high risk for preterm PE according to a Bayes' theorem-based triple test, i.e. those with an adjusted risk for preterm PE of ≥ 1 in 100, received low-dose aspirin from < 16 weeks until 36 weeks' gestation. Outcome measures were the incidence of early preterm birth (24 + 0 to 31 + 6 weeks' gestation) and late preterm birth (32 + 0 to 36 + 6 weeks). The treatment effect of aspirin on the rate of preterm birth, stratified by gestational age at birth, type of delivery and presence of pregnancy complications, was estimated by computing the relative risks (RR) between the aspirin and non-aspirin groups with their 95% CIs. A shift model was designed to evaluate the effect of aspirin on preterm birth, based on the hypothesis that aspirin delays a preterm birth to a more advanced gestational age.

Results: In the randomized trial, 42 897/48 647 women accepted screening for preterm PE. Following exclusions, 10 294 and 27 965 women were included in the non-intervention and intervention phases, respectively. Of the 4688 women at high risk for preterm PE, 2909 (62.05%) received aspirin in the trial. Aspirin was associated with a 42% reduction in the risk of early preterm birth (adjusted relative risk (aRR), 0.577 (95% CI, 0.380-0.852)), and there was a significant upward trend in the rate of late preterm birth accordingly (test for trend, $P < 0.01$). Similar findings were observed for iatrogenic preterm birth and pregnancies with a small-for-gestational-age neonate. Additionally, aspirin was associated with a 60% reduction in the risk of iatrogenic early preterm birth in pregnancies with PE (aRR, 0.398 (95% CI, 0.192-0.788)). However, aspirin did not have a significant effect on iatrogenic late preterm birth in pregnancies with PE. Aspirin significantly delayed early preterm birth, with the effect decreasing by 0.26 (95% credibility interval, -0.40 to -0.05) weeks for each week of advancing gestation. At 24 weeks, aspirin delayed delivery by 3.63 weeks, while at 37 weeks, the delay was only 0.25 weeks.

Conclusions: This secondary explanatory analysis found that early administration of aspirin could effectively reduce the risk of early preterm birth in women at high risk for preterm PE. While the reasons for preterm birth are often multifactorial, this study provides greater insight into the relationship between aspirin and different types of preterm birth at different gestational ages. Our findings support the hypothesis that aspirin helps to prevent preterm birth by delaying the timing of delivery, with a greater impact observed for deliveries that would have occurred at an earlier gestational age had aspirin not been administered.

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[**Effect of kangaroo mother care on cerebral oxygenation, physiological parameters, and comfort levels in late-premature infants: A randomized controlled trial**](#)

[Fatma Tas Arslan¹](#), [Sevinc Akkoyun²](#), [Sibel Küçükoğlu¹](#), [Deniz Kocoglu-Tanyer¹](#), [Murat Konak³](#), [Hanifi Soylu³](#)

Abstract

Objective: To measure the effects kangaroo mother care (KMC) on the regional cerebral oxygen saturation (rSO₂) measured with near-infrared spectroscopy (NIRS) in premature infants and to study the physiological stability and comfort of the infants during such interventions.

Design: This was a prospective, single-centered, single-blind, 2-arm, parallel-group randomized controlled trial conducted.

Settings: The study was carried out in a tertiary neonatal intensive care unit in Medical Faculty Hospital in Konya/Turkey.

Participants: Premature infants born between 24 and 36⁺⁶ weeks. Participants were randomly assigned to one of two groups: kangaroo care (n = 20) and control groups (n = 20). The rSO₂, oxygen saturation (%SpO₂), heart rate (HR), respiratory rate, body temperature, and comfort levels of the infants were evaluated in three stages.

Findings: In the 60th min measurement of the intervention group, rSO₂, body temperature, heart rate, respiratory rate, and, comfort level, the comfort level was found to be higher and significant in the 30th and 60th min measurements (p < 0.001). In the intervention group, the rSO₂ (p < 0.001), body temperature (p < 0.001), HR (p < 0.001), SpO₂ (p < 0.001), respiratory rate (p < 0.001), and comfort levels (p < 0.001) scores with the control group and the group × time interaction was significant.

Key conclusions: KMC moderately increased the rSO₂ levels and also created a moderate effect size on the physiological parameters and comfort levels of the newborns, which implicates its short-term benefits for premature infants.

Practice implications: KMC may be beneficial in stabilizing rSO₂ and physiological parameters and increasing comfort in premature infants.

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[Effect of kangaroo mother care in low birth weight infants on human milk intake: a randomized controlled trial](#)

[Bireshwar Sinha¹](#), [Sarmila Mazumder²](#), [Archana Thakur²](#), [Sarita Devi³](#), [Deepak More²](#), [Per Ashorn⁴](#), [Halvor Sommerfelt⁵](#), [Anura Kurpad³](#), [Nita Bhandari²](#)

Free article

Abstract

Background: It is plausible that one of the key biological pathways through which kangaroo mother care (KMC) improves health outcomes in low birth weight (LBW) infants is by enhancing human milk intake and quality. This hypothesis needs to be tested.

Objectives: This study aims to estimate the effect of promotion and support of KMC in LBW infants compared with control during the neonatal period on human milk intake and human milk components.

Methods: We randomly assigned 550 LBW infants (1500-2250 g) to the intervention arm with promotion of and support for continuous skin-to-skin contact and exclusive breastfeeding through home visits or to no such intervention (control) during the neonatal period. All infants received routine home-based postnatal care visits. We estimated human milk intake

by the infant over a 14-d period using the deuterium dilution technique and measured the concentration of carbohydrate, protein and amino acids, fat, lactoferrin, and secretory immunoglobulin A (sIgA) in human milk of a subsample of 250 mothers.

Results: The mean infant human milk intake was 331 ± 144 g/d or 142 ± 57 g/kg/d in the control arm and 368 ± 135 g/d or 154 ± 50 g/kg/d in the intervention arm participants, yielding a mean difference of 37 [95% confidence interval (CI): 12, 63] g/d or 12 (95% CI: 2, 22) g/kg/d. The mean concentration of carbohydrate in human milk in the intervention arm was 51.2 ± 6.1 g/L against 50 ± 6.8 g/L in the control arm. The corresponding values for protein were 15.0 ± 2.9 g/L and 16.3 ± 4.6 g/L, respectively. We did not find any substantial differences in the concentration of amino acids, fat, lactoferrin, or sIgA between the study arms.

Conclusions: Our findings show that KMC is associated with a substantially higher human milk intake in LBW infants during the neonatal period. There was no evidence of any effect of KMC on the concentration of several human milk components

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doi: 10.1016/S2352-4642(25)00130-0. Epub 2025 May 26.

All-cause mortality and infection-related outcomes of hospital-initiated kangaroo care versus conventional neonatal care for low-birthweight infants: a systematic review and meta-analysis

[Chiara Minotti¹](#), [Kerstin Jost²](#), [Soheila Aghlmandi³](#), [Chloé Schlaeppli⁴](#), [Elske Sieswerda⁵](#), [C Henri van Werkhoven⁶](#), [Sven M Schulzke⁷](#), [Julia A Bielicki⁴](#)

Abstract

Background: Kangaroo care has a well-established role in preterm infant stabilisation and in protecting low-birthweight newborns from mortality. Yet kangaroo care is far from fully embedded in conventional inpatient neonatal care practice. The evidence on infection outcomes of hospital-initiated kangaroo care is unclear. We aimed to evaluate the existing evidence to understand the role of hospital-initiated kangaroo care in preventing mortality, sepsis, and invasive infection in low-birthweight infants.

Methods: In this systematic review and meta-analysis, we searched Embase, MEDLINE, Cochrane Library, and Web of Science databases for literature published between Jan 1, 2013, and Feb 26, 2025. At least two authors independently undertook study selection, data extraction, and quality assessment. Reports of randomised controlled trials presenting data on at least one of our set primary outcomes (all-cause mortality and/or sepsis and/or invasive infection) comparing kangaroo care with conventional neonatal care in low-birthweight infants (<2500 g) were eligible for inclusion. The primary outcomes were all-cause mortality, sepsis, and invasive infection (composite of necrotising enterocolitis, pneumonia, meningitis, and other severe infections). Hypothermia and apnoea were assessed as adverse events. A random effects model was used to estimate the pooled overall effect sizes for each outcome, presented as odds ratios (OR [95% CI]), with between-study heterogeneity assessed by Cochran's Q test and sources of heterogeneity investigated using univariable random effects meta-regression analyses. This study is registered with PROSPERO, CRD42024501546.

Findings: We synthesised data from 29 studies, mainly from lower-middle income countries, including 17 513 low-birthweight infants. Most studies were moderate-to-high quality. 25 (86%) of 29 studies reporting all-cause mortality were included in the meta-analysis of

hospital-initiated kangaroo care, which showed that hospital-initiated kangaroo care reduced all-cause mortality (pooled OR 0.77 [95% CI 0.67-0.89]; high-quality evidence, with $I^2=0\%$). 17 (59%) of 29 trials reported sepsis as an outcome, and the pooled results showed that kangaroo care reduced the odds of sepsis (OR 0.55 [95% CI 0.37-0.82]; moderate-quality evidence, with $I^2=53\%$). Similarly, among the 11 (38%) of 29 studies reporting invasive infection, the pooled results showed that kangaroo care reduced the odds of invasive infection (OR 0.49 [95% CI 0.33-0.74]; moderate-quality evidence, with $I^2=0\%$). Kangaroo care was associated with a significant reduction in the odds of sepsis-related or invasive infection-related mortality (OR 0.63 [95% CI 0.47-0.84], $I^2=0\%$, high-quality evidence), hypothermia (0.28 [0.16-0.46], $I^2=72\%$, moderate-quality evidence), and apnoea (0.46 [0.25-0.85], $I^2=45\%$, moderate-quality evidence). Meta-regression showed that between-study heterogeneity was due to variation in level of kangaroo care offered as part of conventional neonatal care.

Interpretation: The joint protective effect of hospital-initiated kangaroo care against all-cause mortality and infection in low-birthweight infants reinforces its importance in routine neonatal care across settings, in line with WHO recommendations. The extent of the protective effects in low-birthweight infants through averted infections suggests that kangaroo care should be integrated into standard infection prevention and control practice globally.

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Magnesium sulfate for fetal neuroprotection in preterm labor: an updated systematic review and meta-analysis of randomized controlled trials

[Uzair Jafar^{#1}](#), [Ahmad Nawaz^{#2}](#), [Muhammad Zain Ahmad Zahid³](#), [Samavia Saddiqah⁴](#), [Fakiha Zainab²](#), [Shaharyar Naeem²](#), [M Uzair Siddique²](#), [Momina Butt²](#), [Andrea Etrusco⁵](#), [Mislav Mikuš⁶](#), [Antonio Simone Laganà⁵](#)

Abstract

Objective: Antenatal magnesium sulfate has been reported to reduce the risk of neurological impairment in fetuses born to women at risk of preterm labor. However, the evidence to support its use is conflicting. We conducted this meta-analysis to assess the efficacy and safety of magnesium sulfate in women at risk of preterm labor as new research is available from RCTs giving insights into MgSO₄ treatment among differing gestational age groups.

Study design: We searched various electronic databases, including MEDLINE (via PubMed), Embase, the Cochrane Library, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform portal from 1990 till 31st March 2024 to retrieve all randomized controlled trials (RCTs) that investigated the use of magnesium sulfate in women at risk of preterm labor with or without intent of fetal neuroprotection. We used the revised Cochrane Risk of Bias tool (RoB 2.0) to assess the quality of the included randomized controlled trials. RevMan 5.4 was used to conduct all statistical analyses using a random-effects model. Our Meta-analysis was registered with the PROSPERO International Register of Systematic Reviews (CRD42024532421).

Results: Our meta-analysis including eight RCTs showed that magnesium sulfate reduced the risk of cerebral palsy without a significant change in pediatric mortality. The change was

evident in moderate to severe cerebral palsy. Magnesium sulfate showed no beneficial effect in most of the secondary outcomes.

Conclusions: This meta-analysis found antenatal magnesium sulfate reduces the risk of cerebral palsy with no difference in pediatric mortality between the magnesium or no magnesium treatment groups, which is a positive finding. However, there is still substantial heterogeneity between the studies, so there is a need for further exploration and discussion. The implications of this review include a concern for developing nations where resources and availability of magnesium sulfate are limited. Hence, further studies are needed to determine the exact dosage, timing, and whether maintenance dosage of magnesium sulfate is required or not and for how long.

JAMA Netw Open. 2024 Jul 1;7(7):e2421896.

doi: 10.1001/jamanetworkopen.2024.21896.

Parent-Guided Developmental Intervention for Infants With Very Low Birth Weight: A Randomized Clinical Trial

[Rita C Silveira^{1,2}](#), [Nadia C Valentini²](#), [T Michael O'Shea³](#), [Eliane W Mendes^{1,2}](#), [Graciela Froes¹](#), [Lenir Cauduro¹](#), [Carolina Panceri^{1,2}](#), [Rubia N Fuentefria¹](#), [Renato S Procianoy^{1,2}](#)

Abstract

Importance: Early interventions improve neurodevelopmental outcomes after preterm birth, but few studies of early intervention have focused on preterm infants whose families reside in low- or middle-income countries (LMICs).

Objective: To evaluate whether parent-guided early intervention improves the neurodevelopmental outcomes of preterm infants in an LMIC.

Design, setting, and participants: This randomized clinical trial was performed at a high-risk obstetric referral hospital in Brazil, with outcome evaluations by examiners masked to randomization group. Eligibility criteria were (1) birth at the study hospital, (2) residence within 40 km of the birth hospital, and (3) gestational age of less than 32 weeks or birth weight of less than 1500 g. Of 138 enrolled infants, 19 died after randomization and 19 withdrew from the study; all other enrollees (50 per randomization group) were evaluated for the primary outcome. Data were collected from January 1, 2016, to May 31, 2022, and analyzed from June 10 to July 31, 2022.

Interventions: On postnatal day 7, infants were randomized to usual care, consisting of support for lactation, kangaroo care, and routine developmental therapies, or to a parent-guided enhanced developmental intervention, consisting of usual care plus infant massage and enhanced visual stimulation, auditory stimulation, social interactions, and support for motor development, instructed by developmental therapists.

Main outcomes and measures: The primary outcome was the Bayley Scales of Infant and Toddler Development-Third Edition score at 18 months of age adjusted for prematurity.

Results: Among the 100 infants included in the analysis, mean (SD) gestational age was 28.4 (2.2) weeks, and 57 (57%) were male. The mean (SD) gestational age for the intervention group was 28.3 (2.3) weeks; for the usual care group, 28.5 (2.2) weeks. Female infants accounted for 21 infants (42%) of the intervention group and 22 (44%) of the usual care group; male infants, 29 (58%) and 28 (56%), respectively. The enhanced developmental

intervention group had higher cognitive scores at 18 months of corrected age (mean [SD], 101.8 [11.9] vs 97.3 [13.5]; mean difference, 4.5 [95% CI, 0.1-8.9]).

Conclusions and relevance: In this randomized clinical trial of a parent-guided developmental intervention for early cognitive function of very preterm or very low birth weight infants implemented in an LMIC, the intervention improved very preterm infants' neurodevelopmental outcomes at 18 months of adjusted age. Parent-guided early intervention can improve neurodevelopmental outcome of very preterm infants born in LMICs.

Indian J Pediatr. 2025 Apr;92(4):376-382.

doi: 10.1007/s12098-023-04989-9. Epub 2024 Jan 11.

Comparative Growth Outcomes in Very Low Birth Weight Infants: Evaluating Different Feeding Strategies

[Mounika Pedaveeti¹](#), [Faiza Iqbal¹](#), [Jayashree Purkayastha¹](#), [Shruthi K Bharadwaj²](#), [Anand Kumar Patil²](#), [Leslie Edward S Lewis³](#)

Abstract

Objectives: To assess the growth pattern of preterm, very low birth weight (VLBW) appropriate for gestational age (AGA) infants on three different feeding regimens.

Methods: This prospective open label three-arm parallel randomized controlled trial was conducted at neonatal intensive care unit, Kasturba Hospital, Manipal. One hundred twenty VLBW (weight between 1000-1500 g and gestational age 28-32 wk) preterm AGA infants admitted from April 2021 through September 2022 were included. Three feeding regimens were compared: Expressed breast milk (EBM); EBM supplemented with Human milk fortifier (HMF); EBM supplemented with Preterm formula feed (PTF). Primary outcome measure was assessing the growth parameters such as weight, length, head circumference on three different feeding regimens at birth 2, 3, 4, 5 and 6 wk/discharge. Secondary outcomes included incidence of co-morbidities and cost-effectiveness.

Results: Of 112 infants analyzed, Group 2 supplemented with HMF showed superior growth outcomes by 6th wk/discharge of intervention, with mean weight of 2053±251 g, mean length of 44.6±1.9 cm, and mean head circumference of 32.9±1.4 cm. However, infants in Group 3, supplemented with PTF, registered mean weight of 1968±203 g, mean length of 43.6±2.0 cm, and mean head circumference of 32.0±1.6 cm. Infants exclusively on EBM presented with mean weight of 1873±256 g, mean length of 43.0±2.0 cm and mean head circumference of 31.4±1.6 cm.

Conclusions: Addition of 1 g of HMF to 25 ml of EBM in neonates weighing 1000-1500 g showed better weight gain and head circumference at 6 wk/discharge, which was statistically significant. However, no significant differences in these parameters were observed at postnatal or 2, 3, 4, and 5 wk.

BMC Public Health. 2024 Sep 11;24(1):2476.

doi: 10.1186/s12889-024-19969-7.

Effectiveness of a home-based, post-discharge early intervention program for very preterm infants in reducing parental stress: a randomized controlled trial

[Juan Fan¹](#), [Ruiyun He¹](#), [Shasha He¹](#), [Mei Yang¹](#), [Xiaojun Tao¹](#), [Mei Zhou¹](#), [Xiong Gao¹](#), [Weihong Yu²](#), [Jianhui Wang³](#)

Abstract

Background: This study aims to evaluate the impact of a home-based, post-discharge early intervention (EI) program on reducing parental stress levels in families with preterm infants born between 28⁺⁰ and 31⁺⁶ weeks gestational age.

Methods: A randomized controlled trial was conducted, with families randomly allocated to either the EI or standard care (SC) group. A term reference group was also recruited for comparison. The Parental Stress Index-Short Form was used to assess parental stress levels, yielding a total stress score and three subdomain scores. Assessment was performed at baseline, at the 60-day mark of the study, and when the infants reached six corrected months of age. Parents in the reference group were assessed only at six months of corrected age for infants. The intervention comprised three sections: intellectual, physical, and social training, which was administered to the infants in the EI group immediately after discharge and to those in the SC group after 60 days of enrollment.

Results: Seventy-three families were enrolled in this study, with 37 allocated to the EI group, and 36 to the SC group. Prior to intervention, higher stress levels were reported by mothers in both groups than fathers, with no difference observed between the EI and SC groups. Re-assessment performed at 60 days of the study showed that mothers and fathers in the EI group had significantly lower total stress score than those in the SC group (82.00 ± 5.64 vs. 94.26 ± 7.99 , $p < 0.001$; 80.74 ± 7.14 vs. 89.94 ± 9.17 , $p < 0.001$, respectively), which was predominantly due to the lower scores in parental distress and parental-child dysfunction interaction subdomains in the EI group (both had $p < 0.001$). Mothers in the EI group exhibited a more pronounced reduction in total stress score after intervention when compared to fathers (13.15 ± 4.68 vs. 8.26 ± 4.03 , $p < 0.001$). At six months of infant age, the total stress score and subdomain scores of parents in the EI and SC groups were similar, but significantly higher than those of the reference group.

Conclusion: The home-based, post-discharge EI program demonstrated significant effectiveness in reducing parental stress levels among the parents of very preterm infants.

Breastfeed Med. 2024 Sep;19(9):707-714.

doi: 10.1089/bfm.2024.0084. Epub 2024 Jun 21.

[The Effect of Supplemental Feeding Tube Device on Time to Transition to Exclusive Breastfeeding and Discharge: A Randomized Controlled Trial with Preterm Infants](#)

[Ciler Aydin¹](#), [Aynur Aytekin Ozdemir²](#), [Hasan Kahveci³](#)

Abstract

Aim: This study investigated the effect of supplemental feeding tube device (SFTD) method on time to transition to exclusive breastfeeding and discharge time in preterm infants. **Methods:** This randomized controlled trial was conducted in the neonatal intensive care unit of a public hospital in Turkey (Clinical Trial Number: [NCT05815706](#)). The sample consisted of 65 preterm infants randomized into a control ($n = 32$) and an experimental ($n = 33$) group. The experimental group participants were SFTD-fed until they switched to exclusive breastfeeding. The control group participants were fed according to the routine procedure. Data were collected using a questionnaire, a Preterm Infant Monitoring Form, and the LATCH Breastfeeding Assessment Tool. The data were analyzed using numbers,

percentage distributions, means, standard deviations, Pearson's chi-square test, and independent samples *t*-test. The study was approved by an Ethics Committee. Permission was obtained from the hospital. Informed consent was obtained from all parents. **Results:** The experimental group (123.64 ± 63.25 hours) demonstrated an earlier transition to exclusive breastfeeding compared with the control group (187.50 ± 95.30 hours) ($p < 0.05$). The experimental group (361.45 ± 110.46 hours) had significantly shorter hospital stays than the control group (479.25 ± 163.17 hours). The experimental group (35.33 ± 1.14 weeks) had a significantly younger gestational age at discharge than the control group (35.97 ± 1.03 weeks). **Conclusion:** The SFTD is an alternate supportive feeding method that helps preterm infants switch to exclusive breastfeeding sooner, have shorter hospital stays, and have a younger gestational age at discharge than their bottle-fed counterparts.

Reprod Health. 2025 Mar 3;22(1):30.

doi: 10.1186/s12978-025-01965-8.

[Double-blind, non-inferiority, randomized controlled trial of dexamethasone 4, 5 and 6 mg for preventing adverse neonatal and maternal outcomes in very preterm to late preterm pregnancies between 29⁰ and 36⁶ weeks of gestation: study protocol](#)
[Saifon Chawanpaiboon¹](#), [Punnanee Wutthigat²](#), [Sanitra Anuwutnavin³](#), [Sureelak Sutthritpongsa⁴](#)

Abstract

Background: Premature birth poses significant health challenges, including respiratory distress syndrome (RDS). Corticosteroids reduce the incidence of RDS, but higher dexamethasone doses may lead to adverse neonatal outcomes, such as growth restriction and neurodevelopmental issues. Determining the appropriate dose is crucial to balance efficacy and safety. Dexamethasone is inexpensive and widely available in most low- and middle-income countries. This study aims to compare the efficacy and safety of 4-mg, 5-mg and 6-mg dexamethasone in preventing RDS among preterm infants. This trial aims to determine whether lower dexamethasone doses are as effective as the standard dose in preventing RDS in preterm infants. By assessing efficacy and potential adverse outcomes, this study will provide critical insights for optimizing treatment protocols and improving neonatal care.

Methods: This randomized controlled trial will include pregnant women with gestational ages between 29⁰ and 36⁶ weeks admitted to Siriraj Hospital and three secondary centres in Thailand. The participants will be randomly assigned to receive intramuscular dexamethasone at 4 mg, 5 mg or 6 mg, which will be administered every 12 h for a total of four doses over 48 h. The same dose will be used for rescue or repeat courses. The primary outcome will be the incidence of RDS, defined by clinical criteria and confirmed by a neonatologist. The secondary outcomes will include other adverse neonatal and maternal outcomes.

Results: The study requires 1,560 participants, accounting for a 15% loss to follow-up. The data will be analysed via descriptive statistics, chi-squared tests for categorical data, and one-way ANOVA or Kruskal-Wallis tests for continuous data. An independent Data Safety Monitoring Board will conduct interim analyses every 3 months to ensure participant safety and study integrity.

Discussion: This trial addresses the gap in research regarding optimal dexamethasone dosing for preventing RDS in preterm infants. The study will provide evidence on whether

lower doses of dexamethasone (4 and 5 mg) are as effective as the standard 6-mg dose and will examine their potential adverse outcomes. The results will guide adjustments to medical practice guidelines, aiming to align them with clinical practices while ensuring safety and efficacy.

Matern Health Neonatol Perinatol. 2025 Mar 3;11(1):5.

doi: 10.1186/s40748-025-00204-z.

Safety and efficacy of double plastic wrap in reducing insensible water loss in preterm infants in first week of life - a pilot randomized controlled trial from a low-to-middle-income country

[Sreetama Das¹](#), [Somnath Pal²](#), [Syamal Sardar¹](#)

Abstract

Background: Preterm infants experience excessive insensible water loss in postnatal period. Established practices like cling film might not be sufficient alone in reducing this loss. Being expensive, humidified incubators might not be affordable in developing countries. Hence, we tried to explore double plastic wrap (cling film attached to the bassinet wall and occlusive plastic wrap covering the baby) as a low-cost solution of increased insensible water loss in postnatal period.

Methods: In this pilot trial 63 inborn infants of less than 32 weeks of gestation or birth weight less than 1200 g were enrolled and randomized to either single wrap (only cling film attached to the bassinet wall) or double wrap (cling film covering the bassinet and occlusive plastic wrap covering the baby) group after birth. This practice was allowed in addition to radiant warmer care and other routine thermoregulatory measures followed in the unit. Intervention was continued till first 7 days of life unless they met any pre-specified withdrawal criteria. The primary outcome was a difference in total insensible water loss (g/m²) in first seven days of life between two groups. The secondary outcomes were difference in cumulative insensible water loss (g/m²) in the first 72 h of life, 4-7 days of life, average daily insensible water loss in the first week (g/m²/h), neonatal morbidities, mortality and time to event analysis.

Results: Of 63 randomized infants, 32 were allocated to single wrap and 31 to double wrap groups. Cumulative insensible water loss in first 72 h and first week were significantly lower in the double wrap group (2786.5 ± 576 g/m² in single wrap and 2376.8 ± 626 g/m² in double wrap, p value 0.012 for 0-3 days and 6225.48 ± 951 g/m² in single wrap and 5260.61 ± 1091 in double wrap, p value 0.034 for 0-7 days of life respectively). Apart from increased incidence of patent ductus arteriosus in double wrap group (41.94% vs. 15.62%, p 0.027) no other clinically significant outcomes were different between 2 groups. Median times to wean off respiratory support, regain birth weight and discharge from health facility were also similar between the two groups.

Conclusion: Double plastic wrap has been found to reduce cumulative insensible water loss in first week of life compared to cling film alone in the setting of a low-to-middle income-country.

Int J Nurs Stud. 2025 May;165:105027.

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Effectiveness of the nurse-led multi-component BRIDGE program on maternal competence and selected post-discharge outcomes of preterm babies: A randomized controlled trial

[Kavitha K¹](#), [Mallanagouda M Patil²](#), [Basheerahamed J Sikandar³](#), [Vijaya Soraganvi⁴](#)

Abstract

Background: Mothers require sufficient knowledge and skill in caring for a preterm newborn at home after discharge. Infant weight gain and other health parameters can be used to assess the quality of care received. A comprehensive early intervention program can help mothers through this transitional period.

Objective: To examine the effect of the BRIDGE Program versus standard care in improving maternal competence and the selected post-discharge outcomes of preterm newborns admitted to the tertiary-level hospital in India.

Methods: We conducted a single-blinded, two-arm, randomized controlled trial with a repeated measures design. Participants were recruited from a tertiary-level multi-specialty medical college hospital and research center in Vijayapur, India. Overall, 110 preterm babies aged 32 to 37 weeks of gestation and their mothers were randomly allocated to either intervention or control group (55 preterm infants and mother dyad in each group). The BRIDGE program included five phases: (I) family-centered health education on prematurity and preterm care; (II) demonstrations of preterm care procedures such as breastfeeding and burping techniques, kangaroo mother care, oil massage, and so on; (III), a home care guide on DO's and DON'Ts of preterm care; (IV) a home visit on first day of discharge; and (V) digital based follow-up through video call for one-week post-discharge. Outcomes were measured in terms of mothers' competence, preterm newborn weight gain, hospital readmission rate, and neonatal death up to one month after discharge. Data on mothers' competence in preterm care was collected at baseline and 7th-day post-discharge of preterm infants. For newborns, measurements were taken at baseline, discharge, seventh-day post-discharge, 15th-day post-discharge, and 30th-day post-discharge.

Results: After the BRIDGE program intervention, mean knowledge (95 % CI = 23.96-24.57) and skill (95 % CI = 14.02-14.69) scores of mothers in the intervention group has improved significantly than the control group (knowledge: 95 % CI = 18.20-20.60; and skill: 95%CI = 9.96-11.66). Preterm infants exposed to the BRIDGE program weighed 130 g and 790 g more than controls on days 15 and 30 after discharge ($p = 0.016$). However, no statistically significant differences were observed in readmission rate and post-discharge mortality of preterm infants ($p > 0.05$).

Conclusions: Although the BRIDGE program did not affect preterm infants' outcomes, the components of the intervention such as education, home visits, and digital follow-up empowered mothers allowing them to thrive in their surroundings and experience fewer consequences in newborn care.

Neonatal intensive care and care of the sick newborn

Automated oxygen control for preterm infants receiving continuous positive airway pressure in southwest Nigeria: an open-label, randomised, crossover trial

[Rami Subhi¹](#), [Lachlann McLeod²](#), [Adejumoke Idowu Ayede³](#), [Iyabode Olabisi Dedeke⁴](#), [Quadri Risikat⁴](#), [Alao Ridwan Akanbi⁵](#), [Adeola Baliqis Fasasi⁴](#), [Ayobami A Bakare⁶](#), [Oluwatosin Helen Adeniyi⁴](#), [Olugbenga Akinrinoye⁷](#), [Olanrewaju Adeigbe⁷](#), [George F Dargaville⁸](#), [Patrick Walker⁸](#), [Anneke C Grobler⁹](#), [Olufunke Mosebolatan⁷](#), [Shiraz Badurdeen¹⁰](#), [Timothy J Gale²](#), [Adegoke G Falade³](#), [Peter A Dargaville¹¹](#), [Hamish R Graham¹²](#)

Abstract

Background: Titration of oxygen therapy to target safe oxygen saturation (SpO₂) values is a vital part of care for preterm infants, but is difficult to achieve, particularly in settings in which oxygen, monitoring technology, and human resources are scarce. We aimed to evaluate the safety and efficacy of automated titration of oxygen therapy partnered with a low-cost continuous positive airway pressure (CPAP) device versus manual oxygen control in preterm infants requiring CPAP in a high-mortality, low-resource setting.

Methods: In this open-label, randomised, crossover trial, preterm infants with a gestational age younger than 34 weeks (or a birthweight <2 kg if gestation was unknown) who were aged 12 h or older and required CPAP and oxygen were recruited at two hospitals in southwest Nigeria. Participants were randomly assigned (1:1) to one of two intervention sequences (ie, to commence the study on automated oxygen control or manual oxygen control) with block randomisation (blocks of 4 and 6) and stratification by health facility. The study statistician was masked to treatment group assignment, but the participants' parents or caregivers and clinical staff were not. Participants received automated or manual oxygen control for two 24-h periods in random sequence. Automated oxygen titration was done with a control algorithm with proven efficacy in high-resource settings. During periods of manual control, oxygen therapy was adjusted by clinicians. The primary outcome was the adjusted mean difference in the proportion of time participants spent in the SpO₂ target range (ie, SpO₂ 91-95% when receiving oxygen or SpO₂ 91-100% when not receiving oxygen) between automated and manual oxygen control, analysed by intention to treat with weighted repeated measures mixed model linear regression. This trial is registered with ClinicalTrials.gov, [NCT05508308](#), and is completed.

Findings: Between Sept 13, 2022, and Sept 11, 2023, 72 infants were screened, and 49 (22 female, 27 male; median gestation 29 weeks [IQR 28-31]; median birthweight 1.2 kg [1.1-1.5]) were enrolled in the study and randomly assigned. A total of 80 study periods for 46 infants contributed data to the analysis of the primary outcome as three (6%) of the 49 participants had no oxygenation data from either study period. The mean proportion of time spent in the SpO₂ target range was higher during automated control periods than during periods of manual control (adjusted mean 88.1% [95% CI 84.0-92.2] vs 30.1% [20.9-39.3]; adjusted mean difference 58.0% [95% CI 48.0-67.9]; p<0.0001). There were no device-related adverse patient outcomes and short-term safety outcomes favoured automated control.

Interpretation: Automated titration of oxygen partnered with a low-cost CPAP device improved time spent in the safe SpO₂ range compared with manual control. There is high potential for this technology to mitigate the risk of oxygen-mediated complications in preterm infants in low-resource settings.

doi: 10.1007/s13312-025-3373-7.

Prevention of VAP Using Hypertonic Saline Nebulization in NICU: A Randomized Controlled Trial

[Arpit Gupta¹](#), [Mukesh Vir Singh¹](#), [Rajesh Kumar Yadav¹](#), - [Monica²](#), [Anubha Shrivastava³](#)

Abstract

Objective: To evaluate the efficacy and safety of hypertonic saline (HS) nebulization in reducing the occurrence of ventilator associated pneumonia (VAP) by comparison of modified Clinical Pulmonary Infection Score (mCPIS) in HS nebulized and non-nebulized newborns.

Methods: A randomized controlled study with 1:1 participant allocation ratio was conducted in a tertiary centre in North India. Neonates who received mechanical ventilation at the centre were included. Those who had been intubated for >12 hours at outside hospitals were excluded. The study group received nebulization with HS for seven days or till extubation (whichever was earlier). Both groups were compared in terms of occurrence of VAP and mCPIS. mCPIS ≥ 6 was used to suggest VAP. VAP was confirmed by a positive blood culture in ventilated newborns with clinicoinvestigative features of VAP.

Results: A total of 143 neonates were analyzed in each group. VAP rate (per 1000 mechanical ventilation-days) in the HS nebulization and the control groups were 36.72 and 51.51, respectively; $P = 0.031$. A 33.52% reduction in the rate of VAP was observed due to HS nebulization. [RR (95% CI) 0.67 (0.47, 0.95), $P = 0.022$]. The mean (SD) mCPIS in HS group was 5.22 (0.88) compared to 5.94 (1.07) in the control group; $P = 0.030$. Only 5.5% neonates in the intervention group developed wheezing.

Conclusion: Nebulization with HS reduces the incidence of VAP in ventilated newborns without significant side effects.

Indian J Pediatr. 2024 Aug;91(8):794-800.

doi: 10.1007/s12098-023-04756-w. Epub 2023 Aug 14.

Functional Duration of Peripheral Intravenous Cannula in Neonates with or without Splint: A Randomized Controlled Trial

[Nadella Lakshmi Thushara^{1,2}](#), [Poonam Singh³](#), [Mayank Priyadarshi¹](#), [Suman Chaurasia¹](#), [Nowneet Kumar Bhat²](#), [Sriparna Basu¹](#)

Abstract

Objectives: To determine the effect of splint on the functional duration of peripheral intravenous cannula (PIVC) in neonates.

Methods: The trial was prospectively registered with the Clinical Trial Registry of India (CTRI/2021/09/036337). One-hundred-fifty cannulations in 71 neonates were randomized to splint ($n = 75$) and no-splint ($n = 75$) groups, respectively. The median (interquartile range, IQR) functional duration of PIVC was calculated from the time of PIVC insertion till removal due to the development of signs of PIVC failure or treatment completion. Kaplan-Meier survival analysis was used to compute the time to complication of PIVC. Complications related to PIVC were noted and multivariate Cox-proportion hazard analysis was done to find the predictors associated with PIVC failure.

Results: Median (IQR) functional duration of PIVC in the splint and the no-splint group was 28 (23-48) and 30 (25-48) h, respectively ($p = 0.477$). PIVC duration was higher in the splint group in term neonates and the no-splint group in preterm neonates; however, the

differences were not statistically significant. No difference was observed in continuous vs. intermittent infusion subgroups. Time to complication development was also comparable between the groups.

Conclusions: Splint application did not affect functional PIVC duration and its related complications in neonates.

Nurs Crit Care. 2025 Mar;30(2):e13113.

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Effectiveness of breast milk in the healing of medical adhesive-related skin injuries in peripheral intravenous catheter securement: A randomized controlled trial

[Vildan Apaydin Cirik¹](#), [Ayse Sonay Turkmen²](#), [Dudu Beren Alirkiliçarslan³](#)

Abstract

Background: Skin injuries, which are more prevalent among premature infants, can prolong the hospital stay of preterms in neonatal intensive care units.

Aim: This study aimed to assess the effectiveness of breast milk in reducing the healing time of skin injuries caused using medical adhesive for securing peripheral intravenous catheters (PIVCs) in late preterm infants, which was evaluated using the Neonatal Skin Condition Scale (NSCS). A randomized controlled trial was conducted with two parallel groups in a 1:1 allocation ratio.

Study design: It was conducted in the Neonatal Intensive Care Unit of a hospital in Karaman, Turkey between August and November 2022 with 72 preterm infants born at 35-36 weeks with stable health status and having intravenous catheter securement to the skin with medical adhesive tapes, with the tapes remaining on the skin for a minimum of 24 h and a maximum of 32 h. Preterm infants were randomly assigned to breast milk or routine care groups. The site of the skin injuries was evaluated by two independent observers using the NSCS once every 60 min until the injury was completely healed. A one-way ANOVA and repeated measures analysis of variance was used to analyse the data.

Results: The average postnatal age was 3.32 ± 0.99 days, and the total duration of medical adhesive tape on the skin was 28.21 ± 2.59 h. A significant difference was found between the mean skin condition scale scores of the infants in the breast milk group ($F = 117.219$, $p < .001$) and the routine care group ($F = 122.247$, $p < .001$) according to time within the group. The skin injuries of preterm infants in the breast milk group decreased significantly in the first 3 h after the procedure.

Conclusion: Breast milk application was more effective than routine care in reducing the healing time of skin injuries.

Indian Pediatr. 2024 Sep 24:S097475591600701.

Online ahead of print.

Comparison of UVC with PICC Line for Reducing Central Line Associated Blood Stream Infections in Preterm Neonates with Birth Weight < 1250g: An Open-Label Randomized Controlled Trial

[Subhash Arun¹](#), [Srinivas Murki²](#), [Venkateshwarlu Vardhelli¹](#), [Saikiran Deshabhotla¹](#), [Shravani Maram¹](#), [Praveen Rao Vadije¹](#), [Tejo Pratap Oleti¹](#)

Abstract

Objective: To compare the incidence of central line associated blood stream infections (CLABSI) with the use of umbilical venous catheters (UVC) as primary vascular access in preterm neonates with peripherally inserted central catheters (PICC).

Methods: This was an open-label, two parallel-arm, randomized controlled trial which included hospitalized neonates with birth weight <1250g who required a central venous access on day 1 of life. The neonates were randomized to either UVC or PICC line and evaluated for the incidence of CLABSI.

Results: Of the total 238 eligible neonates, 128 and 110 neonates were randomized to the UVC and PICC groups, respectively. The baseline characteristics were comparable in both groups. There was no difference in the incidence of CLABSI among the UVC and PICC groups (21.1% vs 18.2%; $P = 0.57$). Neonates in the PICC group needed multiple attempts at insertion compared to those in the UVC group (43% vs 12%, $P = 0.01$); more time was needed for PICC line insertion [median (IQR) 20 (15, 40) vs 10 (5, 15) minutes, but had longer duration of the primary line [7 (4, 10) vs 5 (3, 7)] minutes. Early removal of the line for leakage was higher in the UVC group and local signs of inflammation were higher in the PICC group. The overall incidence of complications was similar between the groups (53% vs 45%, $P = 1.00$).

Conclusion: In preterm infants with a birth weight of less than 1250 grams, the incidence of CLABSI was similar in the UVC and PICC group when used as a primary central line. The overall complication rates were comparable in UVC and PICC.

Indian J Pediatr. 2024 Aug 1.

doi: 10.1007/s12098-024-05211-0. Online ahead of print.

RAM Cannula versus Short Binasal Prongs for Non-invasive Ventilation in Preterm Infants: An Updated Systematic Review and Meta-analysis

[Jogender Kumar¹](#), [Jitendra Meena²](#), [Pradeep Debata³](#), [Venkateshan Sundaram¹](#), [Sourabh Dutta¹](#), [Praveen Kumar⁴](#)

Abstract

Objectives: To compare the efficacy and safety of RAM cannula with short binasal prongs (SBPs) as nasal interfaces in preterm infants requiring nasal continuous positive airway pressure (nCPAP) or nasal intermittent positive pressure ventilation (NIPPV).

Methods: The authors searched electronic databases (Medline, Embase, and Web of Science) and trial registries from inception until March 15, 2024, for randomized controlled trials (RCTs) comparing the RAM cannula with SBP for delivering nCPAP/NIPPV. They performed a random-effects meta-analysis using RevMan 5.4 software. The primary outcome was failure of nCPAP/NIPPV. Secondary outcomes included nasal injury, mechanical ventilation, air leaks, and mortality.

Results: Five RCTs (825 participants) were included. There was no significant difference in nCPAP/NIPPV failure (RR: 1.04; 95% CI: 0.58 to 1.87) or the need for invasive mechanical ventilation (RR: 1.23; 95% CI: 0.75 to 2.01) between the RAM cannula and SBP groups (low to very low certainty). Compared with infants in the SBP group, those in the RAM cannula group had a significantly lower incidence of moderate to severe nasal injury [(5 RCTs, 825 participants; RR: 0.34; 95% CI: 0.18 to 0.66); low certainty] and any nasal injury [(RR: 0.44; 95% CI: 0.26 to 0.76; very low certainty)]. There was no significant difference in the other clinical outcomes.

Conclusions: In comparison to SBP, the RAM cannula may have little to no effect on nCPAP/NIPPV failure, but the evidence is very uncertain. Low-certainty evidence suggests that the use of RAM cannula possibly results in reduction in moderate to severe nasal trauma in preterm infants receiving nCPAP/NIPPV.

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The effect of developmental care on the length of hospital stay and family centered care practice for very low birth weight infants in neonatal intensive care units: A cluster randomized controlled trial

Research Group of Developmental Care for Very Low Birth Weight Infants in China; TianChan Lyu¹, Rumeng Ye², Li Ling Li³, Li Li Zhang⁴, Juan Xiao⁴, Yue Lan Ma⁵, Fang Li⁶, Hui Rong⁶, Dan Liu⁷, Hua Wang⁷, Yan Wang⁸, Wei Wei Gu⁹, Yan Xuan¹⁰, XiaoChun Chen¹¹, Qiao Ling Fan¹², Yun Fei Tang¹³, Xiang Hui Huang², An Qin¹⁴, Yi Li Zhang¹⁵, Yalan Dou³, Xiao Jing Hu¹⁶

Abstract

Background: Despite previous studies suggesting that developmental care can provide benign stimulation to promote neural development of newborns, more evidence is needed regarding the other clinical benefits of developmental care.

Objective: To evaluate the effect of implementing developmental care on the length of hospital stay, the improvement of care practice in neonatal intensive care units, as well as the short-term outcome of very low birth weight infants.

Design: Cluster-randomized controlled trial.

Setting(s) and participants: From March 1, 2021 to March 1, 2022, 1400 very low birth weight infants were recruited from 14 tertiary neonatal intensive care units in China.

Methods: We assigned 14 neonatal intensive care units to either developmental care or standard care. The length of hospital stay of the infants was the primary outcome analyzed at the individual level. Secondary outcomes were family centered care practice including parental involvement, the skin to skin care, exclusive breast milk, oral immune therapy and breastfeeding. The environmental management (noise and light) and the short-term outcomes were also evaluated.

Results: The length of hospital stay for the developmental care group was 65 % as long as that for the control group (HR: 0.65, 95 % CI, 0.451-0.936, $p = 0.021$). After controlling the covariables, the adjusted HR = 0.755 (95 % CI, 0.515 to 1.107, $p = 0.150$). When compared to the control group, the developmental care group had greater access to SSC, with 22 infants (3.8 %) in the developmental care group compared to 13 infants (1.7 %) in the standard care group ($p = 0.013$). A greater proportion of infants in the developmental care group were fed at the breast, than those in the standard care group (136 [23.6 %] vs 9 [1.1 %]; $p = 0.029$). Compared to the control group, exclusively breast milk was significantly more favorable in the developmental care group (435 [75.6 %] vs 114 [15.0 %]; $p = 0.001$). The difference remained significant even after adjusting for covariates. However, the rate of oral immune therapy and parental involvement was similar in the two groups. The average noise and light levels in the developmental care group were significantly lower than those in the standard care group. After adjusting for confounders, the difference remained significant. There were no significant differences among groups in the mortality and major morbidity.

Conclusions: Developmental care might have developed an accumulated effect over time on the length of hospital stay among very low birth weight infants. The implementation of developmental care can greatly improve family centered care practices and the neonatal intensive care unit environment.

Eur J Pediatr. 2025 Feb 22;184(3):205.

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Non-invasive high-frequency oscillatory ventilation versus non-invasive intermittent mandatory ventilation as a rescue mode in preterm infants with respiratory distress on nasal CPAP-a randomized control trial

[R D Rachana¹](#), [Tejopratap Oleti²](#), [D Saikiran¹](#), [Venkateshwarlu Vardhelli¹](#), [Sruthi Thiruveedi¹](#), [Altaf Hussain¹](#), [Prasen Reddy Tamatam¹](#)

Abstract

To compare NHFOV in decreasing the need for mechanical ventilation in the first 7 days of randomization in preterm infants born before 34 weeks of gestational age having nCPAP failure when used as rescue mode compared to NIMV. All eligible neonates were randomized and allocated to either NHFOV or NIMV group after taking the consent from the parents. Standardized protocol was followed on initiation, titration, weaning, and optimization of all the respiratory supports. In this study, a total of 45 neonates were eligible; among them, 20 neonates were randomized to NIMV group and 20 neonates to NHFOV group remaining 5 infants were missed due to the non-availability of a machine (n = 4) and missed randomization (n = 1). The primary outcome was need for mechanical ventilation within first 7 days of randomization in NIMV and NHFOV group was 45% and 40% (p = 0.85, OR = 1.22 (CI 0.35-4.3)). The secondary outcome was a duration of ventilation within 72 h of randomization was 40% vs. 31.6% in NIMV and NHFOV group (p = 0.58). Bronchopulmonary dysplasia was 5% and 10% in NIMV and NHFOV group with p = 0.548, OR = 0.47 (CI 0.39-5.6), and mortality was one infant in NIMV and 3 infants in NHFOV group (p = 0.568, OR = 0.29 (CI 0.02-3.1)).

Conclusion: NIMV and NHFOV are comparable in reducing the rates of mechanical ventilation within 72 h and within 7 days of post-randomization. Multi-centric trials with large sample sizes are required to prove the hypothesis.

Neonatal nutrition

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Home administration of a multistrain probiotic once per day for 4 weeks to newborn infants in Tanzania (ProRIDE): a double-blind, placebo-controlled randomised trial

[Claus Klingenberg¹](#), [Museveni Justine²](#), [Sabrina John Moyo³](#), [Iren Høyland Löhr⁴](#), [Joshua Gideon²](#), [Paschal Mdoe⁵](#), [Estomih Mduma⁵](#), [Joel Manyahi⁶](#), [Ahmed Bargheet⁷](#), [Veronika Kuchařová Pettersen⁷](#), [John Paschal⁵](#), [Heidi Syre⁸](#), [Eva Bernhoff⁸](#), [Rehema Bukhay⁵](#), [Bjørn Blomberg⁹](#), [Nina Langeland¹⁰](#)

Abstract

Background: Probiotics are commonly given to preterm and term infants to reduce gut colonisation and prevent disease. Evidence for the beneficial effect of probiotic therapy is sparse, particularly in term infants from low-income and middle-income countries with high infant morbidity and mortality. This study aimed to assess whether a 4-week course of probiotic therapy might reduce death and hospitalisation up to age 6 months in healthy infants in Tanzania.

Methods: In this investigator-initiated, single-site, double-blind, placebo-controlled randomised trial conducted at Haydom Lutheran Hospital and in the surrounding area in northeast Tanzania, we randomly assigned healthy infants born in the hospital, in other local health facilities, or at home who weighed 2 kg or more (1:1) to receive a multistrain probiotic mixture (including *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, and *Bifidobacterium longum* subsps *infantis*) or placebo once per day for 4 weeks. Caregivers of study participants, investigators, study staff, hospital clinicians, and individuals involved in data management or analysis were masked to treatment allocation during all the data collection and management phases of the trial. Caregivers were shown how to give five drops (0.2 mL) of allocated treatment solution orally to their infant and then requested to administer this treatment once per day for 4 weeks or until the bottle was empty. During scheduled study visits at ages 1 week, 6 weeks, and 6 months, trained field workers visited each participant's home and used a standardised questionnaire to obtain a history of recent illness, medication use, breastfeeding practice, and the current condition of the child. At the 6-week and 6-month follow-up visits, the participants' weights and lengths were measured, and stool samples were collected. Stool samples were used for analysis of extended-spectrum β -lactamase-producing Enterobacterales (to evaluate gut colonisation rates) and metagenomic sequencing. The primary outcome was a composite of death or hospitalisation during the first 6 months of life, assessed in three populations: a modified intention-to-treat population (mITT), which included all participants with a known primary outcome at 6 months of follow-up; the intention-to-treat population, which included all participants who were enrolled and randomly assigned to a treatment group; and the per-protocol population, which included only infants in the mITT whose caregivers reported having given them the study solution once per day during the 4-week intervention period. This trial is registered with ClinicalTrials.gov, [NCT04172012](https://clinicaltrials.gov/ct2/show/study/NCT04172012), and is complete.

Findings: Between Feb 1, 2022, and Jan 4, 2023, 2000 participants were enrolled and randomly assigned to the probiotic (n=1000) or placebo (n=1000) groups, with administration of the probiotic or placebo treatment beginning on median day 1 (IQR 1-2) of life. 6 months after inclusion, data for the primary outcome were available for 1945 (97.3%) of the 2000 participants. By mITT, there was no statistically significant difference in the primary outcome between the two study groups. Hospitalisation or death occurred in 34 (3%) of 970 participants in the probiotic group and 31 (3%) of 975 participants in the placebo group (crude relative risk 1.10, 95% CI 0.68-1.78). There were also no differences in the overall incidence of adverse events between the groups, but fewer caregiver-reported gastrointestinal events were reported in the probiotic group.

Interpretation: Daily administration of a multistrain probiotic mixture in the first 4 weeks of life did not reduce the rate of death or hospitalisation up to age 6 months among infants in Tanzania and did not cause any short-term safety concerns.

Breastfeed Med. 2024 Jul;19(7):554-559.

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Comparison of Paladai Cup Against Nifty Cup Feeding in Preterm Low-Birth-Weight Infants: An Open-Labelled Randomized Controlled Trial

[Priya Dharshini Duruvasal¹](#), [Usha Devi²](#), [Utkarsh Patil³](#), [Giridhar Sethuraman³](#)

Abstract

Background: Neonatal Intuitive Feeding Technology (NIFTY) cup feeding has been found to be feasible in preterm low-birth-weight babies. However, literature on direct comparison of the same with paladai feeding is lacking. **Methods:** In this open-labeled, randomized controlled trial, preterm infants (<34 weeks/<1800 g) on full oral gastric tube feeding for at least 3 consecutive days, eligible to be given a trial of suck and swallow cup feeding, prior to initiation of direct breastfeeding, were randomized to the two feeding intervention groups: paladai cup and Nifty cup. The primary outcome was the time taken from initiation of oral cup feeds to reaching complete gavage-free cup feeds for at least 24 hours. Secondary outcomes were the ease of use of both instruments, the adverse effects during and within 10 minutes after feeding, and anthropometric parameters (head circumference and weight gain). **Results:** The median (IQR) time taken from initiation to complete transition to full cup feeding for at least 24 hours was not significantly different [4(3,7) days in Nifty cup group versus 3(2,6) days in paladai cup group, $p = 0.25$]. Mean $\pm$ SD weight gain from intervention to discharge was also similar in both the groups (16 ± 6 g/kg/day in Nifty cup group versus 17 ± 5 g/kg/day in paladai cup group, $p = 0.18$). Adverse events did not differ (32.9% in group A versus 27.1% in group B, $p = 0.580$). Nurses did not find any difference in ease of teaching caregivers [median (IQR) Nifty cup group 4(4,5) versus paladai cup group 4(4,5), $p = 0.13$]. **Conclusion:** The efficacy and adverse event rates were similar between Nifty cup feeding and paladai cup feeding in preterm infants. Both feeding modalities can be used prior to transition to direct breastfeeding in preterm low-birth-weight infants.

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Effect of an oral stimulation protocol on breastfeeding among preterm infants: a randomised controlled trial

[Gopalakrishnan Jayapradha¹](#), [Lakshmi Venkatesh¹](#), [Prakash Amboiram²](#), [Radish Kumar Balasubramaniam³](#), [Umamaheswari Balakrishnan²](#)

Abstract

Objectives: The objectives are to assess the effectiveness of a modified and adapted oral sensorimotor intervention (MA-OSMI) protocol for infants in India on the rate and performance of breastfeeding among preterm (PT) infants at discharge.

Design: Single-centre randomised control trial.

Setting: Level III B neonatal intensive care unit in a quaternary care hospital in South India.

Patients: A total of 76 PT infants born between 26 and 33⁺⁶ weeks of gestational age, stratified into <30 weeks and 30-33⁺⁶ weeks, were randomised to intervention group (MA-OSMI) or standard care (SC).

Interventions: MA-OSMI in addition to SC versus SC alone. The stimulation included 12 techniques administered by the principal investigator. SC included kangaroo mother care and non-nutritive sucking.

Outcome measures: Exclusive breastfeeding (EBF) rate and breastfeeding performance at the time of discharge, assessed using standardised tools by clinician and mothers.

Results: Infants in MA-OSMI group (66%) had significantly higher EBF rate compared with the SC group (16%) (OR: 10.25; 95% CI: 3.41 to 30.80). Improved breastfeeding performance was noted as per the clinician's observation. Significantly lower scores for MA-OSMI groups (63.42 ± 36.43) than SC groups (126.61 ± 60.94) on mothers' ratings suggested better feeding skills.

Conclusion: Prefeeding oral stimulation contributed significantly to the achievement of EBF among PT infants at discharge. The present findings may benefit speech-language pathologists, paediatricians/neonatologists and nurses in the intervention of oral feeding among neonates.

J Perinatol. 2024 Nov 7.

doi: 10.1038/s41372-024-02164-2. Online ahead of print.

Effects of rapid enteral feed advancement with early human milk fortification in very low birth weight preterm infants > 30 weeks gestation in a resource limited setting- a randomized controlled trial

[Anitha Ananthan¹](#), [Ganesh Bhatkar²](#), [Haribalakrishna Balasubramanian³](#), [Muthu Vijayanathan²](#), [Lakshmi Srinivasan⁴](#)

Abstract

Objective: To study the effects of rapid enteral feed advancement with early feed fortification in stable very low birth weight (VLBW) infants >30 weeks gestation.

Study design: Preterm infants (N = 92) were randomized to a) rapid feed advancement-early fortification - REF group (enteral feed advanced at 25-30 ml/kg/day, fortification at 50 ml/kg/day) or b) slow feed advancement-late fortification-SLF group (feed advanced at 15-20 ml/kg/day, fortification at 100 ml/kg/day).

Results: The primary outcome-time to regain birth weight was significantly lower in REF group (9 days vs 13 days, $P = 0.02$). REF group reached full enteral feeds earlier (6 days vs 9 days, $P = 0.001$), had lower rates of sepsis (13% vs 38%, $P = 0.007$) and shorter hospital stay (10 days vs 15 days, $P = 0.01$). At one year, the median Z-scores for weight [-1.5 vs -2.2 , $P < 0.001$] and head circumference [1.1 vs 0 , $P < 0.001$] were significantly higher in the REF group.

Conclusions: In VLBW preterm infants >30 weeks, rapid feed advancement with early fortification resulted in early postnatal regain of birth weight with positive effects on growth at one year.

Neonatal respiratory distress

Am J Perinatol. 2024 Dec 19.

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Intratracheal administration of budesonide with surfactant for prevention of death or bronchopulmonary dysplasia in extremely low birth weight infants - a before-after study

[Anish Pillai^{1,2}](#), [Nandkishor Kabra¹](#), [Sharayu Kothavade¹](#), [Anita Chevle¹](#), [Sachin Sakharkar¹](#), [Deepika Tiwari¹](#), [Richa Choubey¹](#), [Haribalakrishna Balasubramanian¹](#)

Abstract

Objectives: Previous studies have suggested a potential role for inhaled corticosteroids, such as budesonide, in reducing bronchopulmonary dysplasia (BPD) among preterm infants. The objective of our study was to investigate the effectiveness of intratracheal administration of corticosteroid with surfactant on the composite outcome of death or BPD at 36 weeks in extremely low birth weight (ELBW) infants.

Study design: This before-after cohort study compared outcomes in ELBW infants with respiratory distress syndrome (RDS) who received intratracheal surfactant with budesonide to a historical cohort who received surfactant alone. Data was collected retrospectively for neonates in the surfactant group and prospectively for those receiving surfactant plus budesonide.

Results: A total of 385 ELBW infants were included. Death or BPD occurred in 123/203 (60.5%) in the surfactant with budesonide group versus 105/182 (57.6%) in the surfactant group; adjusted odds ratio 1.10 (95% CI 0.69 to 1.75; $p=0.69$). Statistical analysis revealed no significant difference in the incidence of the composite primary outcome (death or BPD at 36 weeks of post menstrual gestational age), and its components, between the two study groups.

Conclusion: In our study, co-administration of budesonide and surfactant was deemed safe and feasible among ELBW infants with RDS. However, we did not observe a significant reduction in the rates of composite or individual outcomes of death or BPD. Larger, randomized controlled trials are necessary to explore the potential advantages of this intervention.

J Perinatol. 2024 Dec 17.

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[Nebulized salbutamol for the treatment of transient tachypnea of the newborn: a randomized controlled trial](#)

[Aditi Dhaka^{1,2}](#), [Sonu Kumar¹](#), [Poonam Singh¹](#), [Mayank Priyadarshi¹](#), [Suman Chaurasia¹](#), [Nowneet Kumar Bhat²](#), [Sriparna Basu³](#)

Abstract

Objective: To compare the efficacy of nebulized salbutamol in reducing respiratory distress in late preterm and term neonates with transient tachypnea of newborn (TTN).

Study design: Double-blind, placebo-controlled randomized trial.

Methods: Neonates with TTN ($n = 134$) were allocated to nebulized salbutamol ($n = 67$) versus placebo (normal saline) ($n = 67$). The primary outcome was the duration of tachypnea (respiratory rate $>60/\text{min}$). Secondary outcomes were maximum Downes score and fraction of inspired oxygen (FiO_2) after nebulization, duration of respiratory support, and adverse effects of salbutamol nebulization.

Results: Median duration of tachypnea was 12.5 (10-16) vs. 12 (10.4-14) hours in salbutamol and placebo groups, respectively; $p = 0.489$. Almost all neonates received positive-pressure respiratory support at delivery room and subsequently. Maximum Downe's score, FiO_2 requirement, and duration of respiratory support were similar. No adverse effect of salbutamol was documented.

Conclusion: There was no difference in the duration of tachypnea with nebulized salbutamol compared to placebo in late preterm and term neonates with TTN.

Neonatal resuscitation

Indian J Pediatr. 2024 Oct;91(10):1008-1013.

doi: 10.1007/s12098-023-04938-6. Epub 2023 Nov 28.

[Comparison of Efficacy of Pressure Controlled vs. Traditional Manual Mask Ventilation for Newborn Resuscitation - A Simulation-Based Pilot Randomized Control Trial](#)

[Shilpa Kalane¹](#), [Vaibhavi Upadhye²](#), [Atul V Mulay³](#), [Amrita P Prayag⁴](#)

Abstract

Objectives: To determine efficacy of non-invasive positive pressure face mask ventilation using a ventilator device (NIPPmV) for achieving early effective ventilation compared to that by self-inflating bag (SIB) or T- piece resuscitator (TPR).

Methods: The authors video recorded 33 trained resuscitators using NIPPmV (provided using ventilator device), SIB [a 500 ml silicone SIB without a positive end expiratory pressure (PEEP) valve] and a TPR. Using a continuous pressure recording system and a neonatal manikin, the authors evaluated the efficacy of the ventilation to achieve early effective ventilation during 30 s of ventilation. The primary outcome was time to achieve effective chest rise. Secondary outcomes were peak inspiratory pressure (PIP), ventilation rate and the need to perform ventilation corrective steps during positive pressure ventilation (PPV) among the devices.

Results: Total 99 videos were recorded. The time(s) taken to achieve the first chest rise was significantly lesser in NIPPmV group compared to SIB and TPR (3.0 ± 1.7 vs. 3.7 ± 1.9 vs. 7.5 ± 5.4 , respectively, $p < 0.001$). The mean PIP delivered by NIPPmV compared to SIB & TPR (19.8 ± 1.6 vs. 35.6 ± 7.4 vs. 17.8 ± 2.0 cm H₂O respectively; $p < 0.001$) was more accurate with preset PIP. Ventilation, in terms of breath rate, was observed to be controlled more accurately with NIPPmV compared to SIB & TPR (50 vs. 42 vs. 33 per min respectively; $p < 0.001$).

Conclusions: The non-invasive positive pressure face mask ventilation using a ventilator (NIPPmV) resulted in achieving early, effective and consistent ventilation.

Resuscitation. 2025 Feb 20;209:110556.

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[Remote versus in-person pre-service neonatal resuscitation training: A noninferiority randomized controlled trial in Ethiopia](#)

[Rishi P Mediratta¹](#), [Max K Clary²](#), [Jane W Liang³](#), [Kay Daniels⁴](#), [Lulu M Muhe⁵](#), [Henry C Lee⁶](#), [Beza Eshetu⁷](#), [Melkamu Berhane⁷](#)

Abstract

Background: In-person neonatal resuscitation training in resource-limited settings faces barriers of geographic access, facilitator and participant availability, and high costs. Remote training could overcome these challenges while maintaining effectiveness. We hypothesized that remote neonatal resuscitation training was noninferior to in-person training for acquiring and retaining knowledge and skills for pre-service education in Ethiopia.

Methods: We conducted a randomized, controlled, noninferiority trial comparing remote versus in-person neonatal resuscitation training in Jimma, Ethiopia. Medical students without prior resuscitation training were randomized (1:1) to Zoom or in-person delivery of the Helping Babies Breathe curriculum supplemented with videos. Outcome assessors were unmasked, but investigators not involved in participant recruitment remained masked. The primary outcome was neonatal resuscitation skills assessed by the Objective Structured Clinical Examination B (OSCE B) two months after training. The noninferiority margin was 13%. Group differences were assessed by intention-to-treat analysis using one-sided t-tests. A p-value < 0.05 suggests noninferiority. The trial was registered at Clinicaltrials.gov, [NCT05854745](https://clinicaltrials.gov/ct2/show/study/NCT05854745), and is complete.

Results: Between May 1-June 4, 2023, 354 medical students were randomized to remote or in-person training (177 per group). 262 attended the training and completed assessments (remote n = 123, in-person n = 139; 51% male overall). Two months after training, 199 participants completed assessments (remote n = 94, in-person n = 105). Mean OSCE B scores were 19.8 (SD 3.24) in the remote group and 20.5 (SD 2.24) in the in-person group (difference -0.76 [95% CI -1.53 to 0.01]; p < 0.001 for noninferiority), with similar passing rates (remote 62.8%, in-person 60.0%). No adverse events occurred.

Conclusion: Remote training achieved noninferiority to in-person training in resuscitation skill retention at two months among medical students with minimal resuscitation experience, suggesting an effective and promising approach to expanding essential clinical training access globally in resource-limited settings.

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T-piece resuscitator versus self-inflating bag for resuscitation in the delivery room in preterm neonates: a randomised controlled trial

[Harshit Kumar¹](#), [Suksham Jain²](#), [Deepak Chawla¹](#), [Supreet Khurana¹](#), [Kiran Prakash³](#), [Abhishek Yadav¹](#), [Yaseer Ahmad Mir¹](#)

Abstract

Objective: To compare the efficacy of T-piece resuscitator (TPR) and self-inflating bag (SIB) for resuscitation of preterm neonates in the delivery room.

Settings: Level III neonatal intensive care unit in North India.

Design: Open-label, parallel-group, randomised controlled trial.

Patient: Preterm neonates of >26-34 weeks of gestation requiring positive pressure ventilation (PPV) at birth.

Intervention: Neonates needing PPV at birth were identified using Neonatal Resuscitation Programme guidelines, 2020, and resuscitated using either TPR or SIB as per permuted block random sequence.

Main outcome measures: Primary outcome was need for delivery room endotracheal intubation. Secondary outcomes were duration of PPV, oxygen saturation (SpO₂) at 2 and 5 min, time to spontaneous respiration and heart rate >100 beats per minute.

Results: Mean gestation age (weeks; 30±2.1 vs 31±2) and birth weight (g; 1400±408 vs 1450±427) were comparable. Of the total 120, 8 (13.7%) in the TPR group versus 19 (30.6%) neonates in the SIB group were intubated in the delivery room (risk difference (95% CI), -0.16 (-0.31 to -0.02); p=0.03). SpO₂ mean (SD) at 5 min in TPR group and SIB group were 82.9±8.7%

and $78.9 \pm 12.1\%$, respectively; mean difference (95% CI), 3.99 (0.15 to 7.83); $p=0.04$). Median (IQR) of combined Apgar at 5 min in TPR group and SIB group were 13 (12-14) and 12 (10-13), $p=0.02$. Other outcomes were comparable.

Conclusion: TPR is more efficacious than SIB in terms of lesser delivery room intubation and better SpO₂ at 5 min in preterm neonates.

Perinatal asphyxia, meconium aspiration and pulmonary hypertension

J Trop Pediatr. 2024 Aug 10;70(5):fmae019.

doi: 10.1093/tropej/fmae019.

[Therapeutic hypothermia for neonates with hypoxic-ischaemic encephalopathy in low- and lower-middle-income countries: a systematic review and meta-analysis](#)

[Raj Prakash](#)¹, [Diana Verónica Reyes-García](#)^{2,3}, [Sanjana Somanath Hansoge](#)⁴, [Ted S Rosenkrantz](#)⁵

Abstract

Hypoxic-ischaemic encephalopathy (HIE) is a major cause of mortality and neurodevelopmental disability, especially in low-income countries. While therapeutic hypothermia has been shown to reduce morbidity and mortality in infants with HIE, some clinical trials in low-income countries have reported an increase in the risk of mortality. We conducted a systematic review and meta-analysis of all randomized and quasi-randomized controlled trials conducted in low-income and lower-middle-income countries that compared cooling therapy with standard care for HIE. Our primary outcome was composite of neonatal mortality and neurodevelopmental disability at 6 months or beyond. The review was registered with PROSPERO (CRD42022352728). Our review included 11 randomized controlled trials with 1324 infants with HIE. The composite of death or disability at 6 months or beyond was lower in therapeutic hypothermia group (RR 0.78, 95% CI 0.66-0.92, $I^2 = 85\%$). Neonatal mortality rate did not differ significantly between cooling therapy and standard care (RR 0.92, 95% CI 0.76-1.13, $I^2 = 61\%$). Additionally, the cooled group exhibited significantly lower rates of neurodevelopmental disability at or beyond 6 months (RR 0.34, 95% CI 0.22-0.52, $I^2 = 0\%$). Our analysis found that neonatal mortality rate did not differ between cooled and noncooled infants in low- and lower-middle-income countries. Cooling may have a beneficial effect on neurodevelopmental disability and the composite of death or disability at 6 months or beyond.

Obstet Gynecol. 2024 Aug 1;144(2):161-170.

doi: 10.1097/AOG.0000000000005644. Epub 2024 Jun 3.

[Magnesium Sulfate Before Preterm Birth for Neuroprotection: An Updated Cochrane Systematic Review](#)

[Emily S Shepherd¹](#), [Shona Goldsmith](#), [Lex W Doyle](#), [Philippa Middleton](#), [Stéphane Marret](#), [Dwight J Rouse](#), [Peter Pryde](#), [Hanne T Wolf](#), [Caroline A Crowther](#)

Abstract

Objective: To systematically review the evidence for the effectiveness and safety of magnesium sulfate as a fetal neuroprotective agent when given to individuals at risk of preterm birth.

Data sources: We searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (through March 17, 2023), and reference lists of relevant studies.

Methods of study selection: Randomized controlled trials (RCTs) assessing magnesium sulfate for fetal neuroprotection in pregnant participants at risk of imminent preterm birth were eligible. Two authors assessed RCTs for inclusion, extracted data, and evaluated risk of bias, trustworthiness, and evidence certainty (GRADE [Grading of Recommendations Assessment, Development and Evaluation]).

Tabulation, integration, and results: We included six RCTs (5,917 pregnant participants and 6,759 fetuses at less than 34 weeks of gestation at randomization). They were conducted in high-income countries (two in the United States, two across Australia and New Zealand, and one each in Denmark and France) and commenced between 1995 and 2018. Primary outcomes: up to 2 years of corrected age, magnesium sulfate compared with placebo reduced the risk of cerebral palsy (risk ratio [RR] 0.71, 95% CI, 0.57-0.89; six RCTs, 6,107 children) and death or cerebral palsy (RR 0.87, 95% CI, 0.77-0.98; six RCTs, 6,481 children) (high-certainty evidence). Magnesium sulfate had little or no effect on death up to 2 years of corrected age (moderate-certainty evidence) or these outcomes at school age (low-certainty evidence). Although there was little or no effect on death or cardiac or respiratory arrest for pregnant individuals (low-certainty evidence), magnesium sulfate increased adverse effects severe enough to stop treatment (RR 3.21, 95% CI, 1.88-5.48; three RCTs, 4,736 participants; moderate-certainty evidence). Secondary outcome: magnesium sulfate reduced the risk of severe neonatal intraventricular hemorrhage (moderate-certainty evidence).

Conclusion: Magnesium sulfate for preterm fetal neuroprotection reduces cerebral palsy and death or cerebral palsy for children. Further research is required on longer-term benefits and harms for children, effect variation by participant and treatment characteristics, and the generalizability of findings to low- and middle-income countries.

Dev Med Child Neurol. 2024 Sep;66(9):1157-1172.

doi: 10.1111/dmcn.15899. Epub 2024 Mar 11.

[Neonatal magnesium sulphate for neuroprotection: A systematic review and meta-analysis](#)

[Emily Shepherd^{1,2,3}](#), [Tasneem Karim³](#), [Sarah McIntyre³](#), [Shona Goldsmith³](#), [Amy Keir^{1,2}](#), [Nadia Badawi^{3,4}](#), [Rod W Hunt^{3,5,6,7}](#), [Robert Galinsky^{7,8}](#)

Abstract

Aim: To review the evidence of the effects of neonatal magnesium sulphate for neuroprotection in perinatal asphyxia and hypoxic-ischaemic encephalopathy (HIE).

Method: This was a systematic review of randomized controlled trials (RCTs) (with meta-analysis) and non-RCTs assessing magnesium sulphate for treating perinatal asphyxia and

HIE at 35 weeks or more gestation (primary outcomes: neonatal death and death or long-term major neurodevelopmental disability).

Results: Twenty-five RCTs (2099 infants) and four non-RCTs (871 infants) were included, 23 in low- and middle-income countries (LMICs). In RCTs, reductions in neonatal death with magnesium sulphate versus placebo or no treatment (risk ratio [RR] = 0.68; 95% confidence interval [CI] = 0.53-0.86; 13 RCTs), and magnesium sulphate with melatonin versus melatonin alone (RR = 0.74; 95% CI = 0.58-0.95; one RCT) were observed. No difference in neonatal death was seen for magnesium sulphate with therapeutic hypothermia versus therapeutic hypothermia alone (RR = 0.66, 95% CI = 0.34-1.26; three RCTs), or magnesium sulphate versus phenobarbital (RR = 3.00; 95% CI = 0.86-10.46; one RCT). No reduction in death or long-term neurodevelopmental disability (RR = 0.52; 95% CI = 0.14-1.89; one RCT) but reductions in several short-term adverse outcomes were observed with magnesium sulphate. Evidence was low- to very-low certainty because of risk of bias and imprecision.

Interpretation: Given the uncertainty of the current evidence, further robust neonatal magnesium sulphate research is justified. This may include high-quality studies to determine stand-alone effects in LMICs and effects with and after therapeutic hypothermia in high-income countries.

BMC Pediatr. 2024 Aug 8;24(1):509.

doi: 10.1186/s12887-024-04987-6.

Cooling during transportation of newborns with hypoxic ischemic encephalopathy using phase change material mattresses in low-resource settings: a randomized controlled trial in Hanoi, Vietnam

[Hang T T Tran^{1,2}](#), [Dien M Tran³](#), [Ha T Le³](#), [Lena Hellström-Westas⁴](#), [Tobias Alfvén^{#5,6}](#), [Linus Olson^{#7}](#)

Abstract

Objective: To determine the effectiveness of phase-change-material mattress (PCM) during transportation of newborns with hypoxic ischemic encephalopathy (HIE).

Study design: Randomized controlled trial of newborns with HIE from June 2016 to December 2019. Patients were randomized to transport with PCM or without PCM (control) when transferred to a cooling center in northern Vietnam. Primary outcome measure was mortality rate, secondary outcomes including temperature control and adverse effects.

Result: Fifty-Two patients in PCM-group and 61 in control group. Median rectal temperature upon arrival was 34.5 °C (IQR 33.5-34.8) in PCM-group and 35.1 °C (IQR 34.5-35.9) in control group (p = 0.023). Median time from birth to reach target temperature was 5.0 ± 1.4 h and 5.5 ± 1.2 h in the respective groups (p = 0.065). 81% of those transported with PCM versus 62% of infants transported without (p = 0.049) had reached target temperature within the 6-h timeframe. There was no record of overcooling (< 32 °C) in any of the groups. There was no difference in mortality rate between the two groups (33% and 34% respectively (p > 0.05)).

Conclusion: Phase-change-material can be used as a safe and effective cooling method during transportation of newborns with HIE in low-resource settings.

doi: 10.1093/tropej/fmaf009.

Fluid restriction for term infants with hypoxic-ischemic encephalopathy following perinatal asphyxia-a randomized controlled trial

[Anitha Ananthan¹](#), [Haribalakrishna Balasubramanian²](#), [Ruchi Nanavati¹](#), [Prashanth Raghavendra¹](#)

Abstract

Fluid management in the first postnatal week among infants with perinatal asphyxia and hypoxic-ischemic encephalopathy (HIE) is an important knowledge gap. We aimed to evaluate the effects of fluid restriction on short- and long-term outcomes in infants with HIE. Term infants with moderate or severe HIE on therapeutic hypothermia were randomized within 6 hours of age to receive either restricted intravenous maintenance fluids (45 ml/kg/day on day 1 to a maximum of 120 ml/kg/day on day 6) vs conventional fluid (60 ml/kg/day on day 1 to a maximum of 150 ml/kg/day on day 6). The primary outcome was a composite of mortality or neurological abnormality at hospital discharge. We studied neurodevelopmental disability at 18-24 months using Bayley Scales of Infant Development, third edition. A total of 210 infants were randomized. Three infants died during the hospital stay. The primary outcome of mortality or neurological abnormality at discharge was not significantly different between the restricted and the conventional fluid group [57% vs 53%, RR: 1.07 (95% CI: 0.83, 1.37), P-value .58]. The incidence of cranial magnetic resonance imaging abnormalities was similar in the groups (65% vs 71%, P-value .30). There were no differences in the rates of severe neurodevelopmental disability at 18-24 months in the two groups [27% vs 28%, RR: 0.96 (95% CI: 0.62, 1.50), P-value .88]. Adverse outcomes were similar in both groups. Fluid restriction in the first postnatal week of life did not improve short- and long-term neurodevelopmental outcomes in term infants with moderate or severe HIE.

Arch Dis Child Fetal Neonatal Ed. 2024 Oct 18;109(6):594-601.

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Early and extended erythropoietin monotherapy after hypoxic ischaemic encephalopathy: a multicentre double-blind pilot randomised controlled trial

[Reema Garegrat¹](#), [Atul Londhe²](#), [Swati Manerkar³](#), [Sudhindrashayana Fattepur⁴](#), [Laxmikant Deshmukh²](#), [Amol Joshi²](#), [Savitha Chandriah⁵](#), [Malleesh Kariyappa⁶](#), [Sahana Devadas⁶](#), [Theranirajan Ethirajan⁷](#), [Kalaivani Srivasan⁷](#), [Chinnathambi Kamalarathnam⁷](#), [Anitha Balachandran⁷](#), [Elango Krishnan⁷](#), [Deepthy Sahayaraj⁷](#), [Prathik Bandiya⁸](#), [Niranjan Shivanna⁹](#), [Constance Burgod¹⁰](#), [Ashwini Thayyil¹¹](#), [Annie Alocious¹⁰](#), [Marianna Lanza¹⁰](#), [Pallavi Muraleedharan¹⁰](#), [Stuti Pant¹⁰](#), [Harini Venkateswaran¹²](#), [Maria Moreno Morales¹⁰](#), [Paolo Montaldo¹⁰](#), [Vaisakh Krishnan¹⁰](#), [Thaslima Kalathingal¹³](#), [Anagha Rajeev Joshi¹³](#), [Ajay Vare²](#), [G C Patil¹⁴](#), [Babu Peter Satyanathan⁷](#), [Pavan Hapat¹²](#), [Abhishek Deshmukh¹²](#), [Indramma Shivarudhrappa¹²](#), [Manjesh Kurupalya Annayappa⁵](#), [Mythili Baburaj¹²](#), [Christina Muradi¹²](#), [Esprance Fernandes¹²](#), [Nishad Thale¹²](#), [Ismat Jahan¹⁵](#), [Mohammed Shahidullah¹⁵](#), [Sadaka Moni Choudhury¹⁵](#), [Sanjoy Kumer Dey¹⁵](#), [Sutapa B Neogi¹⁶](#), [Rupsa Banerjee¹⁶](#), [Vanessa Rameh¹⁷](#), [Farah Alobeidi¹⁸](#), [Ellen Grant¹⁷](#), [Sandra E Juul¹⁹](#), [Martin Wilson²⁰](#), [Enrico De Vita²¹](#), [Ronit Pressler¹¹](#), [Paul Bassett²²](#), [Seetha Shankaran²³](#), [Sudhin Thayyil¹⁰](#)

Abstract

Objective: To examine the feasibility of early and extended erythropoietin monotherapy after hypoxic ischaemic encephalopathy (HIE).

Design: Double-blind pilot randomised controlled trial.

Setting: Eight neonatal units in South Asia.

Patients: Neonates (≥ 36 weeks) with moderate or severe HIE admitted between 31 December 2022 and 3 May 2023.

Interventions: Erythropoietin (500 U/kg daily) or to the placebo (sham injections using a screen) within 6 hours of birth and continued for 9 days. MRI at 2 weeks of age.

Main outcomes and measures: Feasibility of randomisation, drug administration and assessment of brain injury using MRI.

Results: Of the 154 neonates screened, 56 were eligible; 6 declined consent and 50 were recruited; 43 (86%) were inborn. Mean (SD) age at first dose was 4.4 (1.2) hours in erythropoietin and 4.1 (1.0) hours in placebo. Overall mortality at hospital discharge occurred in 5 (19%) vs 11 (46%) ($p=0.06$), and 3 (13%) vs 9 (40.9%) ($p=0.04$) among those with moderate encephalopathy in the erythropoietin and placebo groups. Moderate or severe injury to basal ganglia, white matter and cortex occurred in 5 (25%) vs 5 (38.5%); 14 (70%) vs 11 (85%); and 6 (30%) vs 2 (15.4%) in the erythropoietin and placebo group, respectively. Sinus venous thrombosis was seen in two (10%) neonates in the erythropoietin group and none in the control group.

Conclusions: Brain injury and mortality after moderate or severe HIE are high in South Asia. Evaluation of erythropoietin monotherapy using MRI to examine treatment effects is feasible in these settings.

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doi: 10.1186/s12887-024-05107-0.

[Oral sildenafil versus bosentan for treatment of persistent pulmonary hypertension of the newborn: a randomized controlled trial](#)

[Aditya Kallimath](#)¹, [Sujata Deshpande](#)¹, [Pari Singh](#)¹, [Reema Garegrat](#)², [Satyan Lakshminrusimha](#)³, [Rajesh Maheshwari](#)⁴, [Pradeep Suryawanshi](#)⁵

Abstract

Background: Access to inhaled nitric oxide (iNO) is limited in low resource settings due to non-availability and high cost. There is a need for research on low-cost alternative therapies for management of persistent pulmonary hypertension of the newborn (PPHN). We aimed to compare oral sildenafil and bosentan as monotherapy in the treatment of neonates with PPHN.

Study design: In this single-centre open-label randomized controlled trial (RCT), term and late preterm neonates with PPHN, defined as pulmonary arterial systolic pressure (PASP) > 35 mmHg and requiring fraction of inspired oxygen (FiO_2) > 0.21 , were randomized to receive oral sildenafil and bosentan. The primary outcome was reduction of PASP by 25% within 48 h after start of drug.

Results: Thirty-six neonates were analyzed (18 in each group). Initial PASPs were similar in both groups. The median (IQR) time for the primary outcome (PASP to reduce by 25% within 48 h) was 36 (24-48) h and 96 (48-120) h in sildenafil and bosentan groups respectively ($p =$

0.008). There was also a higher need to add other pulmonary vasodilators in bosentan group as compared to sildenafil group ($p = 0.006$).

Conclusion: Sildenafil was associated with quicker reduction of PASP and FiO_2 in neonates with PPHN, as compared to bosentan. Large multicentre blinded trials to assess efficacy and safety of bosentan in comparison with other pulmonary vasodilators would help to get a clearer understanding of its role in the management of PPHN, particularly for use in resource-limited settings that lack iNO.

Neonatal seizures

Indian J Pediatr. 2025 Jan;92(1):29-41.

doi: 10.1007/s12098-023-04905-1. Epub 2023 Nov 8.

[Levetiracetam versus Phenobarbitone for Management of Neonatal Seizures: A Systematic Review and Meta-analysis](#)

[Jogender Kumar^{#1}](#), [Bharti Yadav^{#2}](#), [Jitendra Meena³](#), [Jaivinder Yadav¹](#), [Jitendra Kumar Sahu⁴](#)

Abstract

Objectives: To review whether levetiracetam is non-inferior to phenobarbitone as the first-choice antiseizure medication (ASM).

Methods: The authors searched Medline, Embase, Web of Science, Scopus, and Cochrane Library for randomized controlled trials (RCTs) published until May 31, 2023. RCTs comparing the efficacy and safety of levetiracetam and phenobarbitone as first-line ASM in neonatal seizures were included. Random effects meta-analysis was performed, and the Risk of Bias version 2 tool was used for quality assessment.

Results: Eleven RCTs enrolling 821 neonates [mostly term, with hypoxic-ischemic encephalopathy (HIE)] were included. There was no significant difference in seizure control between levetiracetam and phenobarbitone (10 RCTs, 786 participants; relative risk RR: 1.11; 95% CI: 0.79, 1.54; I^2 88%). Neonates in the levetiracetam group had a significantly lower incidence of hypotension (RR: 0.28; 95% CI: 0.09, 0.86), respiratory depression (RR: 0.36, 95% CI: 0.19, 0.66), and depressed sensorium (RR: 0.52, 95% CI: 0.27, 1.00). Three studies compared neurodevelopmental outcomes; however two of them were cross-over trials where infants received both drugs. Only one RCT enrolled pure cohorts and showed better neurodevelopment in the levetiracetam group at one month of age.

Conclusions: With the limitation of very-low certainty evidence, the results of this systematic review suggest that levetiracetam may be non-inferior to phenobarbitone for managing neonatal seizures. Considering a better safety profile and marginally better neurodevelopment in the short term, levetiracetam may be considered an initial choice for managing neonatal seizures.

Neonatal sepsis

J Perinatol. 2025 Mar;45(3):342-349.

doi: 10.1038/s41372-025-02222-3. Epub 2025 Feb 13.

Early hydrocortisone verses placebo in neonatal shock- a double blind Randomized controlled trial

[Sankalp Dudeja¹](#), [Shiv Sajan Saini²](#), [Venkateshan Sundaram¹](#), [Sourabh Dutta¹](#), [Naresh Sachdeva³](#), [Praveen Kumar¹](#)

Abstract

Objective: To compare early hydrocortisone (initiated along with vasoactive therapy) vs. placebo for all-cause mortality within next 14 days among neonates with fluid-refractory shock.

Study design: Neonates with fluid-refractory shock were randomly assigned to receive hydrocortisone or saline placebo alongside vasoactive drugs. If they developed catecholamine-resistant shock, the study drug was replaced with open-label hydrocortisone.

Result: Eighty-four neonates were randomized (early hydrocortisone=43 and placebo=41). Median gestational age of our cohort (n = 84) was 30.3 weeks [interquartile range (IQR): 27.7, 32.5] and median birth weight was 1148 grams (IQR: 860, 1419). The 14-day all-cause mortality was comparable between early hydrocortisone and placebo groups [OR 0.53 (95% CI 0.19, 1.52)]. Both groups had similar duration of vasoactive drugs and vasoactive-inotrope scores, incidence of adverse effects of hydrocortisone and incidence of medium-term complications.

Conclusion: We did not observe a significant reduction in 14-day mortality with early hydrocortisone compared to placebo in fluid-refractory neonatal shock.

Jaundice

Public Health. 2024 Dec 16;238:221-228.

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Effectiveness of prenatal intervention on neonatal hyperbilirubinemia management in rural Bangladesh: Results from a cluster-randomized trial

[Supta Sarker¹](#), [Farjana Jahan²](#), [Sarker Masud Parvez³](#), [A K M Shoab⁴](#), [Rezaul Hasan⁵](#), [Shams El Arifeen⁶](#), [Sk Masum Billah⁷](#), [Md Mahbubul Hoque⁸](#), [Mahbubur Rahman⁹](#)

Abstract

Objectives: Nearly 80 % of severe neonatal hyperbilirubinemia cases are identified too late for medical treatment in lower-middle-income countries. Parents' understanding of neonatal jaundice is crucial for early detection and effective treatment. This study evaluated the effectiveness of prenatal sensitization in improving maternal knowledge and attitude toward neonatal hyperbilirubinemia management in Bangladesh.

Study design: Cluster-randomized trial.

Methods: Between September 2019 and March 2021, a prospective home-based intervention trial on neonatal hyperbilirubinemia was conducted in 20 interventions and comparison clusters through community health workers (CHW). Participants were pregnant women in their second or third trimester of pregnancy. Proportion-based difference-in-difference (DID) was calculated to determine changes in the mother's knowledge and attitude towards newborn jaundice.

Results: A total of 539 pregnant women were enrolled, 273 in the intervention, and 266 in the comparison arm. Following the intervention, participant's overall knowledge level about

neonatal hyperbilirubinemia increased significantly (DID: 24.9, 95%CI: 19.2, 30.7) from baseline (33.2 %) to endline (70.5 %). Knowledge of newborn jaundice management showed the most improvement (DID: 60), followed by danger signs detection (DID: 40.0). The intervention also enhanced participants' positive attitudes regarding neonatal hyperbilirubinemia (DID: 13.1, 95%CI: 8.1, 18.0). Mothers with improved knowledge of neonatal hyperbilirubinemia were nearly five times more likely to have a favorable attitude toward it than those with counterparts.

Conclusions: CHW-led home-based prenatal sensitization interventions substantially improved mothers' awareness and attitudes toward neonatal hyperbilirubinemia detection and management. Integrating such sensitization into prenatal care of the existing health system could be a practical approach to improve neonatal health outcomes in Bangladesh.

BMJ Paediatr Open. 2024 Oct 11;8(1):e002902.

doi: 10.1136/bmjpo-2024-002902.

Evaluation of efficacy of oral calcium phosphate as an adjunct to standard-of-care regular phototherapy in cases of neonatal jaundice: a hospital-based double-blind, randomised, placebo-controlled trial

[Arnab Ghorui¹](#), [Bhabesh Kant Chowdhry²](#), [Pramod Kumar Manjhi³](#), [Pradeep Kumar¹](#), [Chandra Mohan Kumar⁴](#)

Abstract

Objective: Neonatal jaundice is the most common cause of neonatal morbidity and rehospitalisation in the first week of life, affecting approximately 60% of term and 80% of preterm neonates, with 10% requiring phototherapy to prevent bilirubin-induced neurological dysfunction. Enterohepatic circulation contributes 10%-20% of the body's bilirubin load, and oral calcium-phosphate can inhibit this process by binding to unconjugated bilirubin and acting as a bilirubin-trapping agent in the gut. This study aimed to evaluate the efficacy of oral calcium phosphate as an adjunct to phototherapy in reducing phototherapy duration, improving bilirubin decline rate and lowering rebound hyperbilirubinaemia incidence.

Methods: This double-blind, placebo-controlled randomised controlled trial with a 1:1 allocation ratio was conducted in the neonatal intensive care unit of a tertiary care hospital in Eastern India. The investigator and the analyst were blinded to the treatment assignments. Eligible neonates with neonatal jaundice requiring phototherapy as per the 'American Academy of Pediatrics or 'National Institute for Health and Care Excellence' guidelines were enrolled and randomly assigned to receive either oral calcium phosphate or placebo.

Results: The total duration of phototherapy was significantly lower in the intervention group compared with placebo (18.8±5.63 hours vs 24.3±4.50 hours; mean difference=-5.55 (95% CI -7.82 to -3.28), p<0.001). The rate of fall of bilirubin (mg/dL/hour) was also significantly higher in the intervention group (0.186±0.0137 vs 0.116±0.0088; mean difference=0.0693 (95% CI 0.0642 to 0.0745), p<0.001). The intervention group showed a trend towards a decrease in the incidence of rebound hyperbilirubinaemia, with a relative risk of 0.30 ((95% CI 0.0891 to 1.01), p=0.066).

Conclusion: The use of oral calcium phosphate results in a statistically significant reduction in phototherapy hours, an improvement in the rate of bilirubin decline and a decrease in rebound hyperbilirubinaemia incidence. This allows for shorter hospital stays and reduces

the need for rehospitalisation, resulting in less mother-baby dyad separation, lower hospital resource consumption and reduced financial burden on parents.

Eur J Pediatr. 2025 Jun 2;184(6):383.

doi: 10.1007/s00431-025-06226-1.

Intravenous fluid supplementation in management of severe unconjugated hyperbilirubinemia in preterm neonates-a randomized controlled trial

[Aradhana¹](#), [Santosh Kumar Panda²](#), [Pravati Jena¹](#), [Manas Kumar Nayak¹](#), [Sebaranjan Biswal¹](#), [Manaswinee Sahoo³](#), [Ramakrushna Gudu¹](#), [Soumini Rath¹](#)

Abstract

The purpose of this study is to evaluate the role of intravenous fluid supplementation in reducing total serum bilirubin (TSB) in preterm neonates with hyperbilirubinemia. In this open-label randomized control trial, a total of 72 preterm neonates with a gestational age of 29-33⁺⁶ weeks and a TSB level exceeding 2 mg/dl below the exchange transfusion threshold as per United Kingdom National Institute for Health and Care Excellence (UK-NICE) guidelines were randomized into the fluid supplementation (FS) group and the control group in a ratio of 1:1. Neonates in the FS group received intravenous fluid (5% dextrose on day 2 or N/5 saline with 5% dextrose, amount: 1/4th of total daily fluid intake or maximum 30 ml/kg over 8 h) with phototherapy vs. only phototherapy in the control group. The primary outcome was reduction in TSB level at 6, 18, and 24 h after intervention and duration of phototherapy in FS compared to the control group. The demographic characteristics and mean (SD) TSB levels of enrolled preterm neonates in both groups were comparable. The mean (SD) reduction in TSB level at 6 h in the FS group and the control group were 1.42 (1.19) and 0.32 (0.17), $P = 0.001$; at 18 h, 2.11 (1.35) and 0.79 (0.25), $P = 0.001$; and at 24 h, 2.96 (1.41) and 1.56 (0.46), $P = 0.001$. There was no significant difference in the duration of phototherapy [mean (SD) 44.66(5.45) vs 43.33 (5.93) h, $P = 0.32$] and cases of hyponatremia [14 (40%) vs 09 (24.3%) $P = 0.153$] at 24 h between FS and control group.

Conclusion: Intravenous fluid supplementation helps in the rapid reduction of TSB levels in preterm neonates with severe hyperbilirubinemia with minimal adverse effects, but does not affect the duration of phototherapy.

Nutrition

(see also Anaemia and iron deficiency, Zinc, Maternal nutrition, Vitamin A, Tuberculosis, Helminths and other gastrointestinal infections, HIV case management)

Growth monitoring

BMJ Glob Health. 2024 Aug 16;9(8):e015438.

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The impact of home-installed growth charts and small-quantity lipid-based nutrient supplements (SQ-LNS) on child growth in Zambia: a four-arm parallel open-label cluster randomised controlled trial

[Günther Fink^{1,2}](#), [Lindsey M Locks^{3,4}](#), [Jacqueline M Lauer⁴](#), [Mpela Chembe⁵](#), [Savanna Henderson⁶](#), [Dorothy Sikazwe⁷](#), [Tamara Billima-Mulenga⁵](#), [Doug Parkerson⁶](#), [Peter C Rockers³](#)

Abstract

Background: Childhood stunting remains common in many low-income settings and is associated with increased morbidity and mortality, as well as impaired child development.

Methods: The main objective of the study was to assess whether home-installed growth charts as well as small-quantity lipid-based nutrient supplements (SQ-LNS) can reduce growth faltering among infants. All caregivers of infants between 2 and 10 months of age at baseline, and at least 6 months old at the beginning of the interventions, in 282 randomly selected enumeration areas in Choma, Mansa and Lusaka districts in Zambia were invited to participate in the study. Cluster randomisation was stratified by district. A software-generated random number draw was used to assign clusters to one of four arms: (1) no intervention (control); (2) home installation of a wall chart that contained a growth monitoring tool along with key messages on infant and young child feeding and nutrition (growth charts only); (3) 30 sachets of SQ-LNS delivered each month (SQ-LNS only) or (4) growth charts+SQ LNS. The primary outcomes were children's height-for-age z-score (HAZ) and stunting (HAZ <-2) after 18 months of intervention. Secondary outcomes were haemoglobin (Hb), anaemia (Hb<110.0 g/L), weight-for-height, weight-for-age z-score (WAZ), underweight (WAZ<-2) and child development measured by the Global Scales of Early Development (GSED). Outcomes were analysed intention to treat using adjusted linear and logistic regression models and compared each of the three interventions to the control group. Assessors and analysts were blinded to the treatment-blinding of participating families was not possible.

Results: A total of 2291 caregiver-child dyads across the 282 study clusters were included in the study. 70 clusters (557 dyads) were assigned to the control group, 70 clusters (643 dyads) to growth charts only, 71 clusters (525 dyads) to SQ-LNS and 71 clusters (566 dyads) to SQ-LNS and growth charts. SQ-LNS improved HAZ by 0.21 SD (95% CI 0.06 to 0.36) and reduced the odds of stunting by 37% (adjusted OR, aOR 0.63, 95% CI (0.46 to 0.87)). No HAZ or stunting impacts were found in the growth charts only or growth charts+SQ LNS arms. SQ-LNS only improved WAZ (mean difference, MD 0.17, 95% CI (0.05 to 0.28)). No impacts on WAZ were seen for growth charts and the combined intervention. Child development was higher in the growth charts only (MD 0.18, 95% CI (0.01 to 0.35)) and SQ-LNS only arms (MD 0.28, 95% CI (0.09 to 0.46)). SQ-LNS improved average haemoglobin levels (MD 2.9 g/L (0.2, 5.5)). The combined intervention did not have an impact on WAZ, Hb or GSED but reduced the odds of anaemia (aOR 0.72, 95% CI (0.53 to 0.97)). No adverse events were reported.

Interpretation: SQ-LNS appears to be effective in reducing growth faltering as well as improving anaemia and child development. Growth charts also show the potential to reduce anaemia and improve child development but do not seem as effective in addressing growth faltering. Further research is needed to better understand reduced effectiveness when both interventions are combined.

Nutritional education

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Effect of a Nutritional Education Program on Children's Undernutrition in Indonesia: A Randomized Controlled Trial

[Raden Ahmad Dedy Mardani](#), [Wan-Ru Wu](#), [Zuhratul Hajri](#), [Zurriyatun Thoyibah](#), [Henny Yolanda](#), [Hui-Chuan Huang](#)

Abstract

Introduction: To assess effects of a nutritional education program on improving mothers' undernutrition knowledge, self-efficacy, and complementary feeding practices, and reducing undernutrition in children aged <2 years.

Method: A randomized controlled trial was conducted at a community healthcare center in Indonesia. The intervention group participated in a 4-week nutritional education program; the control group received standard care (n = 80; 1:1 ratio). Measurements consisted of mothers' knowledge of undernutrition, self-efficacy, and complementary feeding practices, and children's anthropometric indicators.

Results: Intervention group mothers improved their understanding of undernutrition, self-efficacy, and complementary feeding practices compared to the control group. Additionally, children in the intervention group exhibited increased mean Z-scores for stunting, wasting, and being underweight at 12 and 24 weeks following the intervention.

Discussion: Healthcare professionals can regularly provide nutritional education programs related to managing undernutrition and complementary feeding practices for mothers with children aged <2 years to prevent and improve undernutrition.

Public Health. 2025 Feb 28;242:28-36.

doi: 10.1016/j.puhe.2025.02.031. Online ahead of print.

Effect of video-assisted educational intervention on improving knowledge, attitude and practice among mothers of children below five years on malnutrition: A systematic review

[Sowmya Pujari](#)¹, [Muhammed Rashid](#)¹, [Girish Thunga](#)¹, [Ranjitha S Shetty](#)², [Suneel C Mundkur](#)³, [Elsa Sanatombi Devi](#)⁴, [Unnikrishnan B](#)⁵, [Sreedharan Nair](#)⁶

Abstract

Objectives: This review aimed to assess the effect of video-assisted educational interventions in enhancing knowledge, attitudes, and practices (KAP) among mothers of malnourished children aged <5 years.

Study design: This was a systematic review.

Methods: A systematic search was conducted across PubMed, Scopus, and EMBASE databases from inception until November 2022. The selection criteria adhered to the PICOS framework, targeting randomized controlled trials (RCTs) involving mothers who received video-assisted educational interventions alongside comparison groups to evaluate malnutrition-associated KAP outcomes. Risk of bias was assessed using the Cochrane risk of bias assessment tool. Two independent reviewers performed study selection, data extraction, and quality assessment, resolving any disagreements through discussion or consultation with a third reviewer.

Results: Among 11,434 screened articles, seven RCTs met the inclusion criteria, focusing on mothers of children aged <5 years. Statistically significant improvements were observed in maternal knowledge (n = 2), attitude (n = 1), and practice (n = 6) with respect to the feeding

practices following video-assisted educational interventions. However, the effect of the educational intervention on children's z-scores remained inconclusive.

Conclusions: Video-assisted educational interventions were effective in KAP concerning feeding practices among mothers of children aged <5 years. However, their impact on children's z-scores remain inconclusive, emphasising the need for further research to explore factors influencing these outcomes. Further research is needed to determine the long-term effect on children's nutritional status.

Nutrients. 2025 Jan 23;17(3):414.

doi: 10.3390/nu17030414.

[A Mobile-Based Approach to Enhance Knowledge of Infant and Young Child Feeding Among Teenage Mothers in Nigeria: A Randomized Controlled Trial](#)

[Mercy E Sosanya](#)^{1,2}, [Oluwatosin D Adesanya](#)², [Hauwa E Rufai](#)², [Jeanne H Freeland-Graves](#)¹

Abstract

Background/Objectives: The second highest prevalence of childhood malnutrition in the world is found in Nigeria. Infant and young child feeding practices (IYCF) are crucial predictors of the nutritional status of children. This study evaluated the effects of utilization of the BabyThrive app versus control on IYCF knowledge of Nigerian teenage mothers. **Methods:** A parallel, randomized controlled trial was conducted with 194 low-income teenage mother-child (0-2 years) dyads in Nigeria. Outcome measures included knowledge concerning food type for an infant, exclusive breastfeeding, complementary feeding, and total IYCF knowledge scores. **Results:** No significant differences in demographic characteristics or IYCF knowledge were found at baseline. Post-intervention, almost all BabyThrive participants vs. only 36.1% of controls were aware that expressed breast milk is the ideal food for an infant <6 months, when a mother resumes work ($p < 0.05$). As compared to the BabyThrive group, knowledge of how to maintain breast milk supply (5.2% vs. 83.5%), the duration of safety of breast milk at room temperature (15.4% vs. 85.6%), responsive feeding (58.8% vs. 96.9) and dietary diversity (15.5% vs. 99%) was substantially lower in controls ($p < 0.05$). Mean knowledge on exclusive breastfeeding (25.17 ± 1.37 vs. 19.87 ± 1.80), complementary feeding (15.68 ± 0.60 , vs. 13.51 ± 1.21) and total knowledge scores (46.8 ± 1.79 vs. 38.65 ± 2.71) was higher in the BabyThrive group ($p < 0.05$). **Conclusions:** In sum, the BabyThrive app significantly increased maternal IYCF knowledge in comparison with controls. It will be a useful tool to improve maternal IYCF knowledge in resource-limited areas.

Matern Child Nutr. 2024 Jul 17:e13702.

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[Text messages to improve young child diets: Results from a cluster-randomized controlled trial in Kanchanpur, Nepal](#)

[Kenda Cunningham](#)¹, [Sidney Cech](#)², [Aman Sen Gupta](#)³, [Pooja Pandey Rana](#)³, [Debbie Humphries](#)², [Edward A Frongillo](#)⁴

Abstract

The objective of this study was to test whether adding a text message campaign about the importance of eating eggs and other nutrition-related behaviours to an on-going package of large-scale, diverse social and behaviour change interventions would improve four types of nutrition-related knowledge and behaviour outcomes: child diets (egg consumption as the primary outcome), maternal diets, maternal nutrition knowledge, and maternal participation in additional interventions. The cluster-randomized controlled trial involved a repeat cross-sectional design, recruiting families with children 12-23 months of age at baseline and endline in one plains district of Nepal. Throughout the 1000-day period, 51 text messages were sent to each household at specific time points to reinforce ideal diets and other nutrition-related practices and promote engagement with community health workers and other intervention platforms. The primary outcome was egg consumption and dietary diversity among young children. We found no population-level effect. Some evidence supports that for those who received and opened the SMS intervention, it improved child egg consumption (odds ratio [OR]: 1.41, 95% confidence interval [CI]: 1.03-1.93), child minimum dietary diversity (OR: 1.36, 95% CI: 1.07-1.73), child dietary diversity scores (β : 0.15, 95% CI: 0.01-0.24), as well as maternal IYCF knowledge (β : 0.21, 95% CI: 0.08-0.35), participation in health mothers' group meetings (OR: 3.03, 95% CI: 1.91-4.84) and Bhanchhin Aama listenership (OR: 1.36, 95% CI: 1.07-1.73). This study highlights the importance of more research to understand the effectiveness of emerging digital interventions for behaviour change among specific populations, to facilitate nuanced targeting to those who can best benefit from these investments

Micronutrients, multivitamins, and food fortification

(See also Vitamin A)

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[Impact of nutritional and multiple micronutrients supplementation to lactating mothers 6 months postpartum on the maternal and infant micronutrient status: a randomised controlled trial in Delhi, India](#)

[Rukman Manapurath^{1,2}](#), [Ranadip Chowdhury¹](#), [Ravi Prakash Upadhyay¹](#), [Beena Bose³](#), [Sarita Devi³](#), [Pratibha Dwarkanath³](#), [Anura V Kurpad³](#), [Nita Bhandari¹](#), [Sunita Taneja¹](#)

Abstract

Objectives: To assess the impact of nutritional and multiple-micronutrient supplementation to lactating mothers on the micronutrient status of mother-infant dyad at 6 months of age postnatally.

Design: This study was a trial that aimed to investigate the impact of maternal nutritional supplementation on infant growth. A secondary objective was to assess the effect on the micronutrient status of mother-infant pairs. The intervention group mothers received snacks with 600 kcal energy, 20 g protein and daily micronutrient tablets.

Setting: Blood samples were collected from both mothers and infants at 6 months.

Participants: The participants in this study were mother-infant pairs. The micronutrient status of these pairs was assessed through blood samples, focusing on vitamins A, D, B₁₂, ferritin, Zn and folate.

Results: Micronutrient analysis of serum samples from 600 mother-infant pairs showed that mothers in the intervention group had higher levels of serum ferritin (mean difference (MD) 14.7 ng/ml), retinol (MD 0.6 µmol/l), folate (MD 3.3 ng/ml) and vitamin D (1.03 ng/ml) at 6 months postpartum. Additionally, the supplementation was associated with a higher mean ± sd of serum ferritin (MD 8.9 ng/ml) and vitamin A (MD 0.2 µmol/l) levels in infants at 6 months.

Conclusions: The study found that supplementing maternal nutrition with additional dietary and micronutrient intakes during lactation improved maternal micronutrient status and slightly increased ferritin and vitamin A levels in infants at 6 months. The findings highlight the importance of nutritional interventions for improving the micronutrient health of mother-infant pairs, with significant public health implications.

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Predictors of Anaemia Among Young Children Receiving Daily Micronutrient Powders (MNPs) for 24 Weeks in Bangladesh: A Secondary Analysis of the Zinc in Powders Trial

Lauren Thompson^{1,2}, Charles Arnold^{1,2}, Janet Peerson², Julie M Long³, Jamie L E Westcott³, M Munirul Islam⁴, Robert E Black^{5,6}, Nancy F Krebs^{3,6}, Christine M McDonald^{6,7}

Abstract

In Bangladesh, anaemia is estimated to affect 52% of children 6-59 months, with the youngest children (6-23 months) experiencing the highest levels of anaemia (71%). Micronutrient powders (MNPs) are designed to increase micronutrient intake in young children; however, in some settings, the prevalence of anaemia may remain elevated despite the high coverage of MNPs. In a secondary analysis of the Zinc in Powders trial (ZiPT), we identified risk factors that were associated with anaemia among Bangladeshi children 9-11 months of age who received standard 15-component MNPs, including 10 mg of iron, daily for 24 weeks. At enrolment, socio-demographic characteristics were collected. Morbidity symptoms were assessed on a semi-weekly basis. Haemoglobin (measured via single-drop capillary blood using Hemocue 301+) and child anthropometry were assessed at enrolment and endline (24 weeks). Risk factors for anaemia at endline (24 weeks) were identified using minimally adjusted (age and sex) logistic regression models. Multivariate models were subsequently constructed, controlling for age, sex and significant risk factors. Of the 481 children randomized to the MNP arm, 442 completed the trial and had haemoglobin data available at endline. Anaemia (haemoglobin < 10.5 g/dL) prevalence declined from 54.1% at baseline to 32.6% at endline. In minimally adjusted models, season of enrolment, underweight at enrolment, asset score, hygiene score and frequent morbidity symptoms were associated with the odds of anaemia at endline. However, some factors lost statistical significance in multivariate models. MNPs are an important tool for anaemia prevention; however, they should be part of an integrated approach for anaemia control.

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The Effectiveness of Zinc-Biofortified Wheat Flour Intake on the Growth and Morbidity Outcomes of Rural Pakistani Children and Adolescent Girls: A Cluster-Randomised, Double-Blind, Controlled Trial

[Swarnim Gupta¹](#), [Mukhtiar Zaman²](#), [Sadia Fatima³](#), [Victoria H Moran¹](#), [Jonathan K Sinclair¹](#), [Nicola M Lowe¹](#)

Abstract

Background: Zinc-biofortified cereals are a promising strategy to combat zinc deficiency, though evidence on health outcomes is limited. This study assessed the effectiveness of consuming zinc-biofortified wheat flour on growth and zinc-related morbidity among adolescent girls (10-16 years; N = 517) and children (1-5 years; N = 517) living in rural north-west Pakistan.

Methods: In this double-blind, cluster-randomised controlled effectiveness trial, 486 households received either zinc-biofortified or control wheat flour for 25 weeks. Anthropometric measurements and lung function tests (LFTs) were performed at the beginning, middle, and endline. Data on the incidence and duration of respiratory tract infection (RTI) and diarrhoea in the preceding two weeks were collected fortnightly. Analyses included baseline-adjusted linear mixed models for continuous outcomes and Pearson's chi-square for categorical data.

Results: At a zinc differential of 3.7 mg/kg for adolescent girls provided by zinc-biofortified wheat flour, the intervention had no significant effect on height or weight. For children, head circumference was significantly greater in the biofortified group at endline (control 48.47 ± 2.03 cm vs. intervention 48.76 ± 1.82 cm; $p = 0.003$), with no differences in other anthropometric parameters. Towards the end of the trial, a lower incidence of RTIs was reported in the intervention arm compared to the control arm for both children (week 26: control 27.4% vs. intervention 17.6%, $p = 0.036$) and adolescent girls (week 24: control 19.3% vs. intervention 11.5%, $p = 0.037$; week 26: control 14.5% vs. intervention 6.1%, $p = 0.014$). When the longitudinal prevalence (cumulative days of sickness as a percentage of total days) of RTI was considered, no treatment effects were observed. No benefits of treatment were reported for diarrhoea or LFT.

Conclusions: The provision of zinc-biofortified wheat flour for 25 weeks did not have a significant effect on the growth of adolescent girls but modestly improved head circumference in children. Longer-term interventions are needed to monitor changes in functional outcomes with the national scale-up of zinc-biofortified wheat varieties.

Nutr Rev. 2025 Jul 1;83(7):1227-1239.

doi: 10.1093/nutrit/nuaf019.

Comparison of Effects of Iron and Multiple Micronutrient Supplementation on Hematological and Growth Indicators among Older Children, Adolescents, and Young Adults in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

[Ai Zhao^{1,2}](#), [Xiaona Na^{1,2}](#), [Fengqi Liu³](#), [Zekun Chen^{1,2}](#), [Huanhuan Yang^{1,2}](#), [Dongqing Wang⁴](#), [Christopher R Sudfeld⁴](#), [Zhihui Li^{1,2}](#), [Wafaie W Fawzi^{5,6}](#)

Affiliations Expand

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Abstract

Context: Middle childhood, adolescence, and young adulthood are characterized by high nutritional demands and vulnerability to anemia. Limited efforts have been made to synthesize the evidence comparing the effects of iron and multiple micronutrient (MMN) supplementation in these populations.

Objective: In this study we sought to examine the effects of iron and MMN on anemia and anthropometric variables among people aged 5 to 24 years in low- and middle-income countries.

Data sources: The PubMed, Embase, Cochrane Library, and CINAHL databases were searched from inception to July 2024 to identify 50 randomized controlled trials (RCTs) of iron or MMN supplementation with outcomes.

Data extraction: Only RCTs that used iron or MMN were included in this analysis.

Data analysis: Compared to placebo, supplementation with iron and MMN was associated with 5.81 g/L (95% CI: 4.19-7.44 g/L) and 4.82 g/L (95% CI: 2.32-7.32 g/L) incremental increases in hemoglobin levels, respectively. The therapeutic effects of MMN (hemoglobin: 9.3 g/L, 95% CI: 1.52-17.09 g/L) and iron (10.24 g/L, 95% CI: 5.10-15.39 g/L) were both observed in populations of older children, adolescents, and young adults with anemia. Stratified analysis showed that with either MMN or iron supplementation, higher iron content (> 30 mg/d) could lead to a higher increment of hemoglobin, while a shorter intervention duration (< 3 months) showed more benefits in improving hemoglobin. For ferritin, the significant benefit of supplementation was observed only with iron and not with MMN. Iron was also found to decrease serum transferrin receptor and zinc protoporphyrin, but there was no effect on C-reactive protein. For growth indicators, iron was found to increase weight (0.52 kg, 95% CI: 0.12-0.93 kg), while MMN was found to increase height (0.87 cm, 95% CI: 0.16-1.59 cm).

Conclusions: Overall, supplementation with iron compared with MMN had similarly beneficial effects on improving the hemoglobin level in older children, adolescents, and young adults, but there was some indication that there may be differential effects on growth indicators.

Probiotics

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Probiotics and Synbiotics Administered to Young Infants: Perceptions and Acceptability Amongst Carers and Healthcare Workers in Western Kenya

[Mary Iwaret Oti^{1,2}](#), [Florence Achieng Were²](#), [Sevim Zaim³](#), [Helen Nabwera¹](#), [Simon Kariuki²](#), [Stephen Allen¹](#)

Abstract

Background/objectives: A contributory factor to childhood undernutrition is poor gut health occurring within the first 6-12 weeks of life despite exclusive breastfeeding.

Pro/synbiotic administration may protect gut health. A qualitative study was conducted amongst mothers/carers and healthcare workers (HCWs) to explore their perceptions and the acceptability of pro/synbiotics administration in early life.

Methods: This study was nested within a randomised, open, clinical trial of pro/synbiotics with 32 doses administered under supervision to infants between ages 0 and 5 months in western Kenya. Semi-structured interviews were conducted with 14 mothers/carers, 12 Peer Mothers and 7 healthcare workers (HCWs) selected by purposive critical and key informant sampling. Interviews were transcribed and analysed using a thematic coding framework.

Results: The satisfaction with the pro/synbiotic administration was very high amongst all three groups. Commonly perceived benefits included protection from diseases, healthy growth of the infant and improved appetite. The main barriers were working mothers and other commitments making it difficult to stick to scheduled administration visits, adverse judgement and opinions in the community, and a lack of engagement from fathers. Insights were gained into different means of administering pro/synbiotics to young infants. Triangulation of the findings of the mothers/carers with HCWs showed that most identified motivations and challenges were similar.

Conclusions: Pro/synbiotic administration was well accepted by the mothers/carers and HCWs and generally perceived to have health benefits. The administration of pro/synbiotics by the mothers/carers themselves to their infants may be feasible and overcome logistical challenges. Greater efforts to sensitise and engage fathers and communities would likely be critical for a community-based program.

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Efficacy of prebiotic, probiotic and synbiotic administration in improving growth in children aged 0-59 months living in low- and middle-income countries: a systematic review and meta-analysis

[Marietou Khouma¹](#), [Mamadou Diallo^{#2}](#), [Doudou Sow^{#3}](#), [Aicha Djigal^{#2}](#), [Ndeye Sokhna Diop^{#4}](#), [Stephen Allen^{#5}](#), [Babacar Faye^{#4}](#)

Abstract

Background: Poor growth is one of the major obstacles to human development, affecting millions of children under the age of 5 years, particularly those living in low- and middle-income countries (LMICs). The objective of this review was to evaluate the efficacy of administering pre-, pro- or synbiotics on the growth of children aged 0-59 months living in LMICs.

Methods: Google scholar, Pubmed, clinical trial.org and Science Direct databases were searched in April 2023 for randomised controlled trials of pre-, pro- or synbiotics that evaluated growth in under fives in LMICs. The primary outcome were weight and height gain. Secondary outcomes were head circumference, body mass index gain and Z score. Random-effects meta-analysis was used to calculate mean differences for continuous outcomes. Grading of Recommendations Assessment, Development and Evaluation criteria was used to assess certainty of the evidence.

Results: Eight trials involving 1375 children under 5 years of age were identified. Meta-analysis of 6 RCTs (n = 991 children) revealed a significant difference in favor of the experimental group (n = 579) compared the control group (n = 412) for weight gain: (MD =

0.33 kg, 95% CI 0.11 to 0.55); low-certainty evidence. Sub-group analysis revealed that pre-, pro-, or synbiotics may be more effective in malnourished than healthy children ($p = 0.003$). Meta-analysis of height gain for 4 RCTs ($n = 845$) found that there was no significant difference between the experimental group ($n = 496$) and the control group ($n = 349$) (MD = 0.31 cm; 95% CI -0.36 to 0.98); low-certainty evidence. In sub-group analysis, prebiotics had a greater impact on height gain than synbiotics ($p = 0.03$). In the only study reporting an increase in head circumference ($n = 32$ children), this was not improved by the administration of synbiotics. However, administration of synbiotics to undernourished children significantly improved BMI gain.

Conclusion: The evidence for the administration of pre-, pro- or synbiotics on the growth of children in LMICs is weak. Administration of pre-, pro- or synbiotics may improve weight gain in both healthy and malnourished children. Prebiotics and synbiotics had a significant effect on weight gain. Further research is needed due to the small number of studies, short duration of administration and small sample size.

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doi: 10.1016/j.tjnut.2024.08.016. Epub 2024 Aug 22.

Iron Absorption from an Iron-Fortified Follow-Up Formula with and without the Addition of a Synbiotic or a Human-Identical Milk Oligosaccharide: A Randomized Crossover Stable Isotope Study in Young Thai Children

[Pornpimol Scheuchzer¹](#), [Sangsom Sinawat²](#), [Anne-Sophie Donzé¹](#), [Christophe Zeder¹](#), [Magalie Sabatier³](#), [Marc Garcia-Garcera³](#), [Cristian Ricci⁴](#), [Thavatchai Kamontham²](#), [Michael B Zimmermann⁵](#), [Jeannine Baumgartner⁶](#)

Abstract

Background: Previous studies showed that pre- and probiotics may enhance iron absorption. Probiotics combined with prebiotics (synbiotics), including human-identical milk oligosaccharides (HiMOs), are commonly added to infant and follow-up formula (FUF). Whether these additions enhance iron absorption from iron-fortified commercial milk formula is uncertain.

Objectives: We determined the effect of adding 1) a synbiotic [galacto-oligosaccharide [GOS] + *Limosilactobacillus reuteri* (*L. reuteri*)] or 2) the HiMO 2'-fucosyllactose (2'FL) to iron-fortified FUF on iron absorption in young Thai children.

Methods: In a randomized, controlled, single-blinded (participants) crossover study, 82 Thai children aged 8-14 mo were enrolled to consume single servings (235 mL) of FUF with isotopically labeled ferrous sulfate (2.2 mg iron) with 1) the synbiotic (400 mg/100 mL GOS and *L. reuteri* DSM 17938), 2) the HiMO 2'FL (100 mg/100 mL), and 3) without synbiotic and 2'FL (control) in random order and a 3-d washout period between administrations. Fractional iron absorption [FIA (%)] was assessed by measuring erythrocyte incorporation of isotopic labels 14 d ($n = 26$) and 28 d ($n = 76$) after consumption of the last test FUF.

Results: Median (IQR) FIA from iron-fortified FUF with the synbiotic [8.2 (5.2, 12.9)%] and with 2'FL [8.4 (5.5, 14.1)%] did not differ from the control FUF [8.1 (4.8, 14.7)%] (synbiotic compared with control, $P = 0.24$; 2'FL compared with control, $P = 0.95$). FIA from all FUF did not differ when measured after 14 and 28 d of erythrocyte incorporation (Time, $P = 0.368$; FUF, $P = 0.435$; Time $\times$ FUF, $P = 0.937$). Fecal pH and hemoglobin were negatively associated with FIA.

Conclusions: In young Thai children, the addition of a synbiotic (GOS + *L. reuteri*) or 2'FL to iron-fortified FUF did not impact FIA from a single serving

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Neonatal administration of *Lactiplantibacillus plantarum* ATCC 202195 with or without fructooligosaccharide in Bangladesh: a placebo-controlled randomized trial

[Lisa G Pell¹](#), [Huma Qamar¹](#), [Diego G Bassani^{1,2,3}](#), [Cole Heasley¹](#), [Celine Funk¹](#), [Chun-Yuan Chen¹](#), [Jakaria Shawon⁴](#), [Karen M O'Callaghan⁵](#), [Eleanor Pullenayegum²](#), [Davidson H Hamer⁶](#), [Rashidul Haque⁴](#), [Mamun Kabir⁴](#), [Tahmeed Ahmed⁴](#), [Ciobha O'Kelly^{1,7}](#), [Md Iqbal Hossain⁴](#), [Afreen Z Khan¹](#), [Miranda G Loutet¹](#), [Mohammad Shahidul Islam⁸](#), [Shaun K Morris^{1,2,7}](#), [Prakesh S Shah^{7,9}](#), [Philip M Sherman^{7,10}](#), [Shamima Sultana⁴](#), [Abdullah Al Mahmud⁴](#), [Samir K Saha⁸](#), [Shafiqul A Sarker⁴](#), [Daniel E Roth^{1,2,3,7}](#)

Abstract

Lactiplantibacillus plantarum ATCC 202195 (LP202195) plus fructooligosaccharide (FOS) for 7 days was previously shown to colonize the infant intestine up to 6 months of age and reduced sepsis rates among young infants in rural India. In a phase 2 randomized controlled trial in Dhaka, Bangladesh ($N = 519$), neonatal administration of LP202195 for 1 or 7 days, with or without FOS, increased LP202195 stool abundance from 14 to 60 days of age, versus placebo. Abundance progressively declined in the post-administration period and did not persist beyond 2 months of age. FOS did not affect LP202195 abundance or its duration of persistence. All regimens were well-tolerated and safe. The absence of LP202195 colonization was inconsistent with results from a prior trial. Additional large-scale trials of LP202195 $\pm$ FOS are needed to establish its efficacy in infants who do not become LP202195-colonized.

Importance: Among infants born in Dhaka, Bangladesh, a 7-day regimen of *Lactiplantibacillus plantarum* ATCC 202195 (LP202195) plus fructooligosaccharide (FOS) did not colonize the infant gastrointestinal (GI) tract. The absence of colonization is inconsistent with a prior study of the same synbiotic regimen in India, in which LP202195 was shown to persist in the infant GI tract for up to 6 months. Sustained LP202195 colonization was thought to be required for the probiotic to impart its beneficial impact on newborn sepsis. Therefore, additional trials are warranted to confirm the previously observed effects of LP202195 on infant clinical outcomes in the absence of LP202195 colonization. Moreover, since regimens of LP202195 that did not include FOS were indistinguishable from the synbiotic in terms of colonization, safety, and tolerability, future trials should assess the role of FOS for clinical efficacy; removing FOS would reduce costs, an important consideration for scale-up.

EBioMedicine. 2024 Oct;108:105362.

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Bifidobacterium longum and microbiome maturation modify a nutrient intervention for stunting in Zimbabwean infants

[Ethan K Gough¹](#), [Thaddeus J Edens²](#), [Lynnea Carr³](#), [Ruairi C Robertson⁴](#), [Kuda Mutasa⁵](#), [Robert Ntozini⁵](#), [Bernard Chasekwa⁵](#), [Hyun Min Geum⁶](#), [Iman](#)

[Baharmand⁶](#), [Sandeep K Gill⁶](#), [Batsirai Mutasa⁵](#), [Mduduzi N N Mbuya⁷](#), [Florence D Majo⁵](#), [Naume Tavengwa⁵](#), [Freddy Francis⁸](#), [Joice Tome⁵](#), [Ceri Evans⁹](#), [Margaret Kosek¹⁰](#), [Andrew J Prendergast¹¹](#), [Ame R Manges¹²](#); [Sanitation Hygiene Infant Nutrition Efficacy \(SHINE\) Trial Team](#)

Abstract

Background: Small-quantity lipid-based nutrient supplements (SQ-LNS), which has been widely tested to reduce child stunting, has largely modest effects to date, but the mechanisms underlying these modest effects are unclear. Child stunting is a longstanding indicator of chronic undernutrition and it remains a prevalent public health problem. The infant gut microbiome may be a key contributor to stunting; and mother and infant fucosyltransferase (FUT) phenotypes are important determinants of infant microbiome composition.

Methods: We investigated whether mother-infant FUT status (n = 792) and infant gut microbiome composition (n = 354 fecal specimens from 172 infants) modified the impact of an infant and young child feeding (IYCF) intervention, that included SQ-LNS, on stunting at age 18 months in secondary analysis of a randomized trial in rural Zimbabwe.

Findings: We found that the impact of the IYCF intervention on stunting was modified by: (i) mother-infant FUT2+/FUT3- phenotype (difference-in-differences -32.6% [95% CI: -55.3%, -9.9%]); (ii) changes in species composition that reflected microbiome maturation (difference-in-differences -68.1% [95% CI: -99.0%, -28.5%]); and (iii) greater relative abundance of *B. longum* (differences-in-differences 49.1% [95% CI: 26.6%, 73.6%]). The dominant strains of *B. longum* when the intervention started were most similar to the proficient milk oligosaccharide utilizer subspecies *infantis*, which decreased with infant age and differed by mother-infant FUT2+/FUT3- phenotypes.

Interpretation: These findings indicate that a persistently "younger" microbiome at initiation of the intervention reduced its benefits on stunting in areas with a high prevalence of growth restriction.

Lipid-based and protein-based nutrition supplements

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[Effectiveness of lipid-based nutrient supplementation during the first 1000 days of life for early childhood development: A community-based trial from Pakistan](#)

[Ayesha Imtiaz¹](#), [Zia Ul Haq^{1,2}](#), [Suhail A R Doi³](#), [Sheraz Fazid¹](#), [Muhammad Naseem Khan³](#)

Abstract

A community-based, cluster non-randomized controlled trial was conducted in Kurram district, Pakistan between January 2018 to December 2020. Age-appropriate lipid-based nutrient supplements and health education (sessions conducted in the households) were given to pregnant women and their born children (6-23 months) in the intervention arm (n = 40 clusters) versus health education only in the control arm (n = 40 clusters) to evaluate its effect on child development. The first and second developmental assessments were completed at ~24 months (n = 689) and ~32 months (n = 608), respectively, using the Caregiver-Reported Early Development Instrument Long form. The overall and domain-

specific (motor, language, cognitive and socio-emotional) scores were computed with higher scores indicating better child development. Higher development scores, including overall ($\beta = 0.40$, 95% confidence interval [CI]: 0.14, 0.65; $p = 0.002$), cognitive ($\beta = 0.27$, 95% CI: 0.10, 0.45; $p = 0.002$), motor ($\beta = 0.39$, 95% CI: 0.22, 0.56; $p < 0.001$) and language ($\beta = 0.33$, 95% CI: 0.14, 0.51; $p = 0.001$) were reported for children who received the intervention compared to the control arm at first developmental assessment. However, the effect was not sustained after the discontinuation of the intervention. The LNS received by the mothers (during pregnancy and first 6 months after delivery) and by children during 6-23 months of age was beneficial for the children.

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Impact of High- and Moderate- Protein Supplementation on Early-life Obesity and Body Composition : A Randomized Controlled Trial in India

Authors [Rukman Manapurath¹](#), [Ranadip Chowdhury²](#), [Ravi Prakash Upadhyay²](#), [Anura V Kurpad³](#), [Beena Bose³](#), [Sarita Devi³](#), [Pratibha Dwarkanath³](#), [Nita Bhandari²](#), [Sunita Taneja⁴](#), [Tor A Strand²](#)

Abstract

Background: Complementary feeding is vital for meeting infants' nutritional needs. In low-to-middle-income countries (LMICs), limited dietary diversity often leads to inadequate protein intake, contributing to growth faltering. Conversely, excessive intake may increase the risk of early-life obesity, but evidence on the optimal balance remains limited.

Objectives: To measure the effects of micronutrient-fortified, isocaloric high- and moderate-protein supplementation in infants from 6 to 12 months on overweight and/or obesity (BMI-for-age z-scores (BMIz) > 2 SD) and body composition i.e, fat mass (FM), fat-free mass (FFM) and percentage fat mass (% FM) at 12 months, and to evaluate obesity-related outcomes at 24 months, compared to a no supplementation group.

Design: This analysis is a secondary objective of a 3-arm randomized controlled trial in Delhi, India. Six-month old infants were allocated (1:1:1) to receive one daily packet of isocaloric high-protein supplementation (5.6 g), moderate-protein supplementation (2.5 g), or no supplementation. The isocaloric supplements provided 30% protein from milk, 30-45% energy from fats, and 80-100% RDA of key micronutrients. Comparisons were made between the no supplementation group and each supplementation group.

Results: Obesity prevalence was low at 12 months (0.8% moderate-protein, 0.4% high-protein, 0.6% no supplementation; $p = 0.65$, no significant difference between groups) and at 24 months (0.6% in supplemented groups, 0.2% no supplementation; $p = 0.56$, not significant). High-protein supplementation led to a modest but statistically significant increase in BMIz at 12 months (adjusted mean difference: 0.12; 95% CI: 0.02, 0.22) compared to the no supplementation group, but not at 24 months (-0.02; 95% CI: -0.12, 0.09). No significant differences were observed in FM, FFM or %FM at 12 months.

Conclusions: High-protein supplementation from 6 to 12 months did not increase fat accretion or obesity risk at 24 months. Nutritional interventions in LMICs should prioritize both protein quality and overall dietary balance to simultaneously prevent undernutrition and excess weight gain.

Environmental enteric dysfunction and microbiome

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Markers of Environmental Enteric Dysfunction Are Associated with Poor Growth and Developmental Outcomes among Young Children in Lusaka, Zambia

[Jacqueline M Lauer¹](#), [Juha Pyykkö²](#), [Mpela Chembe³](#), [Tamara Bilima-Mulenga³](#), [Dorothy Sikazwe⁴](#), [Bertha Chibwe⁵](#), [Savanna Henderson⁶](#), [Doug Parkerson⁶](#), [Jukka M Leppänen⁷](#), [Günther Fink⁸](#), [Lindsey M Locks⁹](#), [Peter C Rockers²](#)

Abstract

Objective: To examine cross-sectional relationships between biomarkers of environmental enteric dysfunction (EED), an acquired subclinical condition of the small intestine, and anthropometric and developmental outcomes among children in Lusaka, Zambia.

Study design: Serum samples were collected from 240 children ages 27 to 35 months enrolled in a cluster-randomized trial assessing the effects of growth charts and small-quantity lipid-based nutrient supplements on linear growth. Samples were analyzed using the 11-plex Micronutrient and EED Assessment Tool, which incorporates two biomarkers of EED, namely intestinal fatty acid-binding protein (I-FABP), a marker of epithelial damage, and soluble CD14 (sCD14), a marker of microbial translocation. Associations between log₂-transformed biomarker concentrations and anthropometric (height-for-age z-score [HAZ], weight-for-height z-score, and weight-for-age z-score₀) and developmental (Global Scales of Early Development [GSED] development for age z-score [DAZ] and saccadic reaction time [SRT]) outcomes were assessed using linear regression analyses adjusted for background characteristics.

Results: Mean $\pm$ SD HAZ was -1.94 ± 1.10 . Higher sCD14 and I-FABP concentrations were significantly associated with lower HAZ (β : -0.21 , 95% CI: -0.41 , -0.01 and β : -0.20 , 95% CI: -0.32 , -0.08 , respectively). Higher I-FABP concentrations were significantly associated with lower DAZ (β : -0.22 , 95% CI: -0.40 , -0.03) and slower SRT (β : 7.37 ms, 95% CI: 2.02 , 12.72) as were higher alpha-1-acid glycoprotein concentrations (HAZ β : -0.38 , 95% CI: -0.72 , -0.03 ; SRT β : 11.14 ms, 95% CI: 0.94 , 21.72).

Conclusions: In children in Lusaka, biomarkers of EED were associated with poor anthropometric and developmental outcomes, underscoring the need for interventions to address EED to improve child health globally.

Am J Trop Med Hyg. 2025 Feb 11;112(4):859-864.

doi: 10.4269/ajtmh.24-0402. Print 2025 Apr 2.

A Pilot Study of Enterade (VS001), an Oral Amino Acid Formulation, in Malnourished Bangladeshi Children with Environmental Enteric Dysfunction

[Masud Alam^{1,2}](#), [Tahsin Ferdous¹](#), [Rifat Ara^{1,3}](#), [Abdulla Siddique¹](#), [Mamun Kabir¹](#), [Rashidul Haque¹](#), [Jeffrey R Donowitz^{4,5}](#)

Abstract

Environmental enteric dysfunction (EED) is a subacute syndrome characterized by increased intestinal inflammation and permeability that affects children in low-income countries. It is associated with growth and neurodevelopmental deficits, and there is currently no known

treatment for EED. VS001 (AmiLyfe Bioscience, LLC, Norwood, MA) is a medical food (beverage) containing free amino acids that has been shown to decrease enteric inflammation and improve gut permeability in murine models. We conducted a double-blind, placebo-controlled pilot study to assess the acceptability and tolerability of VS001 in Bangladeshi children aged 1-2 years ($n = 10$ per arm). We also examined the effects on EED biomarkers (lactulose-mannitol (LM) ratio, fecal lactoferrin, alpha-antitrypsin, myeloperoxidase, and neopterin). Participants received 8 oz. of VS001 or an identical vehicle without amino acids daily for 14 days. Tolerability and acceptability were measured using parental surveys and daily in-home adverse event monitoring. Subjects took an average of 118 minutes to complete the dose each day. Caregivers found the product convenient and easy to administer and either agreed or strongly agreed that they would give this product to their child again. None reported that the intervention negatively affected their child's appetite. There were three mild adverse events deemed possibly related to the intervention, with two occurring in the active arm and one in the control arm. Children in the active arm exhibited a nonsignificant decrease in LM ratios (a marker of intestinal permeability) after treatment compared with the control arm (0.19-0.08 versus 0.19-0.17; $P = 0.16$). VS001 was acceptable to parents and reasonably well tolerated. Given the decrease in permeability observed in the active arm, a larger trial is warranted.

PLoS Negl Trop Dis. 2025 Feb 18;19(2):e0012881.

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Treatment heterogeneity of water, sanitation, hygiene, and nutrition interventions on child growth by environmental enteric dysfunction and pathogen status for young children in Bangladesh

[Zachary Butzin-Dozier¹](#), [Yunwen Ji¹](#), [Jeremy Coyle¹](#), [Ivana Malenica¹](#), [Elizabeth T Rogawski McQuade²](#), [Jessica Anne Grembi³](#), [James A Platts-Mills⁴](#), [Eric R Houpt⁴](#), [Jay P Graham¹](#), [Shahjahan Ali⁵](#), [Md Ziaur Rahman⁶](#), [Mohammad Alauddin⁷](#), [Syeda L Famida⁵](#), [Salma Akther⁵](#), [Md Saheen Hossen⁵](#), [Palash Mutsuddi⁵](#), [Abul K Shoab⁵](#), [Mahbubur Rahman⁵](#), [Md Ohedul Islam⁵](#), [Rana Miah⁵](#), [Mami Taniuchi⁴](#), [Jie Liu⁸](#), [Sarah T Alauddin⁷](#), [Christine P Stewart⁹](#), [Stephen P Luby¹⁰](#), [John M Colford Jr¹](#), [Alan E Hubbard¹](#), [Andrew N Mertens¹](#), [Audrie Lin⁶](#)

Abstract

Background: Water, sanitation, hygiene (WSH), nutrition (N), and combined (N+WSH) interventions are often implemented by global health organizations, but WSH interventions may insufficiently reduce pathogen exposure, and nutrition interventions may be modified by environmental enteric dysfunction (EED), a condition of increased intestinal permeability and inflammation. This study investigated the heterogeneity of these treatments' effects based on individual pathogen and EED biomarker status with respect to child linear growth.

Methods: We applied cross-validated targeted maximum likelihood estimation and super learner ensemble machine learning to assess the conditional treatment effects in subgroups defined by biomarker and pathogen status. We analyzed treatment (N+WSH, WSH, N, or control) randomly assigned in-utero, child pathogen and EED data at 14 months of age, and child HAZ at 28 months of age. We estimated the difference in mean child height for age Z-score (HAZ) under the treatment rule and the difference in stratified treatment effect

(treatment effect difference) comparing children with high versus low pathogen/biomarker status while controlling for baseline covariates.

Results: We analyzed data from 1,522 children who had a median HAZ of -1.56. We found that fecal myeloperoxidase (N+WSH treatment effect difference 0.0007 HAZ, WSH treatment effect difference 0.1032 HAZ, N treatment effect difference 0.0037 HAZ) and Campylobacter infection (N+WSH treatment effect difference 0.0011 HAZ, WSH difference 0.0119 HAZ, N difference 0.0255 HAZ) were associated with greater effect of all interventions on anthropometry. In other words, children with high myeloperoxidase or Campylobacter infection experienced a greater impact of the interventions on anthropometry. We found that a treatment rule that assigned the N+WSH (HAZ difference 0.23, 95% CI (0.05, 0.41)) and WSH (HAZ difference 0.17, 95% CI (0.04, 0.30)) interventions based on EED biomarkers and pathogens increased predicted child growth compared to the randomly allocated intervention.

Conclusions: These findings indicate that EED biomarkers and pathogen status, particularly Campylobacter and myeloperoxidase (a measure of gut inflammation), may be related to the impact of N+WSH, WSH, and N interventions on child linear growth.

Am J Clin Nutr. 2025 Feb;121(2):333-342.

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The effect of an intervention to reduce aflatoxin consumption from 6 to 18 mo of age on length-for-age z-scores in rural Tanzania: a cluster-randomized trial

[Erica Phillips¹](#), [Francis M Ngure²](#), [Neema Kassim³](#), [Paul C Turner⁴](#), [Edna Makule³](#), [Laura E Smith⁵](#), [Nyabasi Makori⁶](#), [Benedikt Cramer⁷](#), [Hans-Ulrich Humpf⁷](#), [Rebecca J Nelson⁸](#), [Rebecca J Stoltzfus⁹](#)

Abstract

Background: Linear growth faltering continues to negatively affect children in low- and middle-income countries and is associated with poor cognitive, developmental, and educational outcomes. Laboratory and observational data suggest that aflatoxin (AF) is a contributor to stunting.

Objective: The Mycotoxin Mitigation Trial was a cluster-randomized, community-based 2-group trial conducted in Kongwa District, Tanzania, between 2018 and 2020. The trial assessed whether a 12-mo intervention to reduce AF consumption increased length-for-age z-scores (LAZ) at 18 mo.

Methods: Low-AF maize and groundnut flours were provided to the intervention group each month; skin lotion was distributed to the control group monthly. Infant and young child feeding education was delivered equally in 52 health facilities (clusters). Anthropometry and the AF blood biomarker serum AF-albumin (AF-alb) were assessed at 6, 12, and 18 mo of age. Outcomes were analyzed as intention-to-treat and per-protocol using linear mixed-effects models.

Results: Two thousand eight hundred forty-two maternal-infant dyads were recruited into the study. The intervention did not create a contrast in AF-alb. At 18 mo, 36% (n = 186/520) of infants had detectable levels of AF-alb compared with 54% (n = 195/364) at baseline, with no difference between groups. Mean LAZ in the intervention group at 18 mo was -1.83 (n = 1231,

95% CI: -1.93, -1.73) compared to -1.90 (n = 1287, 95% CI: -1.99, -1.82) in the control group (P = 0.28).

Conclusions: An intervention to reduce AF exposure did not alter AF-alb nor anthropometric measures between treatment groups. Drought and agricultural data indicated less favorable conditions for toxin production, resulting in low levels of exposure in both trial arms. Annual, seasonal, and geographic heterogeneity of AF contamination make it difficult to study in an ethically designed trial. Our formative research and early trial data indicate that stunting and intermittent AF exposure continue to be a problem in this region. However, the low-AF exposure levels during the trial led to inconclusive results.

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Maternal balanced energy-protein supplementation reshapes the maternal gut microbiome and enhances carbohydrate metabolism in infants: a randomized controlled trial

[Lishi Deng^{#1}](#), [Steff Taelman^{#2,3,4}](#), [Matthew R Olm^{5,6}](#), [Laeticia Celine Toe^{1,7}](#), [Eva Balini⁴](#), [Lionel Olivier Ouédraogo^{1,8}](#), [Yuri Bastos-Moreira^{1,9}](#), [Alemayehu Argaw¹](#), [Kokeb Tesfamariam¹](#), [Erica D Sonnenburg⁵](#), [Giles T Hanley-Cook¹](#), [Moctar Ouédraogo¹⁰](#), [Rasmané Ganaba¹⁰](#), [Wim Van Criekinge²](#), [Lieven Huybregts^{1,11}](#), [Michiel Stock³](#), [Patrick Kolsteren¹](#), [Justin L Sonnenburg^{5,12,13}](#), [Carl Lachat¹⁴](#), [Trenton Dailey-Chwalibóg^{15,16}](#)

Abstract

Balanced energy-protein (BEP) supplementation during pregnancy and lactation can improve birth outcomes and infant growth, with the gut microbiome as a potential mediator. The MISAME-III randomized controlled trial (ClinicalTrials.gov: [NCT03533712](#)) assessed the effect of BEP supplementation, provided during pregnancy and the first six months of lactation, on small-for-gestational age prevalence and length-for-age Z-scores at six months in rural Burkina Faso. Nested within MISAME-III, this sub-study examines the impact of BEP supplementation on maternal and infant gut microbiomes and their mediating role in birth outcomes and infant growth. A total of 152 mother-infant dyads (n = 71 intervention, n = 81 control) were included for metagenomic sequencing, with stool samples collected at the second and third trimesters, and at 1-2 and 5-6 months postpartum. BEP supplementation significantly altered maternal gut microbiome diversity, composition, and function, particularly those with immune-modulatory properties. Pathways linked to lipopolysaccharide biosynthesis were depleted and the species *Bacteroides fragilis* was enriched in BEP-supplemented mothers. Maternal BEP supplementation also accelerated infant microbiome changes and enhanced carbohydrate metabolism. Causal mediation analyses identified specific taxa mediating the effect of BEP on birth outcomes and infant growth. These findings suggest that maternal supplementation modulates gut microbiome composition and influences early-life development in resource-limited settings.

Macronutrient nutrition and complementary feeding

(See also Vitamin A)

Public Health Nutr. 2024 Dec 12:1-31.

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[Effect of egg consumption on early childhood development: Evidence from Un Oeuf study](#)

[Helen Ernyey¹](#), [Chhavi Tiwari²](#), [Heather Stark³](#), [Emma Hunniford³](#), [Aissata Wereme N'Diaye⁴](#), [Yacouba Zare⁴](#), [Anteneh Omer⁵](#), [Sarah Lindley McKune^{2,6}](#)

Abstract

Objective: Recent studies have shown that inclusion of eggs in young children's diet can help meet nutritional requirements associated with cognitive development. This study aims to investigate the effect of egg consumption on Early Childhood Development (ECD) using Ages and Stages Questionnaire-3(ASQ-3) in Burkina Faso.

Design: The study presented here uses data collected during a follow-up of the *Un Oeuf*-a 3 arm clustered randomized controlled trial (RCT), conducted roughly four months after the end of the RCT.

Setting: This research was conducted in 18 rural villages within the Kaya Department of the Sanmatenga Province in Burkina Faso.

Participants: Participants of this study include a total of 244 children aged between 18-33 months, with 78 children in the full intervention group, 83 in the partial group, and 83 in the control group.

Results: Results show that children with consistent egg consumption (in all months) had a lower odd of falling below the cut-off scores in gross motor ($OR = 0.13, p = 0.02$) and personal social skills ($OR = 0.34, p = 0.05$). And a dose response was established; for each additional egg/week, a 1.9% increase in scores for problem-solving skills was observed.

Conclusions: Findings from this study contribute to a growing body of evidence that increasing egg consumption among children in LMICs can improve growth and development. The study highlights the need for additional research in LMICs to better understand the multifactorial relationship between diet and childhood development.

Prev Nutr Food Sci. 2025 Apr 30;30(2):110-119.

doi: 10.3746/pnf.2025.30.2.110.

[Effect of Locally Formulated Complementary Foods on Anthropometric Parameters and Micronutrient Status in Children \(6-23 Months\) in Enugu State, Nigeria: A Randomized Controlled Trial](#)

[Ngozi Mercy Nnam¹](#), [Peace Nwanneka Ani¹](#), [Ngozi Elizabeth Chukwuemeka¹](#)

Abstract

Malnutrition remains a significant challenge in low- and middle-income countries, contributing to stunting, wasting, and micronutrient deficiencies. This study investigated the effect of locally formulated complementary foods on anthropometric parameters and micronutrient status in children aged 6 to 23 months. A randomized controlled trial involving 40 infants explored the effects of experimental diets, including Maize-Soybean, Maize-Soybean-Termite flour, Maize-Soybean-Fishbone powder, and Maize-Soybean-Termite-Fishbone-Pawpaw-Pumpkin (MaSoTFPP), and a control diet on children over a period of 90

days. Anthropometric measurements of weight, height, and mid-upper arm circumference (MUAC) as well as biochemical analyses of blood samples were carried out. Dietary intake was monitored over the 90-day feeding trial period. The data obtained were analyzed using Statistical Product for Service Solution, version 23. Significance was set at $P < 0.05$. The findings revealed significant improvements in the anthropometric parameters, particularly in the MaSoTFPP group, which exhibited the largest percentage increase in height and MUAC. The children fed with the experimental diets demonstrated enhanced serum hemoglobin, iron, and zinc levels, which increased most significantly in the MaSoTFPP group (by 308%, 264%, and 58%, respectively). The study underscores the potential of incorporating locally available food crops in community-based management of acute malnutrition and supports the World Health Organization's recognition of fortified staple foods in improving child growth and development.

J Nutr. 2025 Feb;155(2):602-611.

doi: 10.1016/j.tjnut.2024.12.001. Epub 2024 Dec 9.

[Complementary Food Supplements Fill Energy and Protein Gaps among Children with Dietary Inadequacy in a Complementary Feeding Trial in Rural Bangladesh](#)

[Monica M Pasqualino](#)¹, [Rebecca K Campbell](#)², [Kristen M Hurley](#)³, [Lee S-F Wu](#)³, [Abu Ahmed Shamim](#)⁴, [Saijuddin Shaikh](#)⁵, [Saskia de Pee](#)⁶, [Parul Christian](#)³

Abstract

Background: Few studies have evaluated the dietary impact of complementary food supplements (CFSs) designed to deliver macro- and micronutrients to children at risk for undernutrition. In a randomized controlled trial in rural Bangladesh, we previously reported that CFSs increased children's micronutrient adequacy.

Objectives: To longitudinally characterize energy and macronutrient intakes and inadequacies and evaluate the extent to which CFSs fill intake gaps.

Methods: Children were enrolled at 6 mo and received 1 of 4 CFSs plus caregiver nutrition counseling or counseling alone for 1 y. A semi-quantitative diet questionnaire was administered at 6, 9, 12, 15, 18, and 24 mo. Energy and macronutrient intakes were estimated by age and arm; protein adequacy was adjusted for protein quality and infection. We estimated the proportion meeting intake requirements set by FAO and the Institute of Medicine and compared group-wise differences using log binomial regression models with generalized estimating equations. We used multivariate analysis of variance models to evaluate if CFSs substituted home foods.

Results: Across groups, most children did not meet energy or protein requirements at enrollment (74.6%-81.3% and 77.4%-79.2%, respectively). Estimated energy and macronutrient intakes from home foods increased from 6 to 24 mo. Energy inadequacy was lower in the supplemented groups compared with the control at all ages (e.g. 10.5%-13.8% compared with 31.4% at 18 mo). In the control group, protein inadequacy dropped from 78.4% at 6 mo to 8.3% at 9 mo to 2.8% by 18 mo; adjusted protein estimates were 25.1% at 9 mo and 7.0% at 18 mo. Protein inadequacy was the highest in the control group at all timepoints. CFSs did not substitute home foods.

Conclusions: CFSs can significantly bridge energy and protein intake gaps. With earlier trial findings that CFSs filled micronutrient gaps and improved growth, these findings strengthen evidence supporting using CFSs for improved health outcomes.

Physiol Behav. 2025 Sep 1:298:114954.

doi: 10.1016/j.physbeh.2025.114954. Epub 2025 May 19.

Eating behavior and methods of complementary feeding introduction: A randomized clinical trial in Brazilian children

[Paula Ruffoni Moreira¹](#), [Barbara Cristina Ergang²](#), [Leandro Meirelles Nunes³](#), [Juliana Rombaldi Bernardi⁴](#)

Abstract

Background: A child's early eating experiences, such as the introduction of complementary foods (CF), are critical points for the development of their eating behavior.

Objective: This study aims to analyze the impact of different CF approaches on the eating behavior of children.

Methods: A randomized clinical trial was conducted with mother-infant pairs, followed from 5.5 months to 12 months of age. The sample was randomized into three distinct CF methods: Parent-Led Weaning (PLW), Baby-Led Introduction to Solids (BLISS), or a mixed approach combining both methods. The Child Eating Behavior Questionnaire (CEBQ) was administered online at 12 months, assessing scales such as 'food responsiveness', 'emotional overeating', 'enjoyment of food', 'desire to drink', 'satiety responsiveness', 'slowness in eating', 'food fussiness', 'emotional under-eating', as well as the subscales 'food avoidance' and 'food approach'. ANOVA was used to evaluate differences between the CF methods.

Results: A total of 126 mother-infant pairs were assessed, distributed as follows: n= 41 in the PLW group, n= 44 in the BLISS group, and n= 41 in the mixed group. The analysis revealed no statistically significant differences across the various eating behavior scales, including 'food responsiveness' (p= 0.412), 'emotional overeating' (p= 0.184), 'enjoyment of food' (p= 0.128), and 'desire to drink' (p= 0.177). Similarly, no significant differences were observed in 'satiety responsiveness' (p= 0.922), 'slowness in eating' (p= 0.294), 'food fussiness' (p= 0.929), 'emotional under-eating' (p= 0.972), 'food avoidance' (p= 0.964), or 'food approach' (p= 0.051) between the different CF groups.

Conclusion: No differences were observed in the scores of the eating behavior scales and subscales among children who followed different CF approaches. Further studies are needed to investigate the relationship between the CF approach and child eating behavior.

J Nutr. 2025 Feb;155(2):612-620.

doi: 10.1016/j.tjn.2024.11.001. Epub 2024 Nov 5.

Acceptability of Microbiota-Directed Complementary Foods in Treating Indian Children with Moderate Acute Malnutrition: eACT-MAM Pre-Proof-of-Concept Study

[Sam Marconi¹](#), [Bireshwar Sinha²](#), [Aditi Apte³](#), [Midhun Sasikumar⁴](#), [Gunjan Aggarwal⁵](#), [Rashmi Chabukswar³](#), [Akshaya Vasudevan⁶](#), [Zavid Miyandad⁶](#), [Sowndharya Pandian⁶](#), [Pranita Shambharkar³](#), [Himani Bhardwaj⁵](#), [Girish Dayma³](#), [Dhiraj Agarwal³](#), [Sunita Taneja⁵](#), [Venkata Raghava Mohan⁶](#)

Abstract

Background: In India, currently, there are no standard guidelines for the management of moderate acute malnutrition (MAM). Previous research in Bangladesh has shown that children with MAM have impaired gut microbiota development, and microbiota-directed complementary foods (MDCF) can potentially repair their gut microbiota.

Objectives: The objectives of this study were to evaluate the acceptability and safety of supplementing shelf-stable formulation of MDCF in Indian children with MAM as compared with a locally prepared ready-to-use supplementary food (RUSF) in 3 geographically distinct Indian populations and to establish and pilot systems of intervention delivery, collection, transport, and storage of stool samples using stringent protocols.

Methods: This pre-proof-of-concept (prePOC), multicentric, open-labeled, age-stratified, randomized controlled trial was done in children aged 6-18 mo with MAM. After a run-in period of 2 wk, the participants were supplemented with MDCF or RUSF for 4 wk through direct observation and followed up for another 2 wk post intervention. Maternal responses to the acceptability of the organoleptic properties of supplements were recorded weekly during the intervention phase of 4 wk. Compliance was reported based on the amount of supplement consumed by the children. Feasibility of weekly stool sample collection (except 7th week) within 30 min of passage was recorded. Anthropometric measurements were done at baseline and endline. Monitoring for adverse events was done throughout the course of the study.

Results: A total of 240 children with MAM were randomly selected to receive either MDCF or RUSF, of which 221 (92.1%) completed follow-up. The overall acceptability for >80% of the maternal responses was reported as good or very good for all organoleptic properties in both MDCF and RUSF arms. MDCF and RUSF interventions had good-to-high compliance in 83.0% and 79.8% of participants, respectively. At the end of the intervention phase, 53.2% (58/109) of children in MDCF arm against 42.0% (47/112) in RUSF arm had weight-for-length Z score >-2. The overall incidence of acute gastroenteritis reported was low; higher in MDCF compared with RUSF but not statistically significant.

Conclusion: The prePOC study demonstrates good acceptability and safety of MDCF among Indian children with MAM including the age group of 6-12 mo of age. The study demonstrates the feasibility of conducting a long-term supplementation study in this population

J Nutr. 2024 Jul;154(7):2290-2299.

doi: 10.1016/j.tjnut.2024.05.006. Epub 2024 May 15.

[An Egg Intervention Improves Ponderal But Not Linear Growth Among Infants 6-12 mo of Age in Rural Bangladesh](#)

[Monica M Pasqualino¹](#), [Saijuddin Shaikh²](#), [Md Iqbal Hossain³](#), [Md Tanvir Islam²](#), [Hasmot Ali²](#), [Rezwanul Haque²](#), [Kaniz Ayesha²](#), [Lee S-F Wu⁴](#), [Brian Dyer⁴](#), [Khaled Hasan⁴](#), [Kelsey Alland⁴](#), [Kerry J Schulze⁴](#), [Fatema-Tuz Johura³](#), [Munirul Alam³](#), [Keith P West Jr⁴](#), [Tahmeed Ahmed³](#), [Alain B Labrique⁴](#), [Amanda C Palmer⁴](#)

Abstract

Background: Animal source foods are rich in multiple nutrients. Regular egg consumption may improve infant growth in low- and middle-income countries.

Objectives: To assess the impact of daily egg consumption on linear growth among 6-12-month-olds in rural Bangladesh.

Methods: We conducted a 2×4 factorial cluster-randomized controlled trial allocating clusters ($n = 566$) to treatment for enteric pathogens or placebo and a daily egg, protein supplement, isocaloric supplement, or control. All arms received nutrition education. Here, we compare the effect of the egg intervention versus control on linear growth, a prespecified aim of the trial. Infants were enrolled at 3 mo. We measured length and weight at 6 and 12 mo and visited households weekly to distribute eggs and monitor compliance. We used linear regression models to compare 12-mo mean length, weight, and z-scores for length-for-age (LAZ), weight-for-length, and weight-for-age (WAZ), and log-binomial or robust Poisson regression to compare prevalence of stunting, wasting, and underweight between arms. We used generalized estimating equations to account for clustering and adjusted models for baseline measures of outcomes.

Results: We enrolled 3051 infants ($n = 283$ clusters) across arms, with complete 6 and 12 mo anthropometry data from 1228 infants ($n = 142$ clusters) in the egg arm and 1109 infants ($n = 141$ clusters) in the control. At baseline, 18.5%, 6.0%, and 16.4% were stunted, wasted, and underweight, respectively. The intervention did not have a statistically significant effect on mean LAZ (β : 0.05, 95% confidence interval [CI]: -0.01, 0.10) or stunting prevalence (β : 0.98, 95% CI: 0.89, 1.13) at 12 mo. Mean weight (β : 0.07 kg, 95% CI: 0.02, 0.11) and WAZ (β : 0.06, 95% CI: 0.02, 0.11) were significantly higher in the egg compared with control arms.

Conclusions: Provision of a daily egg for 6 mo to infants in rural Bangladesh improved ponderal but not linear growth.

* in this case ponderal means weight.

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Effect of Behavior Change Intervention on Complementary Food Contamination in Rural Bangladesh: A Cluster-Randomized Controlled Trial

[Tarique Md Nurul Huda^{1,2}](#), [Anna A Müller-Hauser^{3,4,5}](#), [Shafinaz Sobhan^{3,4,5}](#), [Shaheen Hossain²](#), [Jesmin Sultana²](#), [Mahbubur Rahman^{2,6}](#), [Mohammad Aminul Islam^{7,8}](#), [Om Prasad Gautam⁹](#), [Amanda S Wendt^{3,5}](#), [Jillian L Waid^{3,10}](#), [Sabine Gabrysch^{3,4,5}](#)

Abstract

Children in low-resource settings often consume microbially contaminated food, risking their health. We evaluated the impact of a food hygiene intervention on complementary food contamination in Bangladesh. A 3-year homestead food production intervention was complemented by an 8-month behavior change module to improve household food hygiene practices and evaluated in a cluster-randomized controlled trial, including a dedicated study measuring outcomes along the hygiene pathway to intestinal health. We used multilevel regression to assess the intervention's impact on microbial food contamination as well as food hygiene knowledge ($n = 518$) and reported practices ($n = 531$) among mothers of children 6-23 months of age. Complementary food samples were collected from 342 households with children 6-18 months of age and tested for *Escherichia coli*. Overall, 46% of food samples were contaminated with *E. coli* (43% intervention, 51% control), and there was no evidence that the intervention reduced food contamination (odds ratio: 0.65, 95% CI: 0.35-1.21). A higher proportion of intervention mothers could name all key food hygiene practices (23% intervention versus 1% control), had access to a basic handwashing station near the kitchen (24% versus 14%), reported washing hands before food preparation and

child feeding (21% versus 8%), reported washing and storing feeding utensils safely (61% versus 49%), and reported preparing food fresh or reheating stored food (88% versus 79%) compared with control mothers. The intervention thus improved knowledge and reported food hygiene practices among mothers, but this improvement did not result in a substantial reduction of complementary food contamination.

J Hum Nutr Diet. 2025 Feb;38(1):e70022.

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Effectiveness of an Intervention to Prevent Ultra-Processed Foods and Added Sugar in the First Year of Life: A Multicentre Randomised Controlled Trial in Brazil

[Paola S Baratto¹](#), [Daniel J Hoffman²](#), [Júlia L Valmórbida¹](#), [Paula S Leffa³](#), [Carlos A Feldens⁴](#), [Márcia R Vitolo¹](#)

Abstract

Background: The early consumption of ultra-processed foods (UPFs) and added sugars (AS) has been linked to adverse outcomes in infancy. The objective of this study was to determine the effectiveness of a dietary counselling strategy to prevent the consumption of UPFs and AS in the first year of life.

Methodology: A multicentre randomised controlled trial was conducted with 516 mother-child pairs in three state capitals of Brazil. Mothers were randomly assigned to the control group (CG) or intervention group (IG) after childbirth. The IG received orientation based on UNICEF dietary guidelines and five monthly telephone calls to reinforce the intervention. Dietary intake was measured using food introduction questionnaires and 24-h recalls during home visits at 6 and 12 months. Between-group differences were analysed by generalised estimating equations and presented as mean difference (95% CI).

Results: Children in the IG had lower UPF intake at 6 and 12 months of age (-20.69 g/day; 95% CI: -37.87 to -3.50; $p = 0.018$ and -32.51 g/day; 95% CI: -61.03 to -3.99; $p = 0.025$) and lower AS intake at 12 months of age (-4.92 g/day; 95% CI: -9.43 to -0.41; $p = 0.033$). The intervention also had a positive impact on the period of exclusive breastfeeding, reducing the offer of infant formula, cow's milk, and toddler milk in the first year of life.

Principal conclusions: The dietary counselling strategy was effective at preventing the early consumption of UPFs and AS in the first year of life. Future research should focus on social and cultural barriers to improve adherence to infant feeding interventions.

BMC Pediatr. 2024 Nov 20;24(1):753.

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Common gastrointestinal symptoms in healthy infants receiving goat milk-based formula or cow's milk-based formula: a double-blind, randomized, controlled trial

[P Maximino^{1,2}](#), [L van Lee¹](#), [Yvonne N Meijer-Krommenhoek³](#), [L van der Zee¹](#), [H da Costa Ribeiro Junior⁴](#)

Abstract

Objective: To assess common gastrointestinal symptoms in healthy Brazilian infants receiving goat milk-based formula (GMF) compared to cow's milk-based formula (CMF).

Methods: We performed a 24-weeks double-blind, randomized, controlled study in Brazil, enrolling healthy infants from 3 to 12 months of age. Primary outcome were the gastrointestinal (GI) symptoms stool consistency, regurgitation frequency and crying duration. Secondary outcomes were growth trajectories and hemoglobin levels. Repeated mixed models were used to compare outcomes variables between GMF and CMF groups, while adjusting for age at baseline.

Results: Fifty-six infants were recruited and randomly allocated in the GMF ($n = 26$) and the CMF ($n = 30$) group. Scores on all measured GI symptoms were low and similar among the groups throughout intervention period and improved over time. Average age- and sex-adjusted WHO z-scores of weight, length, head circumference, and weight-for-length were all within ± 1 SD and similar between groups, indicating adequate growth. Serum hemoglobin was 11.1 (SD 0.7) g/dL in infants fed GMF and 11.0 (SD 0.8) g/dL in infants fed CMF after the intervention and was similar between groups.

Conclusion: GMF was well tolerated, safe and supported adequate growth in infants. This was shown by the low occurrence of GI symptoms, adequate blood hemoglobin levels and adequate growth within WHO standards.

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Effects of New Complementary Feeding Guidelines on Eating Behaviour, Food Consumption and Growth in Colombian Children: 6-Year Follow-Up of a Randomised Controlled Trial

Gilma Olaya Vega¹, Mary Fewtrell²

Abstract

Complementary feeding (CF) may influence later eating behaviour and growth. Our previous Randomised Control Trial (RCT) reported that new CF guidelines (NCFGs) implemented in 6-12-month-old infants in Bogota, Colombia, had positive short-term effects on red meat, vegetable and fruit consumption. Here, we assessed the effects of the NCFGs on food consumption, eating behaviour and growth at 6 years of age. Weight and height were measured using 50 children (58.8%) from the cohort. Feeding behaviour was measured using the Child Eating Behaviour Questionnaire (CEBQ) and maternal and child food consumption was measured using a semi-quantitative food frequency questionnaire. The control group (CG) had a significantly higher weekly consumption of chocolate milk drinks ($p = 0.05$). The mean food responsiveness (FR) score was significantly higher in the CG ($p < 0.001$). Although HAZ (height for age Z-score) at 6 years of age was significantly higher in the CG ($p < 0.02$), there was no significant difference between groups in the change in HAZ from 6 months and 12 months to 6 years of age. BMIZ (body mass index Z-score) and % overweight (CG 18.5% versus NCFG 13%) or obese (3.7% versus 0%) were not significantly different between groups. BMIZ was positively predicted by FR (β 0.293; $p = 0.014$) and negatively predicted by weekly red meat consumption episodes per week at 12 months (β -0.169; $p = 0.020$). Although there was no direct effect of an intervention on BMIZ at 6 years of age, the results were consistent with an indirect effect via intervention effects on meat consumption at an age of 12 months and FR at 6 years of age. However, further longitudinal studies with a larger sample size are needed.

Breastfeeding

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[Clinical evaluation of Ayush-SS granules in exclusively breastfeeding mothers with insufficient lactation: A randomized, double-blind, placebo-controlled trial](#)

[Upma Saxena¹](#), [Sarada Ota²](#), [Shivshankar Rajput³](#), [Bhavna Anand⁴](#), [Arunabh Tripathi⁵](#), [Richa Singhal⁵](#), [Adarsh Kumar⁵](#), [Abhishek Lachyan⁶](#)

Abstract

Background: Breast milk is essential for infant growth and development, with exclusive breastfeeding (EBF) recommended for the first six months. Many mothers experience insufficient milk production, leading to early supplementation or cessation of breastfeeding. Ayurvedic formulations, such as Ayush-SS granules, have been proposed to enhance lactation. This study evaluated Ayush-SS granules as a galactagogue, with EBF at six months as the primary outcome. Secondary outcomes included infant weight gain over 90 days and maternal perceptions of lactation sufficiency.

Methods: A double-blind, randomized, placebo-controlled trial was conducted between 1 February 2021 and 31 January 2023 at Vardhman Mahavir Medical College and Safdarjung Hospital, Delhi, India. A total of 210 lactating mothers (aged 20-40 years) with full-term singleton infants (≥ 37 weeks, ≥ 2.5 kg) experiencing insufficient lactation were enrolled. Infants who had not regained birth weight by day 14 or gained < 20 g/day after day 15 were included. Participants were randomized (1:1) to receive 6 g of Ayush-SS granules or placebo twice daily for 12 weeks. All participants received standardized breastfeeding counseling. Safety monitoring was conducted, and an intention-to-treat analysis was performed.

Results: At six months, 74 of 106 (69.8%) infants in the Ayush-SS group were exclusively breastfed, compared to 47 of 105 (44.8%) in the placebo group ($p < 0.001$). After 90 days, 81 of 106 infants (76.5%) in the Ayush-SS group gained ≥ 20 g/day compared to 44 of 105 (41.8%) in the placebo group ($p < 0.001$). Maternal perceptions of insufficient lactation were significantly lower in the Ayush-SS group (15.3% vs. 58.2%). No severe adverse events related to the intervention were observed.

Conclusion: Ayush-SS granules significantly improved EBF rates at six months, maternal perceptions of lactation sufficiency, and infant weight gain. These findings suggest their potential as a galactagogue for mothers with insufficient milk production. Further research is needed to explore long-term effects and maternal dietary influences.

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[The relationships between optimal infant feeding practices and child development and attained height at age 2 years and 6-7 years](#)

[Lan Mai Tran^{1,2}](#), [Phuong H Nguyen^{3,4}](#), [Melissa F Young^{1,2}](#), [Reynaldo Martorell^{1,2}](#), [Usha Ramakrishnan^{1,2}](#)

Abstract

Limited evidence exists on the long-term effects of early feeding practices on child growth and development. We examined the relationships between infant feeding practices and child height and development at ages 2 and 6-7 years. We studied 885 mother-child dyads from a randomized controlled trial of preconception supplementation in Vietnam. Early initiation of breastfeeding (EIBF), exclusive breastfeeding (EBF), breastfeeding (BF) duration and minimum dietary diversity (MDD) were assessed using World Health Organization (WHO) guidelines. Child development was assessed by the Bayley Scales of Infant Development-III at 2 years and the Wechsler Intelligence Scale for Children® - IV at 6-7 years. Child height-for-age z-score (HAZ) was calculated from child height and age. Multivariable regression and structural equation models were used in analyses that controlled for confounding. EIBF and EBF at 6 months occurred in 52% and 62% of children, respectively. Mean breastfeeding duration was 18 months and 83% achieved MDD at 1 year. EIBF was associated with motor ($\beta = 0.13$, 95% confidence interval [CI]: 0.00, 0.28) and cognitive development at 2 years ($\beta = 0.12$, 95% CI: -0.01, 0.26), which in turn were positively associated with cognitive development at 6-7 years. EBF was directly associated with development at 6-7 years ($\beta = 0.21$, 95% CI: 0.08, 0.34) whereas motor and cognitive development at 2 years explained 41%-75% of the relationship between EIBF and development at 6-7 years. HAZ at 2 years also mediated 70% of the association between MDD at 1 year and HAZ at 6-7 years. BF duration was not associated with child development and HAZ. Early infant feeding practices, especially EIBF and EBF, have important long-term implications for optimizing child linear growth and cognition as they begin school.

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Assessing a bundle of peer counseling, mobile phone messages, and mama kits in promoting timely initiation of and exclusive breastfeeding in Uganda: A cluster randomized controlled study

[David Mukunya^{1,2,3}](#), [James K Tumwine^{4,5}](#), [Grace Ndeezi⁴](#), [Milton W Musaba⁶](#), [Justin Bruno Tongun⁷](#), [Josephine Tumhamye⁸](#), [Agnes Napyo⁹](#), [Faith Oguttu¹](#), [Daphine Amany¹](#), [Beatrice Odongkara¹⁰](#), [Vincentina Achora¹¹](#), [Thorkild Tylleskar³](#), [Victoria Nankabirwa^{3,12}](#)

Abstract

Background: Timely initiation of and exclusive breastfeeding have been recommended as key interventions to enable countries to attain the sustainable development target of reducing neonatal mortality to no more than 12 deaths per 1000 live births and to reduce mortality of children under 5 years to no more than 25 deaths per 1000 live births.

Methods: We conducted a cluster randomized controlled trial with the main objective to assess the effect of an integrated package consisting of: peer counseling, mobile phone messages, and mama kits on promoting health facility births between January 2018 and February 2019, in Lira district, Northern Uganda. In this article, we assessed the effect of the intervention on our two secondary objectives: timely initiation of and exclusivity of breastfeeding. We used a generalized estimation equation of the Poisson family, with a log or identity link, taking clustering into account to estimate prevalence ratios and prevalence differences.

Results: A total of 64% (594/926) of participants in the intervention arm initiated breastfeeding within the first hour after birth compared to 60% (493/829) in the control arm. The proportion of participants in the intervention arm that initiated breastfeeding within the first hour of life did not significantly differ from that in the control arm [Prevalence Ratio (PR) 1.08 (0.97 to 1.21)] and [Prevalence Difference (PD) 0.05 (-0.02 to 0.12)]. When we restricted the analysis to only mothers who decided on when to breastfeed, there was some evidence of intervention effectiveness [PR 1.20, 95% CI (0.99-1.5)]. In the intervention arm, 89% (804/904) of participants exclusively breastfed their infants in the first month of life compared to 81% (656/813) in the control arm. Participants in the intervention arm were 10% more likely to have exclusively breastfed in the preceding 24 hours compared to mothers in the control arm [PR 1.10 (1.04 to 1.17)] and [PD 0.08 (0.04 to 0.13)], and 16% more likely to have exclusively breastfed since birth compared to mothers in the control arm [PR 1.16 (1.03 to 1.30)] and [PD 0.12 (0.03 to 0.20)].

Conclusion: The intervention improved the proportion of mothers who practiced exclusive breastfeeding in the first month of life, but did not increase the proportion of mothers who initiated breastfeeding in the first hour of life. Future breastfeeding promotion interventions should consider including a health facility component and improving maternal autonomy to promote timely initiation of breastfeeding.

BMC Public Health. 2024 Sep 27;24(1):2643.

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Impact of theory of planned behavior based intervention on breastfeeding patterns of the mothers with preterm infants: a randomized trial

[Shirin Okhovat¹](#), [Mojgan Janighorban²](#), [Ashraf Kazemi³](#)

Abstract

Background: The birth of a preterm infant is considered a crisis for the mother and the family. Given the significance of breastfeeding for these high-risk infants, failure to initiate and maintain exclusive breastfeeding in this group of infants is a prevalent and serious problem. The aim of this research was to investigate the impact of Theory of Planned Behavior based intervention on breastfeeding patterns of the mothers with preterm infants: a randomized trial.

Materials and methods: This study is a field trial conducted in Isfahan, Iran in 2021-2022. It included 72 mothers of late preterm infants, divided into the intervention (n = 36) and control (n = 36) groups. The intervention group received four training sessions focused on breastfeeding patterns based on the Theory of Planned Behavior. Before, immediately after, and two and four months after the intervention, the constructs of the Theory of Planned Behavior related to breastfeeding patterns were assessed using a researcher-made questionnaire, and the infant's breastfeeding pattern was recorded. Statistical analysis was performed using SPSS version 19, g repeated measures ANCOVA, Bonferroni post hoc test, and chi-square test.

Results: The results indicated that immediately after the intervention, as well as two and four months later, the mean scores for attitude ($P < 0.001$), subjective norms ($P < 0.001$), perceived behavioral control ($P < 0.001$), and behavioral intention ($P < 0.001$) were significantly higher in the intervention group than in the control group. Additionally, the results showed that, the rate of breastfeeding immediately, two months, and four months

after the intervention was significantly higher in the intervention group than before the intervention ($P < 0.001$). However, in the control group, the rate of breastfeeding immediately, two months, and four months after the intervention was significantly lower than before the intervention ($P < 0.001$).

Conclusion: Interventions based on the Theory of Planned Behavior can improve exclusive breastfeeding in late preterm infants by changing the attitudes, subjective norms, perceived behavioral control and the behavioral intentions of the mothers of preterm infants.

Indian J Pediatr. 2024 Sep;91(9):906-912.

doi: 10.1007/s12098-023-04859-4. Epub 2023 Oct 5.

Comparison of Two Pumping Strategies to Improve Exclusive Breastfeeding at Discharge in Mothers of VLBW Infants with Low Milk Output - A Pilot Randomized Controlled Trial

[Thaslima Kalathingal¹](#), [Swati Manerkar²](#), [Jayashree Mondkar¹](#), [Pavan Kalamdani³](#), [Saikat Patra³](#), [Samandeep Kaur³](#), [Himani Khandekar¹](#)

Abstract

Objectives: To compare the effect of two strategies of breast pumping -power pumping (PP) vs. routine pumping (RP) over one week in mothers of very low birth weight (VLBW) infants with low milk output to improve breastfeeding rates at discharge.

Methods: Mothers with low milk output, defined as inability to express sufficient breastmilk to meet the feeding requirements of their infant on or after post-natal day 14, were randomized to receive power pumping vs. routine pumping - once daily for 7 d coupled with routine lactation support and hand expression 3 hourly in both groups. The primary outcome was exclusive breastfeeding at discharge.

Results: There was no difference in the two pumping strategies with respect to exclusive breastfeeding rates [61.1% in PP vs. 50% in RP group; ($p = 0.477$, RR 1.2; 95% CI 0.76 to 2.17)]. Median milk volume pumped in the individual power pumping session on 7th day of intervention was significantly higher than that in the individual routine pumping session on the 7th day (50 mL vs. 27 mL, $p = 0.014$). The cumulative median milk volume expressed per individual pumping session over the 7 sessions of power pumping was also higher than that with routine pumping (305 mL vs. 213 mL, $p = 0.054$).

Conclusions: In this pilot trial, expressed milk volume was significantly higher after each individual power pumping session compared to routine pumping. However, the exclusive breastfeeding rates at discharge were similar in the two groups.

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Effects of responsive breastfeeding intervention on breastfeeding and infant growth in China: A randomised controlled trial

[Shuliang Zhao¹](#), [Huimin Jiang¹](#), [Honghong Sun²](#), [Qingchun Shao³](#), [Xinxia Zu³](#), [Yanan Li¹](#), [Yuanyuan Zhang¹](#), [Aihua Wang¹](#), [Xinghui Cui⁴](#)

Abstract

Responsive feeding serves as an important protective factor for infant growth and overall health development. This study based on self-determination theory (SDT) aimed to assess the effects of a responsive breastfeeding (RBF) intervention programme on maternal breastfeeding and infant growth and development. A total of 110 mother-infant pairs were recruited and randomly divided into an intervention group (n = 55) and a control group (n = 55). The primary outcomes were breastfeeding motivation score, breastfeeding self-efficacy (BSE) and exclusive breastfeeding rate; the secondary outcomes were infant physical development at 6 weeks and 3 months. A repeated measures ANOVA indicated that the intervention group had significantly higher Enjoyment scores compared to the control group at three time points: at discharge (MD: 5.28; 95% CI: 3.68 to 6.89; $p < 0.001$), 6 weeks post-partum (MD: 5.06; 95% CI: 3.80 to 6.31; $p < 0.001$) and 3 months post-partum (MD: 5.24; 95% CI: 4.12 to 6.35; $p < 0.001$). Similarly, the intervention group reported significantly higher connection and mother's self-perception scores at discharge (MD: 4.31; 95% CI: 3.07 to 5.56; $p < 0.001$), 6 weeks post-partum (MD: 4.69; 95% CI: 3.71 to 5.68; $p < 0.001$) and 3 months post-partum (MD: 4.93; 95% CI: 4.14 to 5.72; $p < 0.001$), compared to the control group. In contrast, the pressure from significant others scores were higher in the control group relative to the intervention group at discharge (MD: -2.09; 95% CI: -2.88 to -1.31; $p < 0.001$), 6 weeks post-partum (MD: -4.35; 95% CI: -5.20 to -3.49; $p < 0.001$) and 3 months (MD: -4.89; 95% CI: -5.70 to -4.08; $p < 0.001$). Finally, the intervention group also reported higher Instrumental Needs scores at all three time points: at discharge (MD: 1.96; 95% CI: 1.35 to 2.58; $p < 0.001$), 6 weeks post-partum (MD: 3.58; 95% CI: 3.05 to 4.11; $p < 0.001$) and 3 months post-partum (MD: 1.18; 95% CI: 0.68 to 1.69; $p < 0.001$). BSE scores were significantly higher in the intervention group compared to the control group at discharge (MD: 14.29; 95% CI: 10.38 to 18.21; $p < 0.001$), 6 weeks post-partum (MD: 14.04; 95% CI: 11.05 to 17.02; $p < 0.001$) and 3 months post-partum (MD: 6.80; 95% CI: 4.66 to 8.94; $p < 0.001$). The rates of exclusive breastfeeding were higher in the intervention group than in the control group at each stage of the intervention ($p < 0.01$). At 6 weeks post-partum, the intervention group's infants showed slower weight ($t = -0.90$, $p = 0.371$) and length ($t = -0.69$, $p = 0.495$) growth compared to the control group, though not significantly. By 3 months post-partum, there was a significant difference in both weight ($t = -3.46$, $p = 0.001$) and length ($t = -2.95$, $p = 0.004$) between the groups. The findings in this study suggest that the RBF intervention programme based on SDT may be effective in improving mothers' motivation to breastfeed, building breastfeeding self-confidence and increasing the rate of exclusive breastfeeding. The effects of the intervention on infant physical development will need to be verified with longer follow-up in future research.

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Impact of an intervention for perinatal anxiety on breastfeeding: findings from the Happy Mother-Healthy Baby randomized controlled trial in Pakistan

[Anum Nisar^{1,2}](#), [Haoxue Xiang³](#), [Jamie Perin³](#), [Abid Malik⁴](#), [Ahmed Zaidi²](#), [Najia Atif²](#), [Atif Rahman¹](#), [Pamela J Surkan⁵](#)

Abstract

Background: The study examined the effects of Happy Mother-Healthy Baby (HMHB), a cognitive-behavioural therapy (CBT) intervention on breastfeeding outcomes for Pakistani women with prenatal anxiety.

Methods: Breastfeeding practices were evaluated in a randomized controlled trial between 2019 and 2022 in a public hospital in Pakistan. The intervention group was randomized to receive six HMHB sessions targeted towards prenatal anxiety (with breastfeeding discussed in the final session), while both groups also received enhanced usual care. Breastfeeding was defined in four categories: early breastfeeding, exclusive early breastfeeding, recent breastfeeding, and exclusive recent breastfeeding. Early breastfeeding referred to the first 24 h after birth and recent breastfeeding referred to the last 24 h before an assessment at six-weeks postpartum. Potential confounders included were mother's age, baseline depression and anxiety levels, stress, social support, if the first pregnancy (or not) and history of stillbirth or miscarriage as well as child's gestational age, gender. Both intent-to-treat and per-protocol analyses were examined. Stratified analyses were also used to compare intervention efficacy for those with mild vs severe anxiety.

Results: Out of the 1307 eligible women invited to participate, 107 declined to participate and 480 were lost to follow-up, resulting in 720 women who completed the postpartum assessment. Both intervention and control arms were similar on demographic characteristics (e.g. sex, age, income, family structure). In the primary intent-to-treat analysis, there was a marginal impact of the intervention on early breastfeeding (OR 1.38, 95% CI: 0.99-1.92; 75.4% (N = 273) vs. 69.0% (N = 247)) and a non-significant association with other breastfeeding outcomes (OR1.42, 95% CI: 0.89-2.27; (47) 12.9% vs. (34) 9.5%, exclusive early breastfeeding; OR 1.48, 95% CI: 0.94-2.35; 90% (N = 327) vs. 86% (N = 309), recent breastfeeding; OR1.01, 95% CI: 0.76-1.35; 49% (N = 178) vs 49% (N = 175) exclusive recent breastfeeding). Among those who completed the intervention's six core sessions, the intervention increased the odds of early breastfeeding (OR1.69, 95% CI:1.12-2.54; 79% (N = 154) vs. 69% (N = 247)) and recent breastfeeding (OR 2.05, 95% CI:1.10-3.81; 93% (N = 181) vs. 86% (N = 309)). For women with mild anxiety at enrolment, the intervention increased the odds of recent breastfeeding (OR 2.41, 95% CI:1.17-5.00; 92% (N = 137) vs. 83% (N = 123)).

Conclusions: The study highlights the potential of CBT-based interventions like HMHB to enhance breastfeeding among women with mild perinatal anxiety, contingent upon full participation in the intervention.

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doi: 10.3390/nu16193425.

Impact of Maternal *Moringa oleifera* Leaf Supplementation on Milk and Serum Vitamin A and Carotenoid Concentrations in a Cohort of Breastfeeding Kenyan Women and Their Infants

[Suzanna Labib Attia¹](#), [Silvia A Odhiambo^{2,3}](#), [Jerusha N Mogaka^{3,4}](#), [Raphael Ondondo⁵](#), [Aric Schadler¹](#), [Kristen McQuerry⁶](#), [George J Fuchs 3rd¹](#), [Janet E Williams⁷](#), [Michelle K McGuire⁸](#), [Carrie Waterman⁹](#), [Kerry Schulze¹⁰](#), [Patrick M Owuor^{2,11}](#)

Abstract

Background: Childhood vitamin A deficiency leads to increased morbidity and mortality. Human milk is the only source of vitamin A for exclusively breastfed infants. Dried *Moringa oleifera* leaf powder (moringa) is a good food source of provitamin A and other carotenoids. Its effect during lactation on human milk vitamin A and carotenoid content is unclear.

Objectives: Our objective was to investigate the effect of maternal moringa consumption on human milk retinol and carotenoid concentrations and maternal and infant

vitamin A status. **Methods:** We conducted a 3-month pilot single-blinded cluster-randomized controlled trial in breastfeeding mother-infant pairs ($n = 50$) in Kenya. Mothers received corn porridge with (20 g/d) or without moringa with complete breast expressions and maternal and infant serum collected at enrollment (infant <30 days old) and 3 months. Milk was analyzed for retinol and selected carotenoids; maternal/infant serum was analyzed for retinol binding protein (RBP). **Results:** 88% ($n = 44$) pairs completed milk and serum samples. Four mothers (9%) had vitamin A deficiency (RBP <0.07 $\mu\text{mol/L}$); 11 (25%) were vitamin A insufficient (VAI; RBP <1.05 $\mu\text{mol/L}$). Alpha-carotene concentration in milk was higher in the moringa than the control group at baseline ($p = 0.024$) and at exit (least squares means, LSM, 95%CI $\mu\text{g/mL}$ 0.003, 0.003-0.004 moringa vs. 0.002, 0.001-0.003 control, $n = 22/\text{cluster}$; $p = 0.014$). In mothers with VAI, alpha-carotene was higher in the moringa group than controls at exit (LSM, 95%CI $\mu\text{g/mL}$ 0.005, 0.003-0.009 moringa, $n = 3$, vs. 0.002, 0.000-0.004 control, $n = 8$, $p = 0.027$) with no difference at baseline. Milk carotenoids did not correlate with vitamin A status (serum RBP) in infants or mothers. **Conclusions:** Maternal moringa consumption did not impact concentration of milk vitamin A and resulted in limited increase in milk carotenoids in this cohort.

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Effectiveness of a theory-based educational intervention on enhancing milk donation behavior: a cluster randomized controlled trial

[Shirin Shahbazi Sighaldehy^{1,2}](#), [Maryam Moridi¹](#), [Anoshirvan Kazemnejad³](#), [Vafa Ghorban Sabagh^{2,4}](#), [Fateme Shateranni⁵](#)

Abstract

Background: This study aims to assess the impact of an educational intervention based on the theory of planned behavior (TPB) on breastfeeding mothers' knowledge, attitude, subjective norms, perceived behavioral control regarding donor human milk (DHM), intention to donate milk and milk donation behavior.

Method: This cluster randomized controlled trial (CRT) was performed on 67 breastfeeding mothers (intervention, $n = 33$; control, $n = 34$) in health centers affiliated to Tehran University of Medical Sciences (TUMS) from April 2023 to October 2023. Four weekly 60-min educational sessions were conducted based on the TPB through lectures, group discussions, psychodrama method, videos and pictures display for mothers in the intervention group, while the control group received only routine care. The data collection tool was a researcher-made questionnaire based on the TPB. It assessed breastfeeding mothers' knowledge, attitudes, subjective norms, perceived behavioral control regarding milk donation, intention to donate milk, and actual milk donation behavior. The questionnaire was completed by participants in both groups before, immediately and three months after the intervention.

Results: The findings indicated that both the intervention and control groups were similar in terms of demographic and obstetrics variables. Additionally, before the intervention, there were no significant differences between the two groups regarding knowledge ($P = 0.552$), attitude ($P = 0.734$), subjective norms ($P = 0.813$), perceived behavioral control ($P = 0.453$), intention to donate milk ($P = 0.476$) and actual milk donation behavior ($P = 0.105$). However, the intervention group showed significant improvements in the mean score of noted variables immediately and three months after the intervention ($P < 0.05$). Moreover, regarding the frequency of milk donations, three months after the intervention, eight

mothers in the intervention group had donated milk, whereas none of the mothers in the control group had done so ($P = 0.002$).

Conclusion: Our findings showed that the TPB-based educational intervention significantly enhanced milk donation behavior among breastfeeding mothers. Given that donor mothers are crucial for the establishment and sustainability of human milk banks (HMBs), such programs should be implemented to increase milk donation rates and support the development of HMBs.

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Effect of Male Partner-Targeted Breastfeeding Education and Support Interventions on Optimal Breastfeeding Practices in Central Ethiopia: A Cluster Randomized Controlled Trial

[Mulatu Abageda^{1,2}](#), [Belayneh Hamdela Jena³](#), [Tefera Belachew⁴](#)

Abstract

A male partner or husband is the most influential person in the family, especially in Ethiopia. The role of a male partner or husband in promoting and supporting breastfeeding has hardly been investigated in low- and middle-income countries, including Ethiopia. Therefore, the objective of this study was to evaluate the effect of breastfeeding education and support interventions that focus on male partners, with the goal of promoting optimal breastfeeding practices in central Ethiopia. A two-arm parallel design cluster randomized controlled trial was carried out among couples in a community setting in the Hadiya Zone, Central Ethiopia. Fathers and mothers in the intervention group received breastfeeding education and support via social events, home visits and using printed materials, while those in the control group received existing routine care. A total of 408 couples from 16 clusters were randomly assigned to either the intervention group ($n = 204$) or the control group ($n = 204$). A Generalized Estimating Equation (GEE) model was used to evaluate the effectiveness of the interventions. At the end of the interventions, the proportion of optimal breastfeeding practice increased by 19.5% in the intervention group and by 2% in the control group. The differences-in-difference in optimal breastfeeding practice between the intervention and control groups was 17.5% [95% CI: 13.8%-21.2%; $p = 0.001$]. In the GEE model, babies born to mothers in the mother-father pair group had a 38% higher likelihood [RR = 1.38, 95% CI (1.106, 1.723)] of being optimally breastfed at the sixth month compared with babies born to mothers who received standard care. Breastfeeding education and support interventions targeting male partners in low-resource settings improve optimal breastfeeding practices, highlighting the need to give due emphasis to integrating breastfeeding promotion and counselling for male partners into existing maternal and child health services

Community nutrition and home gardens

Obesity

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[Effectiveness of a school-based physical activity intervention on overweight and obesity among children and adolescents in Pakistan](#)

[Moazzam Tanveer^{1,2}](#), [Ejaz Asghar²](#), [Georgian Badicu³](#), [Alexios Batrakoulis⁴](#), [Umar Tanveer⁵](#), [Serge Brand^{6,7,8,9}](#), [Matheus Santos de Sousa Fernandes¹⁰](#), [Luca Paolo Ardigo¹¹](#)

Abstract

Background: Childhood obesity poses a significant public health challenge, yet effective school-based physical activity (PA) interventions remain scarce, especially in Pakistan. There is a lack of data assessing the impact of such interventions on obesity and related health outcomes in Pakistani school children.

Methods: This study aimed to design and implement a school-based intervention targeting multiple levels of the socio-ecological model to increase physical activity and reduce the prevalence of overweight and obesity in Pakistani youth. Conducted from October 2022 to January 2023 in Lahore, Pakistan, the 12-week, non-randomized controlled trial involved 1,200 students from eight schools, with four schools (n = 570) in the intervention group and four (n = 630) in the control group. Primary outcomes included changes in body mass index (BMI), waist circumference, and the prevalence of overweight/obesity, measured through anthropometric assessments. Secondary outcomes involved alterations in moderate-to-vigorous physical activity duration. Descriptive statistics, Chi-square tests, general linear mixed models, and repeated measures ANOVA were used for analysis.

Results: The intervention showed significant improvements across various socio-ecological levels. Intrapersonal factors saw a reduction in fast food consumption from 11.9% to 7.9% ($F(1,1198) = 90.39$, $p < 0.001$; $\eta^2 = 0.074$) and an increase in physical activity frequency from 11.9% to 39.6% ($F(1,1198) = 465.25$, $p < 0.001$; $\eta^2 = 0.028$). Screen time decreased from 27.0% to 7.4% ($F(1,1198) = 219.83$, $p = 0.015$; $\eta^2 = 0.15$), and normal sleep duration increased from 44.6% to 71.8% ($F(1,1198) = 242.73$, $p < 0.001$; $\eta^2 = 0.16$). At the interpersonal level, parental involvement in encouraging sports and providing financial support for sports activities significantly increased. School-level factors also showed positive changes, including improved sports facilities and equipment access. Community-level factors revealed increased opportunities for physical activity and a more supportive community environment. The intervention group's BMI change ($-0.06 \pm 0.07 \text{ kg}\cdot\text{m}^2$) significantly differed from the control group's ($0.19 \pm 0.09 \text{ kg}\cdot\text{m}^2$).

Conclusions: This study demonstrates the effectiveness of a multi-level intervention in boosting physical activity and addressing obesity among Pakistani school-aged children, supporting the implementation of similar school-based interventions.

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Rationale, design, and methodology of My Body Is Fit and Fabulous at school (MyBFF@school) study: a multi-pronged intervention program to combat obesity among Malaysian schoolchildren

[Abdul Halim Mokhtar^{1,2}](#), [Ruziana Mona Wan Mohd Zin^{3,4}](#), [Abqariyah Yahya⁵](#), [Fuziah Md Zain⁶](#), [Rusidah Selamat⁷](#), [Zahari Ishak⁸](#), [Muhammad Yazid Jalaludin³](#)

Abstract

Background: Childhood obesity has increased rapidly in recent years and is now a global epidemic. To combat this, MyBFF@school program, a multi-faceted obesity intervention incorporating physical activity in the form of small-sided games (SSG), nutrition, and psychology components for schoolchildren was designed. This paper is aimed at describing the protocol of the MyBFF@school program and presenting the baseline findings including the overweight and obesity prevalence.

Methods: MyBFF@school is a school-based, cluster randomized controlled trial (C-RCT) study. The investigators selected government schools from Federal Territory of Kuala Lumpur, Selangor and Negeri Sembilan by stratified proportionate random sampling based on the multi-ethnic population and the urban-rural location of schools. Subsequently, the schools were assigned randomly to intervention and control groups. The intervention schools underwent MyBFF@school program, whereas the control followed standard school curriculum for a duration of six months. The intervention modules replaced the existing two physical education classes and one co-curriculum activity per week. Three assessments i.e. at baseline, month-3 and month-6 were conducted. Anthropometric, clinical examination, blood, physical fitness, nutrition, and psychology parameters were collected.

Results: Twenty-three out of 1,196 primary schools (seven interventions and 16 controls) and 15 out of 416 secondary schools (six interventions and nine controls). The investigators screened 11,950 primary (age 9-11 years) and 10,866 secondary (age 13, 14, 16 years) schoolchildren. The investigators found 3,516 primary schoolchildren (29.4%) and 2,910 secondary schoolchildren (26.8%) had BMI z-score of more than + 1SD who were eligible for the study. Of these, 39.7% (N = 1397) of the primary and 35.8% (N = 1041) of the secondary schoolchildren agreed to participate in the study. The mean (SD) characteristics for the participating primary and secondary schoolchildren were: BMI z-score, + 2.29 (± 0.81) and + 2.10 (± 0.71); waist circumference, 75.06 (± 9.6) cm and 85.5 (± 10.9) cm; percentage body fat, 37.8% (± 6.5%) and 39.2% (± 7.3%); and muscle mass, 14.7 (± 2.9) and 23.1 (± 5.2) kg respectively.

Conclusion: MyBFF@school program, a school-based multi-pronged intervention was designed to combat childhood obesity. Screening of 22,816 primary and secondary schoolchildren found 29.4% of primary schoolchildren and 26.8% of secondary schoolchildren to be overweight and obese which reflected the urgency for an effective intervention.

Am J Clin Nutr. 2025 Mar;121(3):620-628.

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Impact of linear growth-improving interventions on childhood overnutrition at 24 months: a randomized controlled trial

[Rukman Manapurath¹](#), [Ranadip Chowdhury²](#), [Sunita Taneja³](#), [Nita Bhandari²](#), [Anura V Kurpad⁴](#), [Sarita Devi⁴](#), [Pratibha Dwarkanath⁴](#), [Tor A Strand⁵](#)

Abstract

Background: Childhood malnutrition, both undernutrition and overnutrition, is a major health concern in many low- and middle-income countries (LMICs). Efforts to reduce early undernutrition could also lead to obesity. In an earlier study, we reported the successful impact of a package of preconception, pregnancy, postnatal, and/or early childhood interventions (health, nutrition, psychosocial support, and water, sanitation, and hygiene) delivered in the first 1000 d, on reducing stunting in low-to-middle-income populations, in comparison with routine care. However, the impact of these interventions on early body composition and subsequent overweight is not known.

Objectives: The objective of this study was to estimate the effect of a package of interventions directed at preventing stunting in the first 1000 d on body composition at 1 mo and childhood overweight and/or obesity at 24 mo of age.

Methods: Infant body composition was measured by deuterium dilution at 1 mo of age, along with the prevalence of childhood overweight and/or obesity at 24 mo, defined by a body mass index-for-Age Z (BMIz) score $>+2$ standard deviation.

Results: Children in the preconception, pregnancy, and early childhood intervention group and those in the pregnancy and early childhood intervention group had higher body mass index z scores than those in routine care. However, the prevalence of overweight and/or obesity was low (ranging from 0.0 to 1.3%). Pregnancy interventions significantly increased neonatal fat-free mass (mean difference 0.1 kg, 95% confidence interval [CI]: 0.01, 0.2). However, there was no significant change in fat mass.

Conclusions: Comprehensive interventions from preconception to early childhood improve linear growth but do not result in overweight and/or obesity at 24 mo. With better resultant linear and ponderal growth, they converge with the World Health Organization's "double-duty actions for nutrition" for LMIC settings, where childhood overweight and/or obesity is a growing concern

F1000Res. 2024 Aug 1:13:859.

doi: 10.12688/f1000research.153483.1. eCollection 2024.

[Effect of a pragmatic lifestyle modification intervention on physical activity levels and body mass index among obese and overweight adolescents in Udupi, India: a cluster randomized trial](#)

[Prateek Srivastav¹](#), [Vaishali K¹](#), [H Vinod Bhat²](#), [Suzanne Broadbent³](#)

Abstract

Background: Determine the effects of a multifactorial lifestyle intervention on physical activity (PA), BMI and health-related quality of life (QoL) in obese and overweight adolescents.

Methods: Nine schools in India were clustered randomly in a 12-month study with students allocated to a multifactorial intervention (MFI), or exercise only (EX) or control (CON) group. Participants were adolescents aged 11-16 years (n=671). In the MFI group, adolescents and their parents received lifestyle education using a validated booklet combined with a PA intervention for school students. The EX group received school-based PA only; the CON group continued regular activities. Primary outcomes were PA levels measured with the PAQ-A, and BMI; the secondary outcome was health-related QoL. A linear regression statistical

model was used to analyse time, group effects and interactions, with Bonferroni correction for within-group differences at baseline (T0) and at 12-weeks (T1) (post-intervention), 6-month (T2) and 12-month (T3) follow-ups.

Results: Significant time and group effects observed for all groups with PA scores ($p < 0.001$), with MFI group having largest increase in PA; with BMI ($p < 0.001$) and MFI showing the least gain in BMI; and HRQOL ($p < 0.001$), with MFI group showing greatest improvement in scores. There were significant increases in PA at T1 and T3 time-points with the EX group, and at T3 time-point only for MFI and CON, with MFI group showing largest increase in HRQOL scores. BMI increased significantly for all groups at T2 (MFI $p = 0.001$, EX $p < 0.001$) and T3 ($p < 0.001$), while HRQOL increased significantly for both MFI and EX at both follow-ups ($p < 0.001$).

Conclusions: School-based lifestyle MFI was more effective for improving PA, lifestyle behaviours and HRQOL than exercise alone for adolescents, although BMI was not reduced. MFI with PA could be an effective school-based approach for behaviour modification but BMI has limitations for measuring body composition changes.

BMC Public Health. 2024 Sep 27;24(1):2579.

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Reducing the incidence of overweight and obesity by a healthy lifestyle intervention program for schoolchildren in Hanoi, Vietnam: a randomized controlled trial

Thuy Thi Phuong Pham¹, Thanh Van Do², Yumi Matsushita³, Mitsuhiro Hara⁴, Mai Thi Hoa Tran⁵, Hung Xuan Le⁶, Thanh Thi The Nguyen⁷, Uyen Thu Hoang⁵, Quyen Huyen Dao⁸, Lien Thi Kim Dinh⁷, Hung Phan⁹, Hiroshi Kajio¹⁰

Abstract

Background: The increasing incidence and prevalence of childhood overweight (OW) and obesity (OB) are major global health challenges. This study aimed to evaluate the effectiveness of a 2-year healthy lifestyle intervention program in reducing the incidence of OW and OB among schoolchildren aged 11-12 years in Vietnam.

Methods: Study design: Randomized controlled trial.

Participants and interventions: In total, 733 students participated in this study. Participants were included from four schools in Hanoi based on a random cluster sampling method. Students' health outcomes were assessed at baseline and after 2 years.

Main outcomes: The primary outcomes were the incidence of OW and OB, and the secondary outcomes were the prevalence and remission of OW and OB. Generalized estimating equations (GEEs) were used to determine the outcomes and risk factors.

Results: After the intervention, the prevalence of OW decreased by 9.24% in the intervention group and 3.01% in the control group. After adjustment for age and sex, the odds of overweight were 36.7% lower in the intervention group than in the control group (OR = 0.633; 95% CI: 0.434-0.925; $P = 0.018$). The incidence of OW was 1.31% in the intervention group compared with 5.33% in the control group. After adjustment for age and sex, the odds of incident overweight in the intervention group were 77.4% lower than in the control group (OR = 0.226; 95% CI: 0.063-0.813; $P = 0.023$). The proportion of patients who achieved OW remission was 41.22% in the intervention group and 28.68% in the control group. After adjustment for age and sex, the odds of OW remission of overweight were 2.219 times greater in the intervention group than in the control group (OR = 2.219; 95% CI: 1.220-4.036; $P =$

0.009). For most OB-related factors, there were no significant differences between the intervention and control groups.

Conclusion: A multicomponent healthy lifestyle intervention was effective in reducing the incidence of OW; however, it had no significant effect on OB among children aged 11-12 years in Hanoi, Vietnam.

Pediatr Obes. 2024 Nov;19(11):e13163.

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Effect of Indo-Mediterranean diet versus calorie-restricted diet in children with non-alcoholic fatty liver disease: A pilot randomized control trial

[Aniket Deshmukh¹](#), [Vikrant Sood¹](#), [Bikrant Bihari Lal¹](#), [Rajeev Khanna¹](#), [Seema Alam¹](#), [Shiv Kumar Sarin²](#)

Abstract

Background: Dietary interventions and increased physical activity are the cornerstones for management of the paediatric non-alcoholic fatty liver disease (NAFLD). Though, no specific diet has been proven superior, Indo-Mediterranean diet (IMD) has shown promise in adult literature. Thus, we aimed to compare the effect of IMD and a standard calorie-restricted diet (CRD) in Indian overweight children and adolescents with biopsy-proven NAFLD.

Methods: Thirty-nine consecutive biopsy-proven NAFLD children between the ages of 8 and 18 years were randomized into either IMD or CRD for 180 days, and various parameters were evaluated at baseline and then after 180 days ([NCT05073588](#)).

Results: A total of 34 subjects (18 in IMD and 16 in CRD group) completed the study. There was a significantly higher decrease in controlled attenuation parameter (CAP) values (as a marker of hepatic steatosis; on transient elastography) (95% CI: 4.2-73.4, $p = 0.042$), weight (95% CI: 0.75-5.5, $p = 0.046$) and body mass index (BMI) (95% CI: 0.21-2.05, $p = 0.014$) (but not in Pediatric NAFLD Fibrosis Index or PNFI; as a marker of hepatic fibrosis) in IMD group compared to the CRD group. Liver stiffness measurement, serum cholesterol and low-density lipoprotein levels and HOMA-IR decreased only in the IMD group ($p < 0.001$). Our statistical model showed that delta-Weight was the only independent variable associated with delta-CAP.

Conclusion: Both IMD and CRD can improve the various anthropometric, clinical, imaging and biochemical parameters but IMD was superior to CRD in terms of reducing CAP values and weight/BMI over 180 days in overweight/obese NAFLD children.

Eur J Pediatr. 2025 Apr 14;184(5):295.

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Effect of dietary approaches to stop hypertension (DASH) diet on adiposity indices in children with overweight and obesity: an 8-week triple-blind randomized controlled trial

[Niloufar Rasaei¹](#), [Reza Bigdeli²](#), [Somayeh Jafrasteh³](#), [Reza Norouzirad⁴](#), [Zahra Bahadoran⁵](#)

Abstract

We aimed to investigate the potential effects of Dietary Approaches to Stop Hypertension (DASH) diet on adiposity indices in children with overweight and obesity. This study was a

triple-blind, randomized controlled trial. Sixty girls and boys (aged 8-12 years) were randomly assigned to either DASH diet or control group, and the intervention duration was 8 weeks. Body weight (BW), height, waist circumference (WC), skinfold thickness (SFT), neck circumference (NC), body mass index (BMI), waist-to-height ratio (WHtR), body round index (BRI), and weight-adjusted waist index (WWI) were assessed before and after the intervention. The primary analysis was conducted on a per-protocol basis, including only participants who completed at least two visits and adhered to the study protocol. This approach was chosen to ensure that the results reflect the actual effects of the intervention among compliant participants. Analysis of covariance (ANCOVA) was used to compare after treatment adiposity indices between groups. Mean $\pm$ SD age and BMI of the participants was 11.8 ± 0.8 years (69% were girls) and 25.9 ± 3.52 kg/m², respectively. A total of 58 patients (n = 29 in DASH group and n = 29 in control group) who completed at least two visits and adhered to the study protocol were included in the final per-protocol analysis. Two participants (one from each group) were lost to follow-up and excluded from the analysis due to incomplete data. After 8 weeks, the DASH group had a significantly lower BW (59.5 vs. 62.6 kg), WC (84.3 vs. 85.5 cm), NC (32.9 vs. 33.3 cm), SFT (3.57 vs. 3.57 cm), BMI (25.9 vs. 25.9 kg/m²), WHtR (0.55 vs. 0.56), BRI (4.57 vs. 4.75), and WWI (10.42 vs. 10.84 cm/ $\sqrt{\text{kg}}$) compared with the controls (P for all < 0.01). The mean change percent of adiposity indices was higher in the control than the DASH group (P for all < 0.05); however, for the WWI, a significant reduction was observed in the DASH group.

Matern Child Nutr. 2025 Jul;21(3):e13802.

doi: 10.1111/mcn.13802. Epub 2025 Mar 4.

[Effect of a Behavioral Change Communication Strategy Coupled With Small-Quantity Lipid-Based or Micro-Nutrient Supplements on Stunting and Obesity in Children in Baja Verapaz, Guatemala: Results From a Cluster Randomized Controlled Trial](#)

[Carolina Gonzalez Acero](#)¹, [Sebastian Martinez](#)², [Ana Perez-Exposito](#)¹, [Solis Winters](#)³

Abstract

The co-existence of childhood stunting and obesity is a public health problem in Guatemala and Latin America. The objective of this study was to assess the effects of unsweetened small-quantity lipid-based nutrient supplements (SQ-LNS) coupled with a behavior change communication (BCC) strategy on the double burden of malnutrition. We conducted a three-arm randomized-control trial with two-stage cluster sampling of households with children under 4.5 months or a mother in the third trimester of pregnancy at baseline from 76 communities in Baja-Verapaz, Guatemala. Some 1268 households were randomly assigned to SQ-LNS or micronutrient powders (MNPs) paired with a multilevel participatory-ludic BCC strategy, or to MNPs only. Measures of mothers' nutrition knowledge and practices were collected at baseline and endline. Children's height, weight, and hemoglobin concentration were measured at endline. Treatment effects were estimated using regression models. The BCC strategy boosted caregiver nutrition knowledge from 4.2 (95% CI: 2.7, 5.7) to 4.6 percentage points (95% CI: 3.1, 6.1). Significant effects on nutrition practices of 3.0 percentage points (95% CI: 1.2, 4.8) were found only for caregivers with children receiving SQ-LNS. We found no detectable treatment effects on stunting or anemia. However, children exposed to SQ-LNS and the BCC strategy were 2.6 percentage points (95% CI: -5.0, -0.2) less likely to be overweight or obese (54.1% lower than the group receiving MNPs only). An

intervention coupling a multilevel participatory-ludic BCC strategy with the use of unsweetened SQ-LNS holds promise for the prevention of childhood overweight and obesity, yet complementary interventions are required to address non-nutritional factors related to stunting in Guatemala.

Oncology

Neuro Oncol. 2025 Mar 8:noaf049.

doi: 10.1093/neuonc/noaf049. Online ahead of print.

[High-precision radiotherapy achieves excellent long-term control and preserves function in pediatric craniopharyngioma - Subset analysis of a randomized trial](#)

[Rakesh Jalali¹](#), [Suman Ghosh¹](#), [Abhishek Chatterjee¹](#), [Savita Goswami¹](#), [Nalini Shah¹](#), [Debnarayan Dutta¹](#), [Uday Krishna¹](#), [Tejpal Gupta¹](#), [Jayant S Goda¹](#)

Abstract

Background: The evolving treatment paradigm in children and adolescents with craniopharyngioma (CP) aims at minimizing late functional sequelae. Advanced radiotherapeutic techniques offer theoretical advantages of preserving neurological functions, however, clinical evidence of such is limited. The current study constitutes a secondary analysis of CP patients in a Randomized Control Trial testing Conventional RT (ConvRT) versus Stereotactic Conformal Radiotherapy (SCRT)([NCT00517959](#)).

Methods: Eighty-two patients of CP (SCRT: 39, ConvRT: 43, Dose: 54Gy in 30 fractions) were analysed, assessing the clinical impact of dosimetric sparing on neurocognitive function, endocrine function, overall survival (OS) and local control (LC). Patients were longitudinally assessed from baseline through five years post-treatment using the WISC/WAIS scales.

Results: The median age was 13 years (IQR= 9-17 years). The 10-year OS and LC rates were 86.4% and 92.7%, respectively, with no significant difference between the arms. SCRT patients showed significant improvement in mean full-scale IQ (difference in slope=3.3 points per year, $p=0.01$) and performance quotient (difference in slope=3.6, $p=0.04$) compared to those treated with ConvRT. Freedom from cognitive decline (a 5-point drop) at 5 years was higher with SCRT (66.6% vs. 38.2%; HR=0.41, $p=0.03$). Younger age (<15 years) was a significant negative predictor of neurocognitive outcomes ($p=0.002$). SCRT patients also experienced lower cumulative incidence of new neuroendocrine dysfunction (25.7% vs. 48.8%, $p=0.029$).

Conclusion: SCRT offers excellent tumour control and similar survival with superior long-term preservation of neurocognitive and endocrine functions in CP patients compared to conventional RT. High precision RT should constitute the standard of care in CP.

Clin Microbiol Infect. 2024 Aug;30(8):1029-1034.

doi: 10.1016/j.cmi.2024.04.007. Epub 2024 Apr 20.

Efficacy and safety of withholding antimicrobial therapy in children with cancer, fever, and neutropenia, with a demonstrated viral respiratory infection: a randomized clinical trial

[Juan P Torres¹](#), [Carolina Ibañez²](#), [Romina Valenzuela³](#), [Salome Rivera³](#), [Veronica De la Maza³](#), [Milena Villarroel¹](#), [Paulina Coria²](#), [Veronica Contardo⁴](#), [Ana M Álvarez⁵](#), [Carmen M Zubieta⁶](#), [Valentina Gutierrez⁷](#), [Karen Ducasse⁸](#), [Daniela Martínez⁹](#), [Maria E Santolaya¹⁰](#)

Abstract

Objectives: To validate the efficacy and safety of withholding antimicrobial therapy in a new cohort of children with cancer and febrile neutropenia (FN) having a demonstrated viral respiratory tract infection.

Methods: Prospective, multicenter, noninferiority, randomized study, approved by the ethical committee, in children presenting with FN at seven hospitals in Chile, evaluated at admission for diagnosis of bacterial and viral pathogens. Children who were positive for a respiratory virus, negative for a bacterial pathogen, and had a favourable evolution after 48-72 hours of antimicrobial therapy were randomized to either maintain or withhold antimicrobial therapy. The primary endpoint was the percentage of episodes with an uneventful resolution, whereas the secondary endpoints were days of fever, days of hospitalization, requirement of antimicrobial treatment readministration, sepsis, paediatric intensive care unit admission, and death.

Results: A total of 301 of 939 children with FN episodes recruited between March 2021 and December 2023 had a respiratory virus as a unique identified microorganism, of which 139 had a favourable evolution at 48-72 hours and were randomized, 70 to maintain and 69 to withdraw antimicrobial therapy. The median days of antimicrobial therapy was 5 (IQR 3-6) versus 3 (IQR 3-6) days ($p < 0.001$), with similar frequency of uneventful resolution 66/70 (94%) and 66/69 (96%); relative risk, 1.01; (95% CI, 0.93 to 1.09), absolute risk difference 0.01; (95% CI, -0.05 to 0.08) and similar number of days of fever and days of hospitalization. No cases of sepsis, paediatric intensive care unit admission, or death were reported.

Discussion: We validated the strategy of withdrawal antimicrobial therapy in children with FN and viral respiratory tract infection based on clinical and microbiological/molecular diagnostic criteria. This will enable advances in antimicrobial stewardship strategies with a possible future impact on antimicrobial resistance.

Psychooncology. 2025 Jan;34(1):e70086.

doi: 10.1002/pon.70086.

Cognitive-Behavioral Intervention for Children With Hematological Cancer Receiving Chemotherapy: A Randomized Controlled Trial

[Tenaw Gualu Melesse^{1,2}](#), [William Ho Cheung Li¹](#), [Janita Pak Chun Chau¹](#), [Mulugeta Ayalew Yimer³](#), [Abdulkadir Mohamedsaid Gidey⁴](#), [Sewbesew Yitayih⁵](#)

Abstract

Objective: Cognitive-behavioral intervention (CBI) has shown positive effects in improving psychological and health-related outcomes in children with cancer. However, no evidence has been found in Ethiopia. This study aimed to evaluate the effects of CBI on anxiety, depression and quality of life (QoL) in Ethiopian children with hematological cancer receiving chemotherapy.

Methods: A parallel, two-armed, assessor-blinded, randomized controlled trial was conducted among 76 children randomized (1:1) to receive CBI or usual medical care. The intervention group received five weekly face-to-face CBI sessions of 30-40 min each, which included an introduction to CBI; identifying and challenging maladaptive thoughts, beliefs and behavior; behavior activation; deep breathing exercises; and treatment evaluation and relapse prevention. The outcomes were measured at baseline (T0), immediately post-intervention (T1) and 1 month post-intervention (T2).

Results: The intervention group showed a significant reduction in anxiety scores from T0 at T1 ($\beta = -6.67$, 95% CI $[-9.16, -4.19]$, $p < 0.001$) and T2 ($\beta = -8.14$, 95% CI $[-10.70, -5.57]$, $p < 0.001$), depression at T1 ($\beta = -4.09$, 95% CI $[-6.94, -1.23]$, $p = 0.005$) and T2 ($\beta = -6.12$, 95% CI $[-9.10, -3.13]$, $p < 0.001$) and improvement in QoL at T2 ($\beta = 3.02$, 95% CI $[0.49, 5.56]$, $p = 0.019$) compared with the control group.

Conclusions: CBI has positive effects in reducing anxiety and depression and in improving QoL in children with hematological cancer receiving chemotherapy. The results suggest the need to incorporate CBI into pediatric hematology-oncology and studies on its long-term effects and cost-effectiveness are warranted.

Leuk Res. 2024 Oct;145:107560.

doi: 10.1016/j.leukres.2024.107560. Epub 2024 Aug 22.

Cost-effectiveness of blinatumomab for the treatment of B-precursor acute lymphoblastic leukemia pediatric patients with high-risk first-relapse in Mexico

Juan Pablo Díaz Martínez¹, Therese Aubry de Maraumont², Luis Miguel Camacho², Laura García³

Abstract

Background: Blinatumomab is a CD3/CD19-directed bispecific T-cell engager molecule that engages T cells to lyse CD19-expressing B cells. Based on a multicenter, open-label, phase 3, randomized clinical trial (Clinical Trials ID: [NCT02393859](#)), we aimed to evaluate the cost-effectiveness (CE) of blinatumomab compared to standard consolidation chemotherapy (SC) for the treatment of pediatric patients with high-risk first-relapsed Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia (B-ALL) from a Mexico healthcare payer perspective.

Methods: A decision-analytic model, a partitioned survival model, was used to estimate the life-years (LYs) and costs over a lifetime horizon. We assumed that patients who remained alive beyond a 5-year period were cured. To account for the lingering impacts of cancer treatment, an excess mortality rate was incorporated into the model. Event-free survival (EFS) and overall survival (OS) were estimated by fitting mixture-cure and standard parametric survival distributions to the time-to-event data from the phase 3 trial. The model accounted for treatment costs, adverse event costs, follow-up costs, subsequent allogeneic hematopoietic stem cell transplantation (alloH SCT) costs, and subsequent treatment costs.

Results: Blinatumomab was associated with a lifetime gained of 5.11 years at an incremental cost of \$621,111 MXN, relative to SC. The ICER for blinatumomab vs Standard of care was estimated to be \$121,526 MXN/LY gained in the base case. Cost-effectiveness was sensitive to varying the time horizon. Blinatumomab had a probability of 99 % of being cost-effective, relative to SC, at the willingness to pay threshold defined in Mexico.

Limitations: Health-related quality of life values were not included in the analysis and therefore we did not estimate the quality-adjusted life-years gained.

Conclusions: Blinatumomab was associated with greater benefit in terms of OS and EFS relative to SC. Probabilistic, deterministic, and scenario analyses indicate that blinatumomab represents the best value for money. Therefore, blinatumomab administered as part of consolidation therapy in B-ALL pediatric patients with high-risk first relapse is a cost-effective option.

Pediatr Blood Cancer. 2025 Jan;72(1):e31400.

doi: 10.1002/pbc.31400. Epub 2024 Nov 6.

Photobiomodulation Therapy in the Prevention of Chemotherapy Induced Oral Mucositis in Children with Acute Myeloid Leukemia: A Randomized, Double-blind, Clinical trial

[Reem E Elkady¹](#), [Reham Khedr^{2,3}](#), [Mohammed Hassan⁴](#), [Samy El Bayoumy⁵](#), [Sonia Mahmoud^{2,3}](#), [Ebtisam Hanafy⁶](#), [Salam ElAraby⁷](#), [Alaa El Haddad^{2,3}](#)

Abstract

Background: Many preventive modalities have been advocated to reduce the incidence and severity of chemotherapy-induced Oral Mucositis (OM). Photobiomodulation, also known as Low-Level laser. Therapy, has shown promising results. This clinical trial was performed to evaluate the effectiveness of Photobiomodulation (PBM) for the prevention of chemotherapy-induced oral mucositis (OM) in children with Acute Myeloid Leukemia (AML).

Patients and methods: A double-blinded randomized clinical trial was performed, including forty-two children diagnosed with Acute Myeloid Leukemia (AML) admitted to receiving chemotherapy (CT) at Children's Cancer Hospital 57357, Cairo, Egypt. Patients were randomly assigned to either the control or test group. Both groups followed the standard preventive protocol for oral mucositis. In the control group I sham therapy, while in the Laser group I had Photobiomodulation sessions for five consecutive days once a day performed by Diode laser (Sirrolaser Blue™, USA) 660nm, 15watt, 10 s. Laser sessions began on day 1 of chemotherapy and were repeated on days 2,3, 4, and 5. The response to both groups was evaluated according to the development of oral mucositis; graded using the classification criteria of the World Health Organization (WHO) and the National Cancer Institute scale (NCI - Common Terminology Criteria for Adverse Events, version 4.0). Incidence of oral mucositis was evaluated from baseline to 5, 12, 19, and 30 days after treatment.

Results: A clinical significant difference between the laser and control group was observed. The laser group showed a higher prevalence of no oral mucositis with decreased incidence of OM, while on day 12, the control group showed a higher prevalence of grades I and II (P-value <0.001, effect size = 0.796). However, the laser group showed higher prevalence of mucosa free of OM; on day 19, the control group showed higher rates of grades II and III, (P-value <0.001, effect size = 0.670). while on day 30 there was higher rates of grades I and II (P-value <0.001, effect size = 0.576) with higher rates of healthy oral mucosa in the laser group.

Conclusion: Photobiomodulation effectively reduces the incidence and severity of chemotherapy-induced oral mucositis in pediatric patients diagnosed with AML.

Ophthalmology and optometry

Ital J Pediatr. 2024 Oct 19;50(1):218.

doi: 10.1186/s13052-024-01781-z.

[Do preterm infants' retinas like bovine colostrum? A randomized controlled trial](#)
[Marwa Mohamed Farag](#)¹, [Mohamed Alaa Eldin Hassan Thabet](#)², [Islam Sh Ahmed](#)³, [Nesrine Fathi Hanafi](#)⁴, [Walaa Samy Elsayy](#)², [Eman Shabban Mohamed](#)²

Abstract

Background: Bovine colostrum (BC) with liposomal delivery system (LDS) is a promising supplement to premature infant formula in absence of mother own milk. We propose that BC with LDS can target multiple etiological factors that threaten the developing retina, making premature infant less liable for retinopathy of prematurity (ROP). The aim of this study was to evaluate the effect of BC with LDS in the prevention of ROP.

Methods: This was a single center, randomized, controlled trial. Two hundred and eleven preterm infants of gestational age ≤ 32 weeks were admitted to the NICU of Alexandria University Children Hospital, Egypt, and randomly allocated into either non-BC group (n = 105) or BC group (n = 106). Patients in BC group received 3.5 ml /kg/day of BC for 14 days. All patients were monitored for development of ROP, anemia, late onset sepsis (LOS), bronchopulmonary dysplasia (BPD), periventricular leukomalacia (PVL) and necrotizing enterocolitis (NEC), in addition to growth assessment. Multivariate binary logistic regression analysis was performed to determine factors predicting ROP development.

Results: Compared with the non-BC group, BC group was associated with a significantly lower incidence of ROP (5/100 vs. 16/100, respectively) with a p-value of 0.033. The administration of BC significantly decreased serum C- reactive protein (CRP) level and increased weight on day-14 of the study in comparison with the CRP level and birthweight at the beginning of study, with Cohen's D= -0.184, D = -2.246, respectively. Patients with suspected sepsis were significantly less in BC than non-BC group, p = 0.004. Patients with BC had significantly higher hemoglobin level on day-14 than non-BC-group, with median (IQR) 12.2 (11.0-13.9) and 11.7 (10.5-12.9), respectively. BC intake is one of factors that decreased development of ROP in univariate analysis. Nevertheless, weight gain and birth weight were the most significant factors affecting ROP development in multivariate-regression model.

Conclusion: BC may reduce the incidence of ROP in preterm neonates aged ≤ 32 weeks. This might be due to keeping better Hb level and growth rate, as well as anti-inflammatory properties through its ability to decrease CRP level.

Nurs Crit Care. 2024 Nov 10.

doi: 10.1111/nicc.13200. Online ahead of print.

[Multisensory stimulation to reduce procedural pain in retinopathy of prematurity: A randomized controlled trial](#)

[Halil Ibrahim Tasdemir](#)¹

Abstract

Background: Retinopathy is frequently seen in the neonatal intensive care unit (NICU), and its examination is a painful procedure for infants.

Aim: This randomized active-controlled trial aimed to investigate the impact of multisensory stimulation (MSS) on neonatal pain during retinopathy of prematurity (ROP) examinations, in comparison with a white noise (WN) and control group receiving standard care.

Study design: Conducted as a three-arm, randomized controlled trial, the study was implemented in the NICU of a local university hospital. Recruitment spanned from July 2023 to November 2023, with preterm infants (gestational age < 37 weeks) randomly assigned to either a MSS, WN or a control group. MSS components included visual, auditory, tactile, olfactory and gustatory stimuli, all designed to create a synergistic, comforting environment for the infant during the procedure. Procedural pain, heart rate and oxygen saturation were assessed at various stages before and after ROP examinations.

Results: Analysis of 90 participants revealed that the MSS group exhibited lower Premature Infant Pain Profile (PIPP) scores than the WN and control groups (mean difference: -2.12, 95% confidence interval [CI]: -2.62 to -1.62; odds ratio [OR]: 0.004, 95% CI [0.001, 0.012], $p < 0.001$). Additionally, heart rates were significantly lower in the MSS group (mean difference: -15.3 beats/min, 95% CI: -20.5 to -10.1; OR: 0.025, 95% CI [0.008, 0.073], $p < .001$) and oxygen saturation levels were higher (mean difference: 3.2%, 95% CI: 1.8% to 4.6%; OR: 1.12, 95% CI [1.05, 1.20], $p < .001$) than in the other groups.

Conclusions: MSS emerges as a favourable, safe and non-pharmacological intervention for pain management in ROP and similar procedures.

Relevance to clinical practice: Multisensory stimulation can be effectively integrated into the routine care provided by critical care nurses during retinopathy of prematurity examinations in preterm infants. This non-pharmacological intervention offers a practical approach for critical care nurses to reduce procedural pain and improve physiological stability in this vulnerable population.

Indian J Ophthalmol. 2024 Jul 1;72(7):976-982.

doi: 10.4103/IJO.IJO_1010_23. Epub 2024 Jun 22.

Effect of topical brinzolamide on visual function and waveform in patients of infantile nystagmus syndrome: A randomized control trial

[Bhupendra Yadav¹](#), [Rohit Saxena¹](#), [Rebika Dhiman¹](#), [Kanwal P Kochhar²](#), [Ashlesh Patil²](#), [Pradeep Sharma¹](#), [Ramanjit Sihota¹](#), [Radhika Tandon¹](#)

Abstract

Purpose: To evaluate the effect of topical carbonic anhydrase inhibitor (brinzolamide) versus placebo on visual function and waveforms in infantile nystagmus syndrome (INS).

Design: Prospective, placebo-controlled, double-blind, cross-over study.

Methods: Setting- A tertiary eye care center. Patients- Cases of idiopathic INS with and without abnormal head posture aged ≥ 10 years who had not received previous treatment for nystagmus. Intervention- Patients were randomized into two groups. Group 1 was given placebo for 3 months, and after a washout period of 7 days started on topical brinzolamide for the next 3 months. In group 2, the order was reversed. The drops were administered topically three times (every 8 hours) in both eyes. Outcome measure- Binocular best corrected visual acuity (BCVA) using the ETDRS chart, eXpanded nystagmus acuity function (NAFX) score and INS waveforms obtained from eye movement recordings, intraocular

pressure (IOP) by Goldmann applanation tonometer, near stereopsis by TNO stereo test, and change in abnormal head posture before and after intervention in the null position.

Results: A total of 29 cases completed the study (23 with abnormal head posture; 6 without abnormal head posture).

A significant improvement was noted in INS waveform characteristics, mean NAFX score ($P < 0.001$), and mean binocular visual acuity ($P < 0.001$) with topical brinzolamide in comparison to baseline as well as placebo. No significant change in head position and stereopsis was noted. No side effects were reported with 3 months of brinzolamide therapy.

Conclusions: While brinzolamide shows improvement in visual acuity and NAFX score in idiopathic INS, its clinical significance needs further evidence.

Ophthalmol Glaucoma. 2024 Aug 22:S2589-4196(24)00142-X.

doi: 10.1016/j.ogla.2024.08.003. Online ahead of print.

Comparison of Bent Ab-Interno Needle Goniectomy and Goniotomy in Primary Congenital Glaucoma: A Randomized Controlled Trial

[Sushmita Kaushik¹](#), [Kajree Gupta²](#), [Shrushti Hunashyal²](#), [Manik Sardana²](#), [Faisal Thattaruthody²](#), [Surinder Singh Pandav²](#)

Abstract

Purpose: Primary congenital glaucoma (PCG) is a potentially blinding disease, and the search for the best surgical option always remains. This study investigated the efficacy of Bent Ab-Interno Needle Goniectomy (BANG) compared to the established standard of traditional goniotomy.

Design: Parallel-group randomized controlled trial.

Participants: Infants with PCG aged 1 month to 1 year with similar clinical features in both eyes.

Intervention: The 2 eyes of eligible patients were randomized to either goniotomy or BANG using a 25-gauge needle bent as a reverse cystitome, and the surgeries were done on the same day in both eyes. Postoperatively each infant was followed up for a minimum period of 1 year.

Main outcome measures: The primary outcomes measured were intraocular pressure (IOP) control and the requirement for antiglaucoma medications (AGMs). The secondary outcome measures included corneal clarity enhancement, axial length stability, incidence of surgical complications, or the need for repeat surgery.

Results: Eight infants with both eyes eligible, were included. In each infant, 1 eye was randomized to BANG and the other to conventional goniotomy. The mean age was 7.6 ± 3.6 months. There was no significant difference in the mean preoperative IOP (16.8 ± 8.87 mm Hg vs. 17 ± 6.0 mm Hg; $P = 0.48$) in eyes randomized to goniotomy or BANG. The mean number of AGMs (1.7 ± 1.11 vs. 2 ± 0.81 respectively; $P = 0.26$) were similar in both groups.

Postoperatively, the IOP at 6 months (14.05 ± 4.1 vs. 16.2 ± 4.07 ; $P = 0.22$) and 1 year (15.3 ± 3.4 vs. 17.1 ± 3.0 ; $P = 0.15$) were similar in eyes that underwent goniotomy or BANG respectively. Both procedures demonstrated significant improvements in corneal clarity and maintained normal axial length growth. However, the BANG group required slightly more AGMs than the goniotomy group. There were no serious complications in either group. Both eyes of 1 patient required repeat surgery for IOP control and underwent a combined trabeculotomy with trabeculectomy at 9 months and 1 year postoperatively, respectively.

Conclusions: This study indicates that goniotomy remains an effective surgical treatment for PCG. The absence of discernible superiority in IOP control or overall outcomes implies that the added complexity of excising the trabecular meshwork in BANG may not confer additional benefits over the established approach.

Am J Ophthalmol. 2024 Nov 6:S0002-9394(24)00509-9.

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Outcomes of circumferential versus hemi-gonioscopy assisted transluminal trabeculotomy for congenital glaucoma

[Shikha Gupta¹](#), [Arnav Panigrahi²](#), [R Anjana²](#), [Anurag Kumar²](#), [Anand Kumar Pathak²](#), [Davinder S Grover³](#), [Viney Gupta²](#)

Abstract

Purpose: To compare the efficacy of circumferential gonioscopy-assisted transluminal trabeculotomy (GATT) versus hemi-GATT in primary congenital glaucoma (PCG).

Design: Prospective randomized controlled trial **METHODS:** This study included children with PCG having corneal diameters <14mm and relatively clear cornea. Based on randomisation, the eyes included, underwent either circumferential GATT (360-GATT) or hemi-GATT (180-GATT). The intra-ocular pressure (IOP) reduction, requirement for glaucoma medications after surgery, need for repeat surgery and the incidence and type of complications in each group were analysed. Surgical success was defined as absolute when IOP ≤ 18 (criterion A) and ≤ 15 mmHg (criterion B) was achieved without medications and qualified when the same was achieved with pressure-lowering medications. Eyes with an IOP ≥ 18 mmHg on maximum medications, those with IOP < 6 mmHg or need for further intervention for IOP control were considered failures.

Results: Fifty-two eyes of children with PCG were randomized into either the 360-GATT group (22 eyes) or the 180-GATT group (30 eyes) and followed up for at least 1 year. The median follow-up duration was 22.5 months (range: 12-30 months). IOP fell by 49% and 20.5% with 360-GATT and 180-GATT respectively, final IOP being significantly lower in the former group ($p=0.0003$). For absolute success the cumulative survival was superior with 360-GATT for both criterion A and B at 1 year ($p=0.009$). Average cup disc ratio, corneal diameter and axial length reversal were significant in the 360-GATT group but not in the hemi-GATT group.

Conclusions: This study reinforces the superior efficacy of circumferential GATT for IOP control in eyes with congenital glaucoma.

Trachoma

PLoS Negl Trop Dis. 2024 Sep 3;18(9):e0012034.

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The impact of modified incision height and surgical procedure on trichiasis surgery outcomes: Results of the maximizing trichiasis surgery success (MTSS) randomized trial

[Emily W Gower¹](#), [Alemayehu Sisay²](#), [Belay Bayissasse²](#), [Dawit Seyum²](#), [Jerusha Weaver¹](#), [Beatriz Munoz³](#), [Alexander P Keil¹](#), [Andrea Bankoski¹](#), [Kristin M Sullivan¹](#), [Hashiya Kana¹](#), [Fisseha Admassu⁴](#), [Demissie Tadesse⁵](#), [Shannath L Merbs⁶](#)

Abstract

Background: Poor surgical outcomes remain a problem in trachoma-endemic countries working to reach elimination thresholds. Methods to improve outcomes could positively impact programmatic success.

Methods: This parallel, three-armed clinical trial conducted in Ethiopia randomized individuals with previously unoperated trichomatous trichiasis (TT) to receive surgery utilizing one of three approaches: bilamellar tarsal rotation with a 3 mm incision height (BLTR-3), BLTR with 5 mm incision height (BLTR-5) and posterior lamellar tarsal rotation (PLTR). We followed participants for one year. The primary outcome was post-operative trichiasis (PTT). Secondary outcomes were eyelid contour abnormalities (ECA) and pyogenic granulomata.

Findings: We randomized and operated on 4,914 individuals with previously unoperated TT (6,940 eyes). Primary analyses include 6,815 eyes with follow-up. Overall, 1,149 (16.9%) eyes developed PTT. The risk difference for PTT was minimal comparing BLTR-3 and PLTR (adjusted risk difference [aRD] 1.8% (98.3%CI: -0.5-4.2%)), but significantly higher for BLTR-5 surgeries compared to BLTR-3 (aRD: 6.7% (3.9-9.4%)) and PLTR (aRD: 8.6% (5.9-11.3%)). BLTR-5 had the lowest ECA (6.1% versus 9.6% BLTR-3, 11.2% PLTR) and granuloma rates (5.2% versus 6.5% BLTR-3 and 7.5% PLTR). One eyelid operated with PLTR experienced an eyelid margin division; four BLTR-3 and eight BLTR-5 eyelids experienced excessive bleeding.

Interpretation: We do not recommend modifying the BLTR incision height of 3 mm. Overall, we did not find a significant difference in PTT between BLTR-3 and PLTR in terms of PTT or ECA.

Am J Trop Med Hyg. 2025 Mar 4;112(5):1091-1095.

doi: 10.4269/ajtmh.24-0732. Print 2025 May 7.

Prevalence of Ocular Chlamydia trachomatis and Active Trachoma among Children in Merhabete District, Amhara, Ethiopia

[Awraaris Hailu Bilchut^{1,2}](#), [Esmael Habtamu^{2,3,4}](#), [Yeshigeta Gelaw⁴](#), [Aemero Abateneh⁴](#), [Belay Beyene⁵](#), [Ambahun Chernet^{5,6}](#), [Tariku Wondie²](#), [Adisu Abebe⁷](#), [Huiyu Hu⁸](#), [Hadley Burroughs⁸](#), [Zhaoxia Zhao⁸](#), [Jessica Shantha^{8,9}](#), [Scott D Nash^{10,11}](#), [Benjamin F Arnold^{8,9}](#), [Thomas M Lietman^{8,9,12}](#), [Catherine E Oldenburg^{8,9,12}](#)

Abstract

There have been significant reductions in the burden of trachoma worldwide. However, some districts have experienced persistently high trachoma prevalence despite many years of intervention. Here, we report the epidemiology of trachoma in Merhabete, Ethiopia, a district in the Amhara Region that has been receiving azithromycin mass drug administration (MDA) since 2009. Data were obtained from the baseline survey of a cluster randomized trial evaluating targeted treatment strategies for trachoma elimination. An enumerative census was conducted in February 2022 to generate lists of children aged 6 months to 9 years in 80 sentinel communities participating in the trial. All children in the sentinel communities who were included in the census were examined. Field grades and conjunctival swabs were

collected to assess active trachoma (based on clinical assessment) and ocular chlamydia (based on polymerase chain reaction to identify *Chlamydia trachomatis*). A total of 5,935 children were examined in 80 communities. The prevalence of trachomatous inflammation-follicular (TF) was 46.6%, trachomatous inflammation-intense (TI) was 17.5%, and ocular chlamydia was 28.0%. The correlation between TF and ocular chlamydia (correlation coefficient 0.54, 95% CI 0.34-0.70) was similar to the correlation between TI and ocular chlamydia (correlation coefficient 0.49, 95% CI 0.30-0.65). The prevalence of ocular chlamydia remained high in this district, which had received more than 10 rounds of azithromycin MDA. Ocular chlamydia was moderately correlated with both TF and TI. Intensive interventions may be required to eliminate trachoma in settings with persistently high ocular chlamydia prevalence despite many years of intervention.

Oral health / dentistry

Front Oral Health. 2025 May 7;6:1542337.

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[The effect of the modified basic package of oral care on adolescent dental caries status in Zambia; a cluster randomized trial](#)

[Severine N Anthony^{1,2,3}](#), [Hawa S Mbawalla²](#), [Febronia K Kahabuka²](#), [Seter Siziya⁴](#), [Anne N Åstrøm³](#)

Abstract

Background: The Basic Package of Oral Care (BPOC) was developed by the World Health Organization (WHO) in order to improve oral health care worldwide, yet evidence of its effectiveness is scarce. This study primarily assessed the outcome of applying modified BPOC on dental caries prevalence and secondarily on knowledge and behaviors related to dental caries among adolescents in Copperbelt Province, Zambia.

Methods: A parallel arms cluster randomized field trial including 22 public secondary schools (11-intervention, 11-control) was carried out between January 2021 and March 2023 in Copperbelt Province, Zambia. A validated questionnaire collected data with respect to socio-demographics, knowledge, and dental caries-related behaviors. The caries assessment spectrum and treatment (CAST) instrument was used to examine the spectrum of carious lesions during the baseline, and the follow-up data collection phases. The 1st and 2nd follow up exams were conducted at 18 and 24 months after baseline, respectively. The intervention group received a six-month duration modified BPOC intervention while, the control group continued with their routine oral self-care. The analysis was based on the intention-to-treat protocol using generalized estimating equations (GEE), and the results were reported as OR (95% CI).

Results: Out of 1,794 participants at baseline, 1,690 (94.2%) and 1,597 (89.0%) were examined at the 1st and 2nd follow up intervals, respectively. Dental caries models showed significant interaction at 18 and 24 months [OR (95% CI) = 0.7 (0.6, 0.8), $p < 0.001$]. Adequate knowledge and use of fluoridated toothpaste models were the only secondary outcomes with significant interactions at 18 and 24 months follow up. Stratified analysis at 18 and 24

months showed that the intervention group had better outcomes for adequate knowledge, use of fluoridated toothpaste and dental caries.

Conclusion: The modified BPOC was effective in reducing the prevalence of dental caries, improving knowledge on dental caries, and increasing the frequency of using fluoridated toothpaste among Zambian adolescents.

Int Dent J. 2025 Apr;75(2):744-751.

doi: 10.1016/j.identj.2024.07.1214. Epub 2024 Sep 24.

Effectiveness of a School-Based Oral Health Promotion Program on Dental Caries Among Iraqi School Children: A Cluster Randomised Controlled Trial

[Hadi Ghasemi¹](#), [Hanan Fadhil Alautry²](#), [Mohammed Hossein Khoshnevisan³](#), [Mahshid Namdari⁴](#)

Abstract

Aim: To assess the effectiveness of a school-based oral health promotion program on dental caries of permanent dentition among Iraqi children.

Methods: A cluster randomised controlled trial was conducted with a parallel study group, comprising 8-10-year-old schoolchildren, 186 in each group. At the beginning of the study, subjects in the intervention group received oral health education and a single dose of 5% sodium fluoride varnish for all teeth surfaces while the control group only received oral health education. The primary outcome data in this study were caries increment and incidence after six months. The secondary outcome data was any change in oral health behaviors in the students of both groups after 3 months. The caries status was recorded according to International Caries Detection and Assessment System (ICDAS). Statistical analyses included the Chi-square test, McNemar test, independent t-test, simple and multiple logistic regression models.

Results: Study participants included 372 children with no significant difference in baseline characteristics between intervention and control groups. An increase was evident in the mean scores of DMFS, DMFT, number of children with DMFT > 0, and DS > 0 for both control and intervention groups at six-month follow-up but this increase was significantly higher for the control than intervention group ($P < .001$). Among all variables included in the multiple logistic regression model, just being in the intervention group showed a significant effect in which children in the control group had a 4.2-fold (95% CI: 2.36-7.54) greater chance for developing new caries than children in the intervention group. There was a statistically significant increase in the percentage of children with favourable levels of behaviors between baseline and 3-month follow-up ($P < .05$, $P < .001$).

Conclusion: Providing access to oral health services such as oral examination, fluoride varnish application, and oral health education to reduce dental caries and improve oral health practices seems to be effective among primary schoolchildren.

Explore (NY). 2024 Jul-Aug;20(4):535-543.

doi: 10.1016/j.explore.2023.12.003. Epub 2023 Dec 15.

Effect of prepared herbal mouthwash in maintaining the oral health of school children: A single-blind randomised control trial

[M F M Fahim¹](#), [Prof Zarnigar²](#)

Abstract

Background and aim: Oral health is a vital indicator of overall well-being, quality of life, and general health, with historical roots in Unani medicine (i.e. preventive measures, oral hygiene, and treatment). This study aims to assess the efficacy and safety of prepared herbal mouthwash in maintaining oral health among school children.

Experimental procedure: 110 schoolchildren were randomly assigned to the test group (treated with herbal mouthwash -Anacyclus pyrenthrum DC, Punica granatum (pericarp), Capparis spinosa (root bark), and Quercus infectoria Oliv (galls)) and the control group (treated with 0.2 % Chlorhexidine Mouthwash) for 30-days. The response was assessed by DMFT, Salivary pH, Oral hygiene index-simplified (OHI-S), Plaque index (Loe & Silness) (PI), Plaque index simplified (O'Leary et al., 1972) (PI-S), Gingival Index (Löe-Silness) (GI), and Bleeding on probing (BOP) on baseline and 30th day GI and PI were further assessed on 60th, 90th and 120th days to determine the sustainable effect of the intervention.

Results: After treatment, Mean OHI-S, PI, PI-S, GI and BOP significantly reduced on the 30th day from baseline ($p \leq 0.001$) in both groups. After discontinuing intervention, both groups showed significantly lower PI and GI scores on the 120th day from baseline. ($p < 0.001$).

Conclusion: This study revealed that prepared mouthwash is safe and significantly effective in maintaining oral health, and it could be used as an adjunct to mechanical oral hygiene measures.

Drug Res (Stuttg). 2024 Oct;74(8):415-420.

doi: 10.1055/a-2368-4336. Epub 2024 Aug 2.

[Antibacterial Efficacy of Hiora: An Ayurvedic Mouthwash in Children](#)

[Sonali Saha¹](#), [Kongkana Kalita²](#), [Kavita Dhinsa¹](#), [Deval Kumar Arora³](#), [Brinda Suhas Godhi⁴](#), [Vidya Gowdappa Doddawad⁵](#)

Abstract

Background: Mouthwashes, as a form of antimicrobial delivery system, rank among the safest and most effective vehicles, particularly in the case of young children. This is attributed to their ability to distribute therapeutic components across all accessible oral surfaces, including interproximal areas.

Objective: To evaluate the antibacterial efficacy of recently introduced Ayurvedic (Hiora) and triclosan-based mouthwashes among children.

Materials and methods: A total of 45 healthy children aged 10-15 years were randomly assigned to three groups: Herbal mouthwash (Hiora), triclosan-based mouthwash (Kidodent), and normal saline as the control group. Saliva samples were collected pre-rinse, 2 minutes, 30 minutes, and 60 minutes post-rinsing with the study mouthwashes. These samples were then inoculated onto Petri dishes containing blood agar culture media, followed by incubation under both aerobic and anaerobic conditions at 37°C for 48 hours. The resulting bacterial colonies of *Streptococcus spp.* and *Lactobacillus spp.* were counted (CFU/ml x 10⁵). Statistical analysis, including ANOVA, Newman Keul's Post-hoc test, and a two-tailed 't' test, was conducted to determine the significance of the results.

Results: The Ayurvedic Hiora mouthwash demonstrated the most substantial reduction in salivary bacterial colony counts of *Streptococcus spp.* and *Lactobacillus spp.* with statistically significant results ($p < 0.01$).

Conclusion: The Ayurvedic Hiora mouthwash exhibited the highest antibacterial effectiveness, followed by the triclosan-based mouthwash in decreasing order, with saline showing the least efficacy.

Evid Based Dent. 2024 Sep;25(3):164.

doi: 10.1038/s41432-024-00995-8. Epub 2024 Mar 14.

Effectiveness of nanosilver fluoride in arresting dental caries in children with one- year follow-up - a systematic review

[Pooja J Shetty¹](#), [Prasanna Mithra²](#), [Rasheed Minhaz³](#), [Prithvi Shetty⁴](#), [Ambili Nanukuttan⁵](#)

Abstract

Objective: This systematic review assesses the effectiveness of nanosilver fluoride in arresting dental caries in children, with one-year follow-up.

Methodology: Multiple databases were searched for RCTs (randomized controlled trials) according to specified inclusion-exclusion criteria. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) reporting guidelines were followed to conduct the systematic review. Nanosilver fluoride was compared against silver diamine fluoride varnish or topical fluoride varnish or placebo. The primary outcome was effectiveness in arresting dental caries. The Cochrane risk of bias tool was used to assess the risk of bias.

Data sources: Articles were searched in the following databases: PubMed, Ovid, Web of Science, Wiley Online, Proquest and Cinahl.

Data selection: The initial search yielded a total of 3660 hits. After deduplication, a total of 2507 articles were obtained. After screening the title and abstract, 11 studies were included. After the full-text screening, a total of three articles that fulfilled the eligibility criteria were included in the analyses.

Data extraction and data synthesis: All the three studies were RCTs carried out in school children, and involved application of the material in primary teeth with a follow-up of one year.

Results: In two studies, nanosilver fluoride varnish group showed significantly higher arrest of dental caries compared to placebo group. In the study comparing nanosilver fluoride and silver diamine, both the groups showed arrest of dental caries and there was no significant difference between the groups. One study showed high risk of bias for allocation concealment.

Conclusion: The included studies in the final review effectively demonstrated the benefit of using nanosilver fluoride in the arrest of dental caries.

Eur Arch Paediatr Dent. 2024 Sep 3.

doi: 10.1007/s40368-024-00939-x. Online ahead of print.

Comparative evaluation of cranberry extract and sodium fluoride as mouth rinses on S. mutans counts in children: a double-blind randomized controlled trial

[K Bansal¹](#), [A Shamoo²](#), [S Mohapatra³](#), [M Kalaivani⁴](#), [P Batra³](#), [V P Mathur²](#), [A Srivastava⁵](#), [R Chaudhry³](#)

Abstract

Background: Recently, research in the field of caries prevention is emphasizing upon identification of edible non-toxic compounds that can interfere with the formation of cariogenic biofilm.

Aim: This trial aimed to assess the effectiveness of non-dialyzable material (NDM) containing cranberry mouth rinse (C-MR) on the *Streptococcus mutans* (*S. mutans*) counts and compare with that of a sodium fluoride (F-MR) mouth rinse.

Methods: 280 children (8-12 years old) were enrolled in this double-blind single center, parallel, one-month, IRB/IEC approved non-inferiority trial. The participants fulfilling the inclusion criteria were randomly allocated into one of the two groups: C-MR and F-MR. All participants were given verbal and written instructions about at-home mouth-rinsing regimen under parental supervision for a month. Dental plaque samples were collected before and after a month of mouth-rinsing and subjected to culture techniques. *S. mutans* counts were assessed and compared in both groups. Primary outcome was the difference in the *S. mutans* counts between two interventions. Both intention-to-treat (ITT) and per-protocol analysis were carried out using two-sample t test with equal variance.

Results: The mean *S. mutans* counts (after log transformation) in C-MR group were: 14.66 (90% CI 14.4,14.9) at baseline and 12.85 (90% CI 12.5, 13.2) colony-forming units/ml (CFU/ml) at one-month post intervention ($p = 0.001$); while these counts were 14.69 (90% CI 14.5, 14.9) at baseline and 12.71 (90% CI 12.3, 13.1) at one-month intervention in F-MR groups ($p = 0.001$). ITT analysis showed an inter- group difference of 0.14 CFU/ml (90% CI - 0.32,0.59) in post-SM counts between groups ($p = 0.629$).

Conclusion: The study demonstrated that the cranberry mouth rinse was non-inferior to the fluoride mouth rinse in terms of *S. mutans* levels change. Cranberry-based mouth rinse can be used effectively to reduce the *S. mutans* counts in children.

Pain

BMJ Paediatr Open. 2024 Sep 9;8(1):e002881.

doi: 10.1136/bmjpo-2024-002881.

[Comparative efficacy of pharmacological and non-pharmacological interventions for mitigating pain and anxiety associated with venipuncture: a randomised controlled trial](#)

[Sherzad Khudeida Suleman](#)¹, [Nizer Yahya](#)², [Stefan Nilsson](#)³, [Karin Enskär](#)⁴

Abstract

Background: Venipuncture is one of the most commonly performed medical procedures in paediatric care, but it can also be one of the most painful and distressing experiences for patients. Finding effective strategies to manage pain and fear associated with venipuncture is crucial for improving the paediatric patient experience and promoting positive health outcomes. This study aimed to evaluate the efficacy of a combined approach using a topical analgesic cream (TKTX cream) and a distraction technique (Trace Image and Colouring for Kids-Book, TICK-B) in reducing pain intensity and fear levels in children undergoing venipuncture procedures.

Methods: We conducted this randomised controlled trial among 176 children aged 6-12 years undergoing venipuncture. Participants were randomly assigned to four groups: TICK-B,

TKTX cream, TICK-B+TKTX cream and a control group. Pain and fear were measured using the Wong-Baker FACES Pain Rating Scale and Children's Fear Scale. The study was carried out from 20 February 2024 to 1 June 2024 at the emergency unit of Heevi paediatric teaching hospital in the Kurdistan region of Iraq. In the intervention groups, TICK-B was applied for 2-3 min before needle insertion, and TKTX cream was applied 20 min before the venipuncture procedure. All outcome measures were evaluated 2-3 min after the completion of the venipuncture procedure.

Results: The combined TICK-B (colouring book) and TKTX cream (topical anaesthetic) intervention was the most effective in reducing both pain intensity (mean score 2.80 vs 7.24 in the control, $p<0.001$) and fear levels (mean score 0.93 vs 2.83 in the control, $p<0.001$) during and after venipuncture procedures compared with individual interventions and control.

Conclusions: The combined TICK-B distraction and TKTX cream topical anaesthetic intervention was the most effective in reducing pain intensity and fear during and after venipuncture in children, providing a practical strategy for healthcare providers to optimise needle procedure management.

Indian Pediatr. 2024 Sep 15;61(9):851-875.

Epub 2024 Aug 26.

Comparative Efficacy of Interventions for Analgesia During Heel Prick in Newborn Infants - A Systematic Review and Network Meta-Analysis

[Thangaraj Abiramalatha¹](#), [Viraraghavan Vadakkencherry Ramaswamy²](#), [Rajendra Prasad Anne³](#), [Nalina Amuji⁴](#), [Jayaraman Thinesh⁵](#), [Vardhelli Venkateshwarlu⁶](#), [Vadije Praveen Rao⁷](#), [Nasreen Banu Shaik²](#), [Abdul Kareem Pullattayil⁸](#), [Bharathi Balachander⁴](#), [Sindhu Sivanandhan⁹](#), [Jogender Kumar¹⁰](#), [Neeraj Gupta¹¹](#), [Deepak Chawla¹²](#), [Praveen Kumar¹⁰](#), [Suman Rao⁴](#)

Abstract

Context: Heel prick is one among the common painful procedures in neonates. We performed a systematic review and network meta-analysis (NMA) to compare the efficacy of different interventions for analgesia during heel prick in neonates.

Evidence acquisition: Medline, Cochrane, Embase and CINAHL databases were searched from inception until February 2023. Randomized and quasi-randomized trials that evaluated different pharmacological and non-pharmacological interventions for analgesia during heel prick for neonates were included. Data from the included trials were extracted in duplicate. A NMA with a frequentist random-effects model was used for data synthesis. Certainty of evidence (CoE) was assessed using GRADE. We adhered to the PRISMA-NMA guidelines.

Results: One-hundred-and-three trials comparing 51 different analgesic measures were included. Among the 38 interventions, for pain "during" heel prick, non-nutritive suckling (NNS) plus sucrose [SMD -3.15 (-2.62, -3.69)], followed by breastfeeding, glucose, expressed breast milk (EBM), sucrose, NNS and touch massage, had a high certainty of evidence (CoE) to reduce pain scores when compared to no intervention. Among the 23 interventions for pain at 30 seconds after heel-prick, moderate CoE was noted for facilitated tucking plus NNS plus music, glucose, NNS plus sucrose, sucrose plus swaddling, mother holding, EBM, sucrose and NNS.

Conclusions: Oral sucrose 2 minutes before combined with NNS during the procedure, was the best intervention for reducing pain during heel prick. It also effectively reduced pain

scores 30 seconds and 1 minute after the procedure. Other interventions with moderate to high CoE for a significant reduction in pain during and at 30 seconds after heel prick are oral sucrose, oral glucose, EBM and NNS. All these are low-cost and feasible interventions for most of the settings.

Adv Neonatal Care. 2025 Apr 1;25(2):103-112.

doi: 10.1097/ANC.0000000000001247. Epub 2025 Mar 26.

Evidenced-Based Recommendation for Involving Mothers to Reduce the Procedural Pain and Stress in High-Risk Neonates: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

[N Siva¹](#), [Manisha Praharaj](#), [Kshirabdhhi Tanay](#), [Sasmita Das](#), [Baby S Nayak](#), [Leslie Edward S Lewis](#), [Judith A Noronha](#)

Abstract

Background: Neonates admitted to the neonatal intensive care unit (NICU) undergo several painful procedures, causing significant stress. Maternal involvement in neonatal care significantly reduces pain and stress, thereby supporting better neurodevelopment in neonates.

Clinical question: How do maternal involvement strategies reduce neonatal pain and pain-related stress in the NICU?

Data sources: A systematic search was conducted on CENTRAL, PubMed Medline, EMBASE, CINAHL, Scopus, Web of Science, ProQuest databases, and Google Scholar for studies published between January 2007 and March 2024.

Study selection: A search across 7 databases yielded a total of 1360 studies, which were exported to Rayyan software for screening. Two independent authors conducted the screening based on the eligibility criteria.

Data extraction: Cochrane data collection forms were used to extract the data from the included studies.

Results: Out of 1360 titles identified during the initial search, a total of 27 randomized controlled trials were eligible and were included. Although there is a slight inconsistency in results, meta-analysis findings revealed that skin-to-skin care, holding, massage, feeding the baby, and maternal voice stimulation, significantly reduce procedural pain and pain-related stress, in neonates admitted to the NICU.

Implications for practice and research: Given the consistent results, this systematic review strongly supports NICU healthcare professionals in encouraging mothers to engage in neonatal care activities to reduce procedural pain and related stress. More research is needed, including navigating the mothers on the importance of their involvement in neonatal care throughout the NICU admission and after hospital discharge.

Ann Pharm Fr. 2024 Sep;82(5):898-904.

doi: 10.1016/j.pharma.2024.05.003. Epub 2024 May 15.

Rectal versus intravenous administration of acetaminophen; Clinical investigation of plasma level, analgesic, and antipyretic effects on 6-month to 6-year-old children in Zabol city, Iran

[Iraj Shahramian¹](#), [Anita Jahanpanah²](#), [Neda Rashki²](#), [Farideh Shiehzhadeh³](#), [Soudabeh Hamed-Shahraki⁴](#), [Pouya Ostadrahimi⁵](#), [Masoud Tahani⁵](#), [Mandana Moradi⁶](#)

Abstract

Objectives: Acetaminophen is the most widely antipyretic analgesic medicine used in adults and children worldwide. Rectal acetaminophen is widely used in children who resist or cannot take oral medications. This study was designed to compare the efficacy of rectal and IV acetaminophen in children with fever and mild to moderate pain.

Patients and methods: Total 60 children aged six months to 6 years, with fever and pain, that were treated with rectal or intravenous acetaminophen were selected and assigned in two groups. The IV group received 10mg/kg paracetamol as an IV infusion, and the rectal group received a 15mg/kg dose immediately after admission. Pain score was calculated using the FLACC method, and the axillary temperature was recorded at baseline and then 0.5, 1, 2, 4, and 6 hours after drug administration. Blood samples were collected at baseline and then at 30min-intervals for the first 90 minutes.

Results: The trend of changes in mean pain score at different time intervals was significantly different between the two groups. Body temperature decrease was more prominent in the IV group. The plasma concentration increased in both groups significantly with time. This increase was sharper in the IV group, just in the first 60 minutes after drug administration.

Conclusions: IV acetaminophen has more rapid onset of action, while rectal dosage form control fever and pain for longer duration. Considering its favorable effects with ease of administration and lower cost, rectal acetaminophen can be a reasonable option in selected patients with pain or fever.

Clin Otolaryngol. 2025 May;50(3):427-437.

doi: 10.1111/coa.14276. Epub 2024 Dec 27.

Local Application of Honey for Postoperative Pain Management and Associated Outcomes Following Tonsillectomy in Children: A Systematic Review and Meta-Analysis
[Seyed Javad Hosseini¹](#), [Seyed Reza Hosseini²](#), [Amirreza Jamshidbeigi³](#), [Gholam Reza Mahmoodi-Shan⁴](#), [Fatemeh Hajiabadi⁵](#), [Masoud Abdollahi⁶](#), [Mahbobeh Firooz⁷](#)

Abstract

Background: This study investigates the effect of locally applied honey on pain intensity, analgesia consumption, pain relief and nighttime awakenings in children following tonsillectomy, addressing conflicting evidence and the lack of differentiation between adult and paediatric populations in previous reviews.

Methods: A systematic search was conducted across multiple databases, including Cochrane Library, ClinicalTrials.gov, MEDLINE, Web of Science and Google Scholar. Randomised controlled trials (RCTs) comparing pain outcomes in children receiving honey in addition to standard treatments versus those receiving standard treatments alone were included. Pain intensity was measured with the VAS tool. Meta-analysis was performed using STATA version 14 software. Also, risk of bias and certainty of evidence were evaluated.

Results: Out of 537 articles, seven studies (n = 710) with RCT design met the inclusion criteria. The average duration for measuring pain intensity was 7.37 days. Pooled effect size showed a statistically significant reduction in pain intensity in the honey intervention group compared to the control group (WMD: -0.90, 95% CI [-1.32, -0.48], p < 0.001, I²: 92.5%; certainty of evidence: low). Also, the results demonstrated that honey significantly decreased the average time required for pain relief and analgesic consumption in the intervention group compared to the control group. One study was deemed low risk of bias, four studies were of intermediate quality and two studies were evaluated as high.

Conclusion: While honey shows promise in reducing post-tonsillectomy pain, cautious use is advised due to the limited quality of evidence. More robust RCTs are needed to address biases and reinforce confidence in the findings.

Poisoning and toxins

(See envenomation)

Refugee health and humanitarian settings

Lancet Child Adolesc Health. 2024 Aug;8(8):571-579.

doi: 10.1016/S2352-4642(24)00130-5.

[A community case detection tool to promote help-seeking for mental health care among children and adolescents in Ugandan refugee settlements: a stepped wedge cluster randomised trial](#)

[Myrthe van den Broek¹](#), [Sandra Agondeze²](#), [M Claire Greene³](#), [Rosco Kasujja⁴](#), [Anthony F Guevara⁵](#), [Racheal Kisakye Tukahiirwa⁶](#), [Brandon A Kohrt⁷](#), [Mark J D Jordans⁸](#)

Abstract

Background: Strategies to promote mental health care help-seeking among children are needed, especially in low-income and middle-income countries and in complex settings. The aim of this trial was to compare a vignette-based, community-level, proactive case detection tool (CCDT) against standard awareness raising for promoting mental health help-seeking among children and adolescents.

Methods: This stepped wedge cluster randomised trial was conducted in the Bidi Bidi, Kyaka II, Kyangwali, Omugo, and Rhino refugee settlements in Uganda. Community gatekeepers received a 2-day training session on using the CCDT to proactively detect children with mental health concerns and encourage children (or their caregivers) to use the mental health-care service run by Transcultural Psychosocial Organization Uganda. At baseline, organisations implemented routine detection or mental health awareness-raising activities. At cross-over to CCDT implementation, gatekeepers used the tool in their daily activities. The primary outcome was mental health-care service use by children and adolescents. Child population size estimates at the zone level were not available. Therefore, service use was calculated using total population size. We report the effect of CCDT implementation as an incidence rate ratio (IRR), which we produced from a model that accounts for calendar time, exposure time, and person-time. IRRs were estimated for the analysis of effect over time in the per-protocol and intention-to-treat populations. The trial is registered with the ISRCTN registry, number ISRCTN19056780.

Findings: 28 administrative zones were selected for trial participation by October, 2021. Between Jan 1, and Nov 8, 2022, seven clusters of four zones sequentially crossed over from routine care to CCDT implementation in 1-month intervals. The CCDT was implemented by 177 trained community gatekeepers. In 9 months, 2385 children visited a mental health-care service; of these, 1118 (47%) were girls and 1267 (53%) were boys (mean age 12·18 years [SD 4·03]). 1998 children made a first or re-entry visit to a service; of these, 937 (47%) were girls and 1061 (53%) were boys (mean age 12·08 years [SD 4·06]). Compared to standard

awareness-raising activities, CCDT implementation was associated with an increase in mental health-care service use in the first month after implementation (20·91-fold change [95% CI 12·87-33·99]). Despite a slight decline in service use over time in both the CCDT and pre-CCDT zones, CCDT zones maintained a time-average 16·89-fold increase (95% CI 8·15-34·99) in mental health service use.

Interpretation: The CCDT enabled community gatekeepers to increase mental health-care service use by children and adolescents. Vignette-based strategies rooted in the community could become a valuable contribution towards reducing the mental health-care gap among children, especially when accompanied by accessible mental health-care services.

Glob Ment Health (Camb). 2025 Jan 23;12:e12.

doi: 10.1017/gmh.2025.3. eCollection 2025.

Findings from the Tushirikiane-4-MH (supporting each other for mental health) mobile health-supported virtual reality randomized controlled trial among urban refugee youth in Kampala, Uganda

[Carmen H Logie^{1,2,3,4}](#), [Moses Okumu^{5,6}](#), [Zerihun Admassu¹](#), [Frannie MacKenzie¹](#), [Lesley Gittings^{7,8}](#), [Jean-Luc Kortenaar⁹](#), [Naimul Khan¹⁰](#), [Robert Hakiza¹¹](#), [Daniel Kibuuka Musoke¹²](#), [Aidah Nakitende¹²](#), [Brenda Katisi¹¹](#), [Peter Kyambadde^{13,14}](#), [Richard Lester¹⁵](#), [Lawrence Mbuagbaw^{16,17,18,19,20,21}](#)

Abstract

Virtual reality (VR) for mental health promotion remains understudied in low-income humanitarian settings. We examined the effectiveness of VR in reducing depression with urban refugee youth in Kampala, Uganda. This randomized controlled trial assessed VR alone (Arm 1), VR followed by Group Problem Management Plus (GPM+) (Arm 2) and a control group (Arm 3), with a peer-driven and convenience sample of refugee youth aged 16-25 in Kampala. The primary outcome, depression, was measured with the Patient Health Questionnaire-9. Secondary outcomes included: mental health literacy, mental health stigma, self-compassion, mental well-being and adaptive coping. Analyses were conducted at three time points (baseline, 8 weeks, 16 weeks) using generalized estimating equations. Among participants ($n = 335$, mean age: 20.77, standard deviation: 3.01; cisgender women: $n = 158$, cisgender men: $n = 173$, transgender women: $n = 4$), we found no depression reductions for Arms 1 or 2 at 16 weeks compared with Arm 3. At 16 weeks, mental health literacy was significantly higher for Arm 2 compared with Arm 3, and self-compassion was significantly higher in Arm 1 and Arm 2 compared with Arm 3. VR alongside GPM+ may benefit self-compassion and MHL among urban refugee youth in Kampala, but these interventions were not effective in reducing depression.

J Behav Health Serv Res. 2024 Jul;51(3):377-394.

doi: 10.1007/s11414-023-09870-3. Epub 2023 Dec 12.

Implementing a Non-Specialist Delivered Psychological Intervention for Young Adolescents in a Protracted Refugee Setting: a Qualitative Process Evaluation in Lebanon

[Rayane Ali^{1,2}](#), [Felicity L Brown^{1,3}](#), [Kerrie Stevenson^{4,5}](#), [Mark Jordans^{1,3}](#), [Karine Taha^{1,2}](#), [Mounif El Amine^{1,2}](#), [Frederik Steen¹](#), [Bassel Meksassi^{1,2}](#), [Joseph Elias^{1,2}](#), [May Aoun^{1,2}](#), [Bayard Roberts⁴](#), [Marit Sijbrandij⁶](#), [Pim Cuijpers⁶](#), [Aemal Akhtar^{7,8}](#), [Aiysha Malik⁹](#), [Aniek Woodward^{10,11}](#), [Daniela C Fuhr^{12,13}](#); [STRENGTHS Consortium](#)

Abstract

There has been an increase in the evaluation and implementation of non-specialist delivered psychological interventions to address unmet mental health needs in humanitarian emergencies. While randomized controlled trials (RCTs) provide important evidence about intervention impact, complementary qualitative process evaluations are essential to understand key implementation processes and inform future scaling up of the intervention. This study was conducted as part of an RCT of the Early Adolescents Skills for Emotions (EASE) psychological intervention for young adolescents with elevated psychological distress (predominantly with a Syrian refugee background) in Lebanon. Our aims were firstly to conduct a qualitative process evaluation to understand stakeholder experiences and perceived impact of the intervention and identify barriers and facilitators for implementation, and secondly to explore considerations for scaling up. Eleven key informant interviews and seven focus groups were conducted with 39 respondents including adolescent and caregiver participants, trainers, providers, outreach workers, and local stakeholders. Data were analyzed using inductive and deductive thematic analysis. Respondents perceived the intervention to be highly needed and reported improvements in adolescent mental health and wellbeing. Key implementation factors that have potential to influence engagement, adherence, and perceived impact included the socio-economic situation of families, mental health stigma, coordination within and between sectors (particularly for scaling up), embedding the intervention within existing service pathways, having clear quality and accountability processes including training and supervision for non-specialists, and sustainable funding. Our findings provide important context for understanding effectiveness outcomes of the RCT and highlights factors that need to be considered when implementing a mental health intervention on a larger scale in a complex crisis.

Child Abuse Negl. 2025 Apr;162(Pt 2):106335.

doi: 10.1016/j.chiabu.2023.106335. Epub 2023 Jul 1.

[Effectiveness of the caregiver support intervention on child psychosocial wellbeing among Syrian refugees in Lebanon: Mediation and secondary analysis of a Randomized Controlled Trial](#)

[M J D Jordans¹](#), [I Bakolis²](#), [M Arnous³](#), [G V Koppenol-Gonzalez⁴](#), [F Tossyeh³](#), [A Chen⁵](#), [K E Miller⁶](#)

Abstract

Background: War and violence have a serious negative impact on the wellbeing and mental health of many children. Caregivers play an important role in mitigating or exacerbating this impact.

Objective: This study evaluates the impact of the nine session Caregiver Support Intervention on improving children's wellbeing and examines putative mediators of changes in children's psychosocial wellbeing.

Participants and setting: 240 female caregivers were randomly allocated (1:1) to the CSI or a waitlist control comparison condition. The study was implemented in Lebanon, in an area characterized by high levels of poverty and a high number of the Syrian refugees.

Methods: A parallel group Randomized Controlled Trial reporting on caregiver-reported child-level wellbeing. We used a combination of the Kid- and Kiddy-KINDL (parent version) for index children ages three to 12. Putative mediators of the CSI on children's psychosocial wellbeing included harsh parenting, caregiver psychological distress, caregiver wellbeing. Measurements were conducted at baseline, post-intervention and 3-months follow-up.

Results: We demonstrated a statistically significant change in caregiver reported children's psychosocial wellbeing at post-intervention ($M_{diff} = 4.39$, 95 % CI = 1.12, 7.65, $p < 0.01$, $d = 0.28$) but not at follow-up ($M_{diff} = -0.97$, 95 % CI = -4.27, 2.32, $p > 0.05$). The proportion of the total effect of the CSI intervention on child psychosocial wellbeing mediated by caregiver distress, caregiver wellbeing and harsh parenting was 77 %.

Conclusion: The CSI holds potential for down-stream short-term effect on improving children's psychosocial wellbeing, beyond the previously reported positive caregiver outcomes. This effect was not sustained three months post intervention. The study confirms caregiver wellbeing and parenting support as dual pathways mediating child psychosocial wellbeing.

Confl Health. 2024 Sep 20;18(1):58.

doi: 10.1186/s13031-024-00616-2.

Delivering therapy over telephone in a humanitarian setting: a pilot randomized controlled trial of common elements treatment approach (CETA) with Syrian refugee children in Lebanon

[Michael Pluess^{#1,2}](#), [Fiona S McEwen^{#3,4}](#), [Claudinei Biazoli^{3,5}](#), [Nicolas Chehade⁶](#), [Tania Bosqui^{7,8}](#), [Stephanie Skavenski⁹](#), [Laura Murray⁹](#), [Roland Weierstall-Pust¹⁰](#), [Paul Bolton⁹](#), [Elie Karam^{11,12,13}](#)

Abstract

Background: In recent years, the number of forcibly displaced persons has risen worldwide, with approximately 40% being children and adolescents. Most of them are hosted in low- and middle-income countries (LMICs). Many individuals meet the criteria for mental health issues, which can also be exacerbated by a number of risk factors, including low socioeconomic status, displacement, and stressors linked to conflicts in their country or region of origin. However, the vast majority never receive treatment for their psychological problems due to multiple reasons, including a shortage of mental health professionals in LIMCs, transportation challenges in accessing clinics, and clinic hours conflicting with family commitments. In the current study we investigated whether individual psychotherapy delivered by trained lay counsellors over telephone to Syrian refugee children living in Lebanon is effective and overcomes barriers to treatment access.

Methods: After adaptation of Common Elements Treatment Approach (CETA) to remote delivery over telephone (t-CETA), preliminary effectiveness of the treatment modality was assessed with a pilot single blind randomised controlled trial including a total sample of 20 refugee children with diagnosed mental health problems. Data was analysed applying a Bayesian approach.

Results: There was a significant session-by-session decrease in self-reported mental health symptoms over the course of treatment. Independent assessments showed that t-CETA resulted in a greater reduction of symptoms than standard in-person treatment as usual. There was no difference between groups for impairment. Importantly, the majority of children allocated to t-CETA completed treatment whilst no children in the treatment as usual condition were able to do so.

Conclusion: The study provides preliminary evidence that telephone-delivered psychotherapy in a humanitarian setting, delivered by lay counsellors under supervision, works and significantly increases access to treatment compared to traditional in-person treatment. However, findings remain to be replicated in larger trials.

Sci Rep. 2025 Mar 20;15(1):9554.

doi: 10.1038/s41598-025-94426-y.

The impact of earthquake preparedness training on mothers with physically disabled children: a randomized controlled study

[Abdullah Adiyaman](#)^{1,2}, [Veysel Can](#)³, [Abdullah Sarman](#)⁴

Abstract

This study aimed to evaluate the effect of earthquake preparedness training on the psychological resilience and earthquake preparedness levels of mothers with physically disabled children. The study was conducted at a special education and rehabilitation center in a province in eastern Turkey between January and April 2024, using a pre-test/post-test control group experimental design. A total of 78 mothers participated, with 39 randomly assigned to the experimental group and 39 to the control group. The experimental group received earthquake preparedness training. Data were analyzed using SPSS version 26. It was determined that 38.5% of the mothers in the experimental group were between 32-39 years of age, equal numbers of primary (35.9%) and secondary (35.9%) school graduates, 84.6% had nuclear families and 89.7% lived in urban areas. In the control group, 38.5% of the mothers were between 25-31 years of age, 33.3% were primary school graduates, 79.5% had nuclear families and 97.4% lived in urban areas. The experimental and control groups were similar in terms of baseline characteristics. Before the training, Adult Psychological Resilience Scale (APRS) scores were comparable between groups. After the training, the experimental group showed a significant increase in psychological resilience compared to the control group ($p < .05$). Similarly, Disaster Preparedness Scale (DPS) scores were comparable before the training, but the experimental group showed a significant increase in earthquake preparedness after the training ($p < .05$). The training enhanced both psychological resilience and earthquake preparedness in mothers, increasing their knowledge and awareness about earthquakes. Developing earthquake preparedness training and materials specifically for families with physically disabled children will contribute to the safety and well-being of both families and their children.

Clin Psychol Psychother. 2024 Jul-Aug;31(4):e3039.

doi: 10.1002/cpp.3039.

Family Therapy for Kosovar Mothers Who Experienced Conflict-Related Sexual Violence and Their Children in Postwar Times: A Pilot Randomised Waitlist-Controlled Trial

[Christina Seery¹](#), [Feride Rushiti²](#), [Sebahate Pacolli Krasniqi²](#), [Selvi Izeti Çarkaxhiu²](#), [Vjosa Devaja Xhemaili²](#), [Dafina Arifaj Limani²](#), [Qëndresa Prapashtica²](#), [Vesa Turjaka²](#), [Nebahate Zekaj²](#), [Mimoza Salihu²](#), [Line Hjort^{3,4}](#), [Joanne Ryan⁵](#), [Sara Helene Kaas-Petersen⁶](#), [Shr-Jie Sharlenna Wang⁶](#)

Abstract

Women who have experienced conflict-related sexual violence report significant long-term effects, including posttraumatic stress disorder (PTSD), depression and relationship difficulties. Research has demonstrated that maternal trauma is associated with children's behavioural difficulties and challenges in family functioning, such as impaired communication and harsh parenting. This pilot study is aimed at evaluating the preliminary effectiveness of family therapy for Kosovar mothers who experienced conflict-related sexual violence in 1998-1999 and later developed PTSD and their children in improving family functioning and reducing behavioural difficulties in postwar times. Sixty-four mothers were randomised to an intervention group or a waitlist control group. Data was collected during a screening phase, at baseline before intervention initiation, after the intervention group completed family therapy and once the waitlist control group received the intervention. Generalised linear mixed models were used to analyse group differences in family functioning and children's behaviours over time. At follow-up, mothers in the intervention group reported improved family functioning. However, mothers in the waitlist control group reported significantly fewer behavioural difficulties than mothers in the intervention group before the control group had started family therapy. There was no significant interaction between group condition and time for child-rated family functioning. Overall, this pilot study suggests that family therapy could be effective in reducing the effects of intergenerational trauma related to PTSD and conflict-related sexual violence. Future research should evaluate the long-term effects of family therapy to assess if immediate effects were maintained.

Sci Rep. 2024 Aug 1;14(1):17822.

doi: 10.1038/s41598-024-68903-9.

Effectiveness of a community-led shared book reading intervention in Syrian refugee children: a randomised controlled trial

[Kristin Hadfield¹](#), [Mays Al-Hamad²](#), [Rana Dajani³](#), [Amal El Kharouf⁴](#), [Julia Michalek⁵](#), [Lina Qtaishat⁶](#), [Sophie von Stumm⁷](#), [Isabelle Mareschal⁵](#)

Abstract

Community-led, shared book reading programs may help improve refugee children's reading abilities and attitudes towards reading. We Love Reading (WLR)-a light-touch, community-led, shared book reading program-was evaluated in a pre-registered, wait-listed, randomised controlled trial (AEARCTR-0006523). 322 Syrian refugee mother-child dyads (children: 4-8-year-olds, 50.0% female) in Jordan were tested at two timepoints, 15 weeks apart. WLR did not significantly affect child literacy or child-reported child attitudes toward reading ($p > 0.05$). Mothers did report improved child attitudes toward reading from WLR ($p = 0.046$, $\eta^2 = 0.013$). The intervention did not lead to improvements in family relationships ($p > 0.05$). WLR may have promise in improving attitudes toward reading in forcibly displaced children but did not affect literacy or child-reported attitudes toward reading; these results provide

insight into what changes are needed for effective shared book reading interventions in this population.

Euro Surveill. 2024 Sep;29(39):2400159.

doi: 10.2807/1560-7917.ES.2024.29.39.2400159.

"Vaccinating your child during an emergency is more important than ever": a randomised controlled trial on message framing among Ukrainian refugees in Poland, 2023

[Maike Winters¹](#), [Agnieszka Sochoń-Latuszek²](#), [Anastasiia Nurzhynska²](#), [Kseniia Yoruk²](#), [Katarzyna Kukuła²](#), [Mutribjon Bahruddinov²](#), [Aleksandra Kusek²](#), [Dorota Kleszczewska³](#), [Anna Dzielska⁴](#), [Tomasz Maciejewski⁵](#), [Joanna Mazur⁶](#), [Hannah Melchinger⁷](#), [John Kinsman¹](#), [Piotr Kramarz¹](#), [Sarah Christie⁸](#), [Saad B Omer⁷](#)

Abstract

Background: Since February 2022, the start of the full-scale war in Ukraine, millions of women and children have fled the country. Vaccination of refugee children is important to protect this vulnerable population from disease.

Aim: We investigate the determinants of vaccination intention in refugee mothers from Ukraine residing in Poland and test the effect of three message frames.

Methods: Participants were randomised into either a control group or one of three intervention groups encouraging vaccination using a specific frame: (i) trust in the Polish health system, (ii) ease of access to vaccination or (iii) risk aversion. Primary outcomes were intention to vaccinate a child in Poland and clicking on a vaccination scheduling link.

Results: The study was completed by 1,910 Ukrainian refugee mothers. Compared with the control group, the risk aversion message significantly increased vaccination intention (adjusted odds ratio (AOR): 2.35, 95% confidence interval (CI): 1.25-4.42) and clicking on the vaccine scheduling link (AOR: 1.53, 95% CI: 1.12-2.09). Messages around trust and ease of access did not have an effect. Important determinants of vaccination intention were perceived importance of vaccination (AOR: 1.12 95% CI: 1.01-1.25) and trusting vaccination information official health institutes (AOR: 1.40 95% CI: 1.06-1.83) and social media (AOR: 2.09 95% CI: 1.33-3.27).

Discussion: Using a risk aversion frame highlighting the vulnerability to infection that refugees face resulted in increased vaccination intention and clicks on a vaccination scheduler. Health workers who interact with Ukrainian refugees could use this frame in their vaccination communication.

Trials. 2024 Sep 19;25(1):620.

doi: 10.1186/s13063-024-08459-1.

Implementing a pragmatic randomised controlled trial in a humanitarian setting: lessons learned from the TISA trial

[D S N'Diaye¹](#), [S Frison²](#), [M Ba³](#), [M L Lê²](#), [A E Cabo³](#), [F Siroma³](#), [A Devort³](#), [C MacLeod⁴](#), [J Lapègue²](#), [M Seye⁵](#), [A B Traoré³](#), [T Cerveau³](#), [D Léger³](#), [K Gallandat⁴](#), [Y Gnokane³](#), [A Vargas Brizuela⁶](#), [S Stern²](#), [L Braun⁴](#), [O Cumming⁴](#)

Abstract

Introduction: High-quality evidence is crucial for guiding effective humanitarian responses, yet conducting rigorous research, particularly randomised controlled trials, in humanitarian crises remains challenging. The TISA ("traitement intégré de la sous-nutrition aiguë") trial aimed to evaluate the impact of a Water, Sanitation and Hygiene (WASH) intervention on the standard national treatment of uncomplicated Severe Acute Malnutrition (SAM) in children aged 6-59 months. Implemented in two northern Senegalese regions from December 22, 2021, to February 20, 2023, the trial faced numerous challenges, which this paper explores along with the lessons learned.

Methods: The study utilised trial documentation, including field reports, meeting minutes, training plans, operational monitoring data and funding proposals, to retrace the trial timeline, identify challenges and outline implemented solutions. Contributions from all TISA key staff-current and former, field-based and headquarters-were essential for collecting and interpreting information. Challenges were categorised as internal (within the TISA consortium) or external (broader contextual issues).

Results: The TISA trial, executed by a consortium of academic, operational, and community stakeholders, enrolled over 2000 children with uncomplicated SAM across 86 treatment posts in a 28,000 km² area. The control group received standard outpatient SAM care, while the intervention group also received a WASH kit and hygiene promotion. Initially planned to start in April 2019 for 12 months, the trial faced a 30-month delay and was extended to 27 months due to challenges like the COVID-19 pandemic, national strikes, health system integration issues and weather-related disruptions. Internal challenges included logistics, staffing, data management, funding and aligning diverse stakeholder priorities.

Discussion and conclusion: Despite these obstacles, the trial concluded successfully, underscoring the importance of tailored monitoring, open communication, transparency and community involvement. Producing high-quality evidence in humanitarian contexts demands extensive preparation and strong coordination among local and international researchers, practitioners, communities, decision-makers and funders from the study's inception.

Research

Front Epidemiol. 2024 Aug 15;4:1417419.

doi: 10.3389/fepid.2024.1417419. eCollection 2024.

[A landscape analysis of clinical trials and infant clinical trials in Kenya, Ethiopia, and Nigeria](#)

[Patrick Amboka](#)¹, [Daniel Kurui](#)¹, [Marylene Wamukoya](#)¹, [Julius Kirimi Sindi](#)¹, [Marta Vicente-Crespo](#)^{1,2}

Abstract

Introduction: Global inequality in clinical research capacity and service delivery can be indicated simply by the proportion of clinical trials that a country or region has registered in clinical trial registry databases. The proportion of clinical trials registered in Africa is very low at 0.02%, even though the region accounts for approximately 15% of the world's population. Despite the economic challenges in most African countries, they have shown potential for growth and change in recent years.

Methods: We conducted desk reviews on the interventional clinical trials done in Kenya, Ethiopia, and Nigeria between 2015 to May 2023. The search was done in clinical trials repositories, and journal repositories. The search focused on intervention clinical trials. Data was extracted by screening through the publications and clinical trial platforms. The data extracted from the publications included the type of clinical trial, clinical trial phase, diseases, etc. The data extracted from the reports included: challenges in conducting clinical trials, capacity-building efforts, and the impact of the clinical trial.

Results: The number of clinical trial studies identified in Kenya was 113 (28 were on infant clinical trials). The study identified 97 clinical trials in Nigeria, of which 11 studies were on infant clinical trials. In Ethiopia, there were 28 clinical trials and only five were on infant clinical trials. The landscape review also expanded to capacity and gaps in clinical trials in the three countries. The largest proportion of clinical trials carried out in Kenya was on injury, occupational disease, and poisoning, 30.5% ($n = 18$) and the smallest proportion was on kidney disease, neonatal disease, obstetrics, and gynecology. Most Infant clinical trials were carried out in the area of infections and infestations 33.3% ($n = 7$). Most of the challenges faced by clinical trials in the three countries include a lack of infrastructure, a lack of human resources, and a lack of financial resources.

Implications: There is a need to map clinical trials done by African researchers based in Africa to exclude the trials done by non-African researchers based in Africa. Opportunities for clinical trials should be supported and challenges addressed.

Quality of care

Schistosomiasis

Lancet Glob Health. 2024 Nov;12(11):e1826-e1837.

doi: 10.1016/S2214-109X(24)00280-8.

The effect of intensive praziquantel administration on vaccine-specific responses among schoolchildren in Ugandan schistosomiasis-endemic islands (POPVAC A): an open-label, randomised controlled trial

[Gyaviira Nkurunungi¹](#), [Jacent Nassuuna²](#), [Agnes Natukunda³](#), [Ludoviko Zirimenya⁴](#), [Bridgious Walusimbi²](#), [Christopher Zziwa²](#), [Caroline Ninsiima²](#), [Joyce Kabagenyi²](#), [Prossy N Kabuubi²](#), [Govert J van Dam⁵](#), [Paul L A M Corstjens⁶](#), [John Kayiwa⁷](#), [Moses Kizza²](#), [Alex Mutebe²](#), [Esther Nakazibwe²](#), [Florence A Akello²](#), [Moses Sewankambo²](#), [Samuel Kiwanuka²](#), [Stephen Cose⁴](#), [Anne Wajja⁸](#), [Pontiano Kaleebu²](#), [Emily L Webb⁹](#), [Alison M Elliott⁴](#); [POPVAC trial team](#)

Abstract

Background: Vaccine responses differ between populations and are often impaired in rural and low-income settings. The reasons for this are not fully understood, but observational data suggest that the immunomodulating effects of parasitic helminths might contribute. We hypothesised that *Schistosoma mansoni* infection suppresses responses to unrelated vaccines, and that suppression could be reversed—at least in part—by intensive praziquantel administration.

Methods: We conducted an open-label, randomised controlled trial of intensive versus standard intervention against *S mansoni* among schoolchildren aged 9-17 years from eight

primary schools in Koome islands, Uganda. Children were randomly allocated to either an intensive group or a standard group with a computer-generated 1:1 randomisation using permuted blocks sizes 4, 6, 8, and 10. Participants in the intensive group received three praziquantel doses (approximately 40 mg/kg) 2 weeks apart before first vaccination at week 0, and every 3 months thereafter. Participants in the standard group were given one dose of approximately 40 mg/kg praziquantel after the week 8 primary endpoint. Participants in both groups received the BCG vaccine (Serum Institute of India, Pune, India) at week 0; the yellow fever (Sanofi Pasteur, Lyon, France), oral typhoid (PaxVax, London, UK), and first human papillomavirus (HPV) vaccination (Merck, Rahway, NJ, USA) at week 4; and the HPV booster and tetanus-diphtheria vaccine (Serum Institute of India) at week 28. The primary outcome was vaccine response at week 8 (except for tetanus and diphtheria, which was assessed at week 52). The primary analysis population was participants who were infected with *S mansoni* at baseline, determined retrospectively using either plasma circulating anodic antigen (CAA) or stool PCR. The safety population comprised all randomly allocated participants. The trial was registered at the ISRCTN Registry (ISRCTN60517191) and is complete.

Findings: Between July 9 and Aug 14, 2019, we enrolled 478 participants, with 239 children per group. 276 (58%) participants were male and 202 (42%) participants were female. Among participants who were positive for *S mansoni* at baseline (171 [72%] in the intensive group and 164 [69%] in the standard group) intensive praziquantel administration significantly reduced pre-vaccination infection intensity (to median 30 CAA pg/mL [IQR 7-223] vs 1317 [243-8562], $p<0.001$) compared with standard treatment. Intensive praziquantel administration also reduced week 8 HPV-16-specific IgG response (geometric mean ratio 0.71 [95% CI 0.54-0.94], $p=0.017$), but had no effect on other primary outcomes. Among all participants (regardless of *S mansoni* status at baseline) intensive praziquantel administration significantly improved week 8 BCG-specific IFN γ ELISpot response (1.20 [1.01-1.43], $p=0.038$). Recognised adverse effects of praziquantel were reported more frequently in the intensive group. There were no recorded serious adverse events in either group.

Interpretation: We show evidence suggesting that praziquantel administration improves the BCG-specific cellular response, but not humoral responses to other vaccines. Despite observational evidence that helminths impair vaccine response, these results show minimal immediate benefits of reducing helminth burden. The effect of longer-term helminth control should be investigated.

Antimicrob Agents Chemother. 2025 Feb 13;69(2):e0073924.

doi: 10.1128/aac.00739-24. Epub 2024 Dec 19.

[Efficacy and safety of praziquantel plus artemisinin-based combinations versus praziquantel in the treatment of Kenyan children with *Schistosoma mansoni* infection: open-label, randomized, head-to-head, non-inferiority trial](#)

[Charles O Obonyo¹](#), [Vincent O Were¹](#), [Peter Wamae¹](#), [Erick M O Muok¹](#)

Abstract

Praziquantel alone is insufficient for the control of schistosomiasis due to poor efficacy against juvenile worms and increasing concerns about the risk of drug resistance. We compared the efficacy and safety of praziquantel combined with four different artemisinin-based combinations to praziquantel alone in treating *Schistosoma mansoni* infection in

Kenyan children. In this randomized, open-label, five-arm, head-to-head, non-inferiority trial, children (aged 9-15 years) with *S. mansoni* infection according to duplicate Kato Katz thick smears from a stool sample in the Mwea irrigation scheme of central Kenya, were enrolled. Participants were randomly assigned (1:1:1:1:1) via a computer-generated block randomization procedure to receive a single oral dose of praziquantel (PZQ) (40 mg/kg/day) alone or in combination with a 3-day course (4 mg/kg of artesunate) of artesunate plus sulfalene-pyrimethamine (As + SP), artesunate plus amodiaquine (As + AQ), artesunate plus mefloquine (As + MQ) or dihydroartemisinin-piperaquine (DHAP). Laboratory technicians were masked to treatment allocation, but participants, clinicians, and study nurses were not. The primary outcomes were the cure rate and frequency of adverse events, which were assessed 6 weeks after treatment in the available case population using a per-protocol analysis. The non-inferiority margin was set at -10% for the risk difference in cure rates between combination therapy and PZQ alone. Between 12 September 2018 and 11 January 2019, 540 participants were assigned to receive PZQ alone ($n = 108$), PZQ plus As + SP ($n = 108$), PZQ plus As + AQ ($n = 108$), PZQ plus As + MQ ($n = 108$), or PZQ plus DHAP ($n = 108$). Primary outcome data were available for 523 (96.9%) participants. The cure rate was 82.5% (85/103) in PZQ alone, 81.7% (85/104) in PZQ plus As + SP, 76.2% (80/105) in PZQ plus As + AQ, 88.7% (94/106) in PZQ plus As + MQ, and 85.7% (90/105) in PZQ plus DHAP arm. Non-inferiority was declared for PZQ plus As + MQ (difference 6.2 [95% confidence interval: -3.3 to 15.6]) and PZQ plus DHAP (3.2 [-6.7 to 13.1]) but not for PZQ plus As + SP (-0.8 [-11.2 to 9.6]) or PZQ plus As + AQ (-6.3 [-17.3 to 4.6]). Adverse events were reported by 26% (138/540) of participants, including abdominal pain, headache, and vomiting. There were no serious adverse events. Alternatives to praziquantel should include praziquantel plus artesunate-mefloquine or praziquantel plus dihydroartemisinin-piperaquine. However, further multicentre trials are needed in different epidemiological settings and population groups to confirm these findings

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Safety and efficacy of praziquantel 40 mg/kg versus 80 mg/kg in preschool-aged children with intestinal schistosomiasis in Uganda: a 2 × 2 factorial, double-blind, placebo-controlled, phase 2 randomised trial

[Amaya L Bustinduy¹](#), [Andrew Edielu²](#), [Gloria K Ayebazibwe³](#), [Racheal Nakyesige³](#), [Victor Anguajibi⁴](#), [Simon Mpooya⁴](#), [Jacent Nassuna³](#), [Moses Adriko⁴](#), [Alison Elliott²](#), [Govert van Dam⁵](#), [Paul Corstjens⁶](#), [Sophie Pach⁷](#), [Hannah Wu⁸](#), [Susannah Colt⁸](#), [Patrice A Mawa⁹](#), [Edridah Muheki⁴](#), [Narcis B Kabatereine⁴](#), [Emily L Webb¹⁰](#), [Jennifer F Friedman¹¹](#)

Abstract

Background: Optimal dosing of praziquantel for schistosomiasis for children younger than 5 years is not established and some studies suggest this age group might need a higher dosing per kilogram. Our aim was to assess the safety and efficacy of a split dose of 80 mg/kg of praziquantel tablets given in a single day to preschool children versus the recommended single dose of 40 mg/kg for treatment of *Schistosoma mansoni*.

Methods: We did a 2 × 2 factorial design, placebo-controlled, phase 2 randomised trial in Uganda. Children aged 12-47 months infected with *Schistosoma mansoni* were randomly assigned in a 1:1:1:1 ratio to receive crushed praziquantel tablets at single standard (40 mg/kg) versus double standard dosing (80 mg/kg delivered as two 40 mg/kg doses 3 hours

apart) and same dose or placebo at 6 months. Coprimary outcomes were parasitological cure and egg reduction rate at 4 weeks. Secondary outcomes included antigenic cure at 4 weeks, adverse events and clinical toxicity 12 h after treatment, and key morbidity markers at 6 months and 12 months. This trial is registered with ClinicalTrials.gov ([NCT03640377](https://clinicaltrials.gov/ct2/show/study/NCT03640377)).

Findings: Between Feb 18 and Dec 14, 2021, 354 children were randomly assigned to either praziquantel 40 mg/kg at baseline and placebo at 6 months (n=88); 40 mg/kg at baseline and 40 mg/kg at 6 months (n=86); 80 mg/kg at baseline and placebo at 6 months (n=89); or 80 mg/kg at baseline and 80 mg/kg at 6 months (n=91). 181 (51%) of 354 participants were boys. The median age was 36 months (28-42). Cure rate at 4 weeks was 67% in the 40 mg/kg group and 90% in the 80 mg/kg group (absolute difference 23% [95% CI 14-31]; $p<0.001$); for egg reduction rate the difference was 2% (95% CI 1-3; $p<0.001$) based on geometric mean and 22% (5-59; $p<0.001$) based on arithmetic mean. There were no differences in adverse event rates between the trial groups. At 12 months, biannual versus annual treatment reduced prevalence of faecal occult blood and 80 mg/kg dose reduced prevalence of faecal calprotectin. No severe adverse events related to the study drug were reported.

Interpretation: Two 40 mg/kg doses given 3 hours apart are safe, well tolerated, and more effective in achieving parasitic cure than the current proposed single 40 mg/kg dose. Until a paediatric formulation of praziquantel is available in endemic areas, the use of crushed tablets with this dosing strategy can be recommended for young children living in *S. mansoni* endemic areas. In addition, twice-a-year treatment compared with once-a-year treatment affected some intestinal morbidity markers.

School health and education

(See Adolescent health, Schistosomiasis)

J Affect Disord. 2025 Jan 1:368:695-703.

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[Effectiveness of a universal resilience-focused intervention for children in the school setting: A randomized controlled trial](#)

[Wenjuan Huang](#)¹, [Peipei Wu](#)¹, [Jing Li](#)¹, [Yi Zhou](#)¹, [Zhou Xiong](#)¹, [Puyu Su](#)², [Yuhui Wan](#)², [Fangbiao Tao](#)³, [Ying Sun](#)⁴

Abstract

Background: Psychological resilience can be augmented through the acquisition of specific cognitive or emotional regulation skills, enabling children to adapt to or recover from stressful events, disadvantages, or adversities. We aimed to evaluate the efficacy of a Tianchang Resilience-focused intervention program (TRT¹ program) on resilience and mental health conditions of Chinese children.

Methods: This study was a two-arm cluster-randomized controlled trial, performed in Tianchang, a county in China. Students from 20 classes in a local primary school (aged 8.7-11.2 years) were randomly allocated to receive a resilience-focused intervention or waitlist group. The intervention comprised weekly 40-min sessions for 14 weeks and co-led by lay counsellors. Measures of emotional symptoms, behavioral difficulties, and resilience were collected at pre-, post-intervention, 6-months, and 12-months follow-up.

Results: Between June 16, 2022, and September 4, 2022, 775 eligible students were recruited (mean age 9.93 years; 420 [54.2 %] boys). Relative to the waitlist group (N = 391), the intervention group (N = 384) reported a significant reduction in depressive and anxiety symptoms at post-intervention (all $p < 0.001$), 6-months ($p = 0.007$; $p = 0.002$) and 12-months follow-up ($p = 0.018$; $p = 0.018$), respectively. The intervention group effects were also observed on resilience at post-intervention follow-up ($p = 0.006$), and remained stable over 6-months ($p < 0.001$) and 12-months follow-up ($p = 0.022$).

Conclusions: This study demonstrated that the TRT program, a universal resilience-focused intervention for children in the school setting, showed long-term effectiveness in improving resilience and mental health conditions. This minimally trained laypersons-delivered intervention might enhance the program's generalizability to other communities.

Discov Ment Health. 2025 Jun 18;5(1):90.

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Comparative child mental health and academic outcomes after primary school teachers deliver task-shifted mental health care in India

[Priscilla Giri¹](#), [Molly M Lamb^{2,3}](#), [Venessa C Fuentes⁴](#), [Arpana Thapa¹](#), [Surekha Bhattarai¹](#), [Choden Dukpa¹](#), [Catherine C Shrestha¹](#), [Setareh Ekhteraei⁵](#), [Juliana L Vanderburg⁶](#), [Breanna Windsor²](#), [Abhishek K Rauniyar²](#), [Karen Hampanda^{3,7}](#), [Bradley N Gaynes^{4,8}](#), [Rinzi Lama⁹](#), [Michael Matergia^{10,11}](#), [Christina M Cruz^{12,13}](#)

Abstract

Teachers are promising lay counselors but have limited time for traditional therapy. To viably leverage teachers to deliver care, we developed Teachers Leading the Frontlines (Tealeaf), where teachers deliver a novel therapy, "education as mental health therapy" (Ed-MH); measures are an extension of classroom management, not an added task. We investigated whether Tealeaf teachers improved child mental health symptoms and academic achievement versus teachers delivering an enhanced usual care (EUC) comparator, Responding to Students' Emotions through Education (RE-SEED), a truncated version of Tealeaf. We conducted a pragmatic, mixed methods, post hoc analysis using data from 2019 of an open trial of Tealeaf running in parallel with the all-EUC first step of a stepped wedge cluster randomized controlled trial (SW-CRCT). We compared postintervention child mental health symptom scores and academic achievement. Semi-structured interviews and focus groups were analyzed using inductive content analyses. Tealeaf teachers observed lower mental health symptom severity ($n = 23$ children in Tealeaf, $n = 104$ in RE-SEED; Cohen's $d = 0.70$; $p = 0.024$). Students in Tealeaf ($n = 26$, $n = 183$ in RE-SEED) performed better in math ($d = 0.63$; $p = 0.0006$) and reading ($d = 0.83$; $p = 0.001$). Caregivers of children in RE-SEED ($n = 177$), the comparator condition, reported lower severity of overall mental health difficulties and internalizing difficulties for their children compared to caregivers' reports of their children in Tealeaf ($n = 25$). Tealeaf teachers displayed a greater depth in mental health understanding in mixed methods findings. Evidence supports teachers' potential to improve child mental health and academics in school while underscoring the need for additional home-based supports.

J Sch Psychol. 2024 Oct;106:101349.

doi: 10.1016/j.jsp.2024.101349. Epub 2024 Jul 4.

The effectiveness of a contextually grounded social emotional learning program in Haiti: A pilot cluster randomized control trial

[Laura Miller-Graff¹](#), [Catherine Maloney²](#), [Lucka Jouthe Beauvil³](#), [Myrlande Octave Feuille³](#)

Abstract

Social emotional learning (SEL) has a robust evidence basis, but there remains a large gap in literature on the effectiveness of programs across educational settings in low- and middle-income countries and conflict-affected settings. The present study was a pilot trial aimed at evaluating the effects of a classroom based SEL program on dimensions of classroom climate and individual student social emotional skills. In the present study, fourth through sixth grade classrooms in 10 schools (N = 39 teachers, 75.68% female; N = 1048 students, 62.3% female) were randomly allocated to the SEL or wait-list control condition. The SEL program was associated with significant improvements in teacher reports of student achievement orientation ($d_r = 1.21$) and responsible decision-making ($d_r = 0.49$). There were no significant differences between conditions on peer sensitivity, teacher-pupil interactions, student interpersonal skills, or overall social emotional skills. Findings suggest that this community-developed, contextually relevant SEL curriculum may hold promise even in the context of ongoing adversity, including the COVID-19 pandemic and heightened insecurity due to political violence.

Interact J Med Res. 2025 Jun 25;14:e54189.

doi: 10.2196/54189.

Impact of Fortified Malt-Based Food on Immunity Outcomes in School Children in India: Cluster Randomized Controlled Trial

[Anuradha Khadilkar¹](#), [Vinay Rawat²](#), [Jaladhi Bhatt³](#), [Devyani Chaturvedi⁴](#), [Vivek Garg²](#), [Pankaj Verma²](#)

Abstract

Background: Nutritional inadequacy and consequent diminished immunity among school-age children is a public health problem in India. Nutrition interventional studies using a cluster randomized controlled trial (RCT) design can avoid ethical issues inherent in double-blind individual RCTs in children involving daily administration of an empty-calorie placebo.

Objective: We tested the hypothesis that daily administration of a fortified malt-based food (FMBF), a multivitamin supplement, would improve immunity outcomes against common infectious diseases, nutritional status, and gut health in Indian school-age children by using a cluster RCT design. This report presents the study design attributes and the baseline characteristics of the study population.

Methods: This was an open-label, 2-arm, parallel-group, matched-pair cluster RCT, stratified by gender, in children aged ≥ 7 to ≤ 10 years old with height-for-age z scores (HAZ) of ≥ -3 to ≤ -1 and good general health. Four schools located in Pune city in India participated in the study. Each school was deemed as a cluster and was randomized to the test group (FMBF and dietary counseling) or control group (dietary counseling alone). A total of 924 participants from the 4 randomized schools were enrolled in the study.

Results: Observed mean age (SD) was 8.0 (SD 0.81; range: 7-10) years. There was no significant difference in mean age ($P=.06$), gender ($P=.55$), race ($P>.99$), HAZ category

($P=.051$), HAZ ($P=.17$), and BMI ($P=.03$). A very large proportion of children had micronutrient inadequacies in terms of vitamin D (97.5%), folate (79.2%), zinc (66%), and vitamin A (34.3%) at baseline. The study design meant that administration of the study intervention at a cluster level was easy. Mean compliance with the test product was 99.99% and retention in the study was 98%.

Conclusions: The findings highlight the extent of nutritional inadequacies in Indian school-age children, reaffirming the need for nutritional strategies to optimize the nutritional status among these children. A cluster RCT design can be effectively used in nutritional intervention trials with children by maintaining high compliance and retention.

Cureus. 2024 Jul 6;16(7):e63950.

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The Effect of Two Health Education Packages on Nutritional Knowledge, Practices, and Physical Activity Levels Among School-Going Adolescents in Rishikesh: A Cluster Randomized Trial

[Rupsha Mallick¹](#), [Ranjeeta Kumari¹](#), [Yogesh Bahurupi¹](#), [Anjali M¹](#), [Nisarg Aravindan²](#), [Meghna Singh¹](#)

Abstract

Introduction Adolescence is a critical period known for presenting specific challenges in disease treatment and health promotion. Studies have highlighted that increased nutritional awareness is associated with healthier eating habits, while regular physical activity aids in controlling and preventing non-communicable diseases. Equipping adolescents with health education in schools prepares them to adopt and maintain healthy lifestyles throughout their lives. To assess and compare the efficacy of health education packages targeting nutrition knowledge, practices, and physical activity levels, a cluster-randomized trial was conducted among school-going adolescents. Methodology Two distinct health education packages were developed for the two intervention groups. In group 1, a health talk supported by a flip chart was delivered, followed by pamphlet distribution. In contrast, in group 2, only information pamphlets were distributed. The study was conducted in government schools in Rishikesh, with four schools selected. Two schools were randomly allocated to each intervention arm. In each school, a questionnaire was administered to assess the students' nutrition knowledge, practices and physical activity levels. This was followed by the intervention, and the students were reassessed for the same parameters after two weeks. Result The pre-intervention and post-intervention comparisons within the same group- the mean scores for nutrition knowledge, food practice, sleep duration, and recreational screen time were comparable in the intervention group 1 ($p>0.05$). There was a decrease in the mean physical activity score and screen time for studies in intervention group 1, and these differences were statistically significant ($p<0.05$). The mean scores for nutrition knowledge, physical activity, sleep duration, and screen time for studies were comparable in the intervention group 2 ($p>0.05$). There was an increase in the mean food practice score and a decrease in recreational screen time in intervention group 2, and these differences were statistically significant ($p<0.05$). On comparing the groups with each other, it was found that Group 2 exhibited a significantly higher mean food practice score compared to group 1 post-intervention. While there was a statistically significant decrease in

the mean physical activity score in intervention group 1, this group still had higher physical activity levels than group 2. Post-intervention, group 2 exhibited a higher screen time for studies compared to group 1. Both groups had comparable sleep durations at baseline and post-intervention, with intervention group 1's mean sleep duration falling within the recommended range set by the American Academy of Sleep Medicine. Regression analysis provided valuable insights into the relationship between baseline values of various variables and their post-intervention values, aiding in understanding the impact of the health education packages. Conclusion The findings emphasize the significance of incorporating nutrition and physical activity education into the curriculum of students.

Glob Health Sci Pract. 2024 Dec 20;12(6):e2300483.

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Process Evaluation of Teaching Critical Thinking About Health Using the Informed Health Choices Intervention in Rwanda: A Mixed Methods Study

[Michael Mugisha^{1,2}](#), [Andrew D Oxman³](#), [Laetitia Nyirazinyoye²](#), [Anne Marie Uwitonze²](#), [Clarisse Marie Claudine Simbi²](#), [Faith Chesire^{4,5}](#), [Ronald Ssenyonga^{4,6}](#), [Matt Oxman^{3,7}](#), [Allen Nsangi⁶](#), [Daniel Semakula⁶](#), [Margaret Kaseje⁵](#), [Nelson K Sewankambo⁶](#), [Sarah Rosenbaum³](#), [Simon Lewin^{3,8,9}](#)

Abstract

Introduction: We evaluated the Informed Health Choices secondary school intervention in a cluster randomized trial in Rwanda. The intervention was effective in helping students to think critically about health. In parallel to the trial, we conducted a process evaluation to assess factors affecting the implementation, impacts, and scale-up of the intervention.

Methods: We used a mixed methods approach that included quantitative and qualitative methods. We collected quantitative data from teachers to evaluate the teacher training and each lesson. We conducted focus group discussions with students (n=10) and their parents/guardians (n=5). We conducted lesson observations (n=16) and key informant interviews with teachers (n=10) and school administrators (n=10) from intervention schools and policymakers (n=2). We analyzed the quantitative data using descriptive statistics. We used framework analysis and thematic content analysis to analyze the qualitative data.

Results: Teachers noted that the teacher training supported their delivery of the intervention and that they made only small adaptations to fit student, teacher, or contextual needs. Students reported obtaining important skills, including recognizing health claims, understanding the need for research, and "thinking twice" before deciding. Participants saw the design of the intervention, students' and teachers' motivation, and school and home support as key facilitators for the implementation and impact of the intervention. Implementation barriers identified included the content of the lessons not being included in national examinations, competing priorities, and time constraints. Participants identified several factors that could facilitate intervention scale-up, including the need for the skills taught in the lessons and compatibility of the intervention with the national curriculum.

Conclusion: We found that it was feasible to implement the intervention in Rwandan secondary schools and that students benefited from the intervention. Scaling up the intervention will likely require addressing the barriers identified in this study.

Glob Health Sci Pract. 2024 Dec 20;12(6):e2300485.

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Process Evaluation of Teaching Critical Thinking About Health Using the Informed Health Choices Intervention in Kenya: A Mixed Methods Study

[Faith Chesire^{1,2}](#), [Andrew D Oxman³](#), [Margaret Kaseje⁴](#), [Violet Gisore⁴](#), [Michael Mugisha^{2,5}](#), [Ronald Ssenyonga^{2,6}](#), [Matt Oxman^{3,7}](#), [Allen Nsangi⁶](#), [Daniel Semakula⁶](#), [Laetitia Nyirazinyoye⁵](#), [Nelson K Sewankambo⁶](#), [Heather Munthe-Kaas³](#), [Christine Holst³](#), [Sarah Rosenbaum³](#), [Simon Lewin^{3,8,9}](#)

Abstract

Introduction: We evaluated the Informed Health Choices secondary school intervention to help students in Kenya think critically about health choices. We conducted this process evaluation to explore if the intervention was implemented as planned, identify factors that facilitated or hindered implementation, potential benefits of the intervention, and how to scale up the intervention beyond the trial.

Methods: This was a mixed methods process evaluation nested in a cluster-randomized trial of the Informed Health Choices intervention. We analyzed quantitative data from teacher training evaluation forms completed by 39 teachers, 10 lesson evaluation forms completed by 40 teachers allocated to the intervention, and 72 structured classroom observation forms. We conducted a framework analysis of qualitative data from 14 group interviews (with 96 students, 23 teachers, and 18 parents) and 22 individual interviews (with 8 teachers, 5 school principals, 6 curriculum developers, and 3 policymakers). We assessed confidence in our findings from the qualitative analysis using a modified version of Confidence in the Evidence from Reviews of Qualitative Research.

Results: Lesson objectives were achieved with minimal adaptations. Factors that might have facilitated the implementation of the intervention include teacher training; perceived value of the intervention by students, teachers, and policymakers; and support from school administration. Time constraints, teachers' heavy workloads, and the lessons not being included in the curriculum or national examination are factors that might have impeded implementation. Both students and teachers demonstrated the ability to apply key concepts that were taught to health choices and other choices. However, they experienced difficulties with 2 of the lessons.

Conclusion: Scale-up of this intervention in Kenyan schools is feasible but may depend on adjusting the time allocated to teaching the lessons, modifying the 2 lessons that teachers and students found difficult, and including the lesson objectives and assessment in the national curriculum.

J Adolesc Health. 2024 Jul;75(1):115-126.

doi: 10.1016/j.jadohealth.2024.02.032. Epub 2024 Apr 8.

Meals, Education, and Gardens for In-School Adolescents: A Cluster Randomized Trial of an Adolescent Nutrition Intervention Package in Tanzania

[Dongqing Wang¹](#), [Leonard K Katalambula²](#), [Andrea R Modest³](#), [Abbas Ismail⁴](#), [Augustine Malero⁵](#), [Dayana Bray⁶](#), [Haley Cinq-Mars⁶](#), [Amani Tinkasimile³](#), [Mary Mwanyika Sando³](#), [Said Vuai⁷](#), [Wafaie W Fawzi⁸](#)

Abstract

Purpose: This study aimed to implement and evaluate integrated, school-based nutrition intervention packages for adolescents in Dodoma, Tanzania.

Methods: A cluster randomized controlled trial was conducted among six secondary schools in Dodoma, Tanzania. Two schools received the full-intervention package of school meals, nutrition education, school gardens, and community workshops. Two schools received the partial-intervention package without the school meals component. Two schools served as the controls and did not receive any intervention. The intervention was implemented over one academic year. The analytical sample included 534 adolescents aged 14 to 17 at baseline and 286 parents. Outcomes included nutrition knowledge, food preferences, diet quality, food insecurity, physical activity, growth, and anemia. Linear models were used to estimate mean differences, and logistic regression models were used to estimate odds ratios (ORs).

Results: Compared to the control, both the partial (OR: 0.59; 95% confidence interval [CI]: 0.35, 1.00) and full (OR: 0.49; 95% CI: 0.40, 0.59) interventions were associated with lower odds of poor diet quality among adolescents. Among the parents, both the partial (OR: 0.28; 95% CI: 0.20, 0.40) and full (OR: 0.28; 95% CI: 0.13, 0.58) interventions were associated with lower odds of poor diet quality. The partial (OR: 0.29; 95% CI: 0.18, 0.47) and full (OR: 0.47; 95% CI: 0.30, 0.72) interventions were associated with lower odds of adolescent overweight or obesity.

Discussion: School-based nutritional intervention packages incorporating multiple actions may improve the diet quality of adolescents and their household members and reduce the double burden of adolescent malnutrition.

Public Health. 2024 Dec;237:135-140.

doi: 10.1016/j.puhe.2024.09.024. Epub 2024 Oct 9.

[Effectiveness of health literacy education on health literacy in early adolescence: A randomized controlled trial](#)

[Büşra Nur Yüksek¹](#), [Sultan Ayaz-Alkaya²](#)

Abstract

Objectives: The present study was conducted to measure the effectiveness of health literacy education on the health literacy level of children in early adolescence.

Study design: A parallel group randomized controlled trial was conducted.

Methods: The study group consisted of sixth and seventh-grade students (aged 12-13 years) studying in a secondary school in Ankara. The study was completed by 80 students, 40 in the intervention group and 40 in the control group. The Health Literacy Education program, consisting of four sessions, was presented to the intervention group. The instruments were administered to both groups before the intervention (pre-test), one month (post-test), and three months after the intervention (follow-up test). The data was analyzed using the chi-square test, and the two-way mixed-design variance analysis with Bonferroni Multiple Comparison Test.

Results: Before the study, the adolescents in the intervention and control groups were similar regarding descriptive characteristics ($p > 0.05$). There was no statistically significant difference between the pre-test health literacy mean scores of the intervention and control groups ($p > 0.05$). After the health literacy education, health literacy post-test scores and follow-up test mean scores of the intervention group increased significantly compared to the

control group ($p < 0.05$). The intervention had a large effect size ($F = 414.683$; $\eta^2 = 0.91$) at the 95 % confidence interval.

Conclusions: The study revealed that health literacy education was effective in increasing the level of health literacy in early adolescence. It is recommended that health literacy education be added to the school education curriculum of adolescents.

Sepsis and serious bacterial infection

Pediatrics. 2024 Aug 1;154(Suppl 1):e2024066588F.

doi: 10.1542/peds.2024-066588F.

[Efficacy of Antibiotic Regimens for Sepsis or Possible Serious Bacterial Infection in Young Infants Aged 0 to 59 Days: A Systematic Review and Meta-analysis](#)

[Krysten North](#)^{1,2}, [Sitarah Mathias](#)^{2,3}, [Naomi Schmeck](#)⁴, [Yumin Kim](#)⁴, [Tessa Kehoe](#)¹, [Lian V Folger](#)¹, [Amber Hoey](#)⁵, [Carrie Wade](#)⁶, [Sophie Driker](#)¹, [Roger Chou](#)⁷, [Karen M Edmond](#)⁸, [Anne Cc Lee](#)^{1,2}

Abstract

Context: Sepsis is a leading cause of young infant mortality.

Objective: To evaluate the efficacy of different antibiotic regimens to treat young infant sepsis or possible serious bacterial infection (PSBI) on clinical outcomes.

Data sources: MEDLINE, Embase, CINAHL, World Health Organization Global Index Medicus, Cochrane Central Registry of Trials.

Study selection: We included randomized controlled trials (RCTs) of young infants 0 to 59 days with sepsis or PSBI (population) comparing the efficacy of antibiotic regimens (intervention) with alternate regimens or management (control) on clinical outcomes.

Data extraction: We extracted data and assessed risk of bias in duplicate. We performed random-effects meta-analysis, and used Grading of Recommendations, Assessment, Development, and Evaluation to assess certainty of evidence.

Results: Of 2390 publications, we included 41 RCTs ($n = 18\,054$). Thirty-five trials were hospital-based and 6 were nonhospital-based. Meta-analysis of 4 trials demonstrated similar rates of treatment success with intramuscular/intravenous third generation cephalosporins versus intramuscular/intravenous penicillin or ampicillin + gentamicin (RR 1.03, 95% CI 0.93-1.13; $n = 1083$; moderate certainty of evidence). Meta-analysis of 3 trials demonstrated similar rates of treatment failure with oral amoxicillin + intramuscular gentamicin versus intramuscular penicillin + gentamicin for nonhospital treatment of clinical severe illness (RR 0.86, 95% CI 0.72-1.02; $n = 5054$; low certainty of evidence). Other studies were heterogeneous.

Limitations: RCTs evaluated heterogeneous regimens, limiting our ability to pool data.

Conclusions: We found limited evidence to support any single antibiotic regimen as superior to alternate regimens to treat young infant sepsis or PSBI.

Pediatrics. 2024 Aug 1;154(Suppl 1):e2024066588C.

doi: 10.1542/peds.2024-066588C.

Global Management of Serious Bacterial Infections in Young Infants Aged 0 to 59 Days: An Overview of Systematic Reviews

[Karen M Edmond¹](#), [Georgia R Whisson²](#), [Derek C Swe²](#), [Natalie A Strobel²](#)

Abstract

Background: To inform World Health Organization guidelines for the management of serious bacterial infection (SBI) (suspected or confirmed sepsis, pneumonia, or meningitis) in infants aged 0-59 days.

Objective: To conduct an "overview of systematic reviews" to: (1) understand which systematic reviews have examined diagnosis and management of SBI in infants aged 0-59 days in the last 5 years; and (2) assess if the reviews examined PICOs (population, intervention, comparator, outcomes) and regimens currently being recommended in low and middle income countries (LMICs) by the World Health Organization.

Data sources: MEDLINE; Embase; Cochrane Library; Epistemonikos; PROSPERO.

Study selection: Systematic reviews of randomized controlled trials or observational studies of infants aged 0-59 days examining diagnostic accuracy and antibiotic regimens for SBI from January 1, 2018 to November 3, 2023.

Data extraction: Dual independent extraction of study characteristics, PICOs, and methodological quality.

Results: Nine systematic reviews met our criteria. Two reviews examined diagnostic accuracy for sepsis, and no reviews examined pneumonia or meningitis. Five reviews examined antibiotic effectiveness (sepsis [n = 4]; pneumonia [n = 1]), and no reviews examined meningitis. One review examined antibiotic duration for sepsis and one for meningitis, and no reviews for pneumonia. Only 4 of the 9 systematic reviews met criteria for high-quality.

Limitations: Our review was limited to the last 5 years to inform current guideline updates.

Conclusions: Few studies have examined antibiotic regimens currently being used in LMICs and quality is of concern in many studies. More high-quality data are needed to inform management of SBI in newborns, especially in LMICs.

Clin Microbiol Infect. 2025 Apr;31(4):551-559.

doi: 10.1016/j.cmi.2024.11.035. Epub 2024 Dec 4.

Oral switch vs. continued intravenous antibiotic therapy in patients with bacteraemia and sepsis: a systematic review and meta-analysis

[Qinyuan Li¹](#), [Qi Zhou²](#), [Jiangbo Fan³](#), [Siyuan Huang³](#), [Yaolong Chen⁴](#), [Fujian Song⁵](#), [Zhou Fu¹](#), [Enmei Liu¹](#), [Daolin Tang⁶](#), [Ling Zeng⁷](#), [Zhengxiu Luo⁸](#)

Abstract

Background: Bacteraemia and sepsis have traditionally required continued intravenous (IV) antibiotics.

Objectives: This study aims to evaluate if early transition to oral antibiotics is non-inferior to continued IV antibiotic therapy in treating patients with bacteraemia and sepsis.

Data sources: Data sources include MEDLINE, Embase, Web of Science, the Cochrane Library, and Wanfang databases from inception to 13 July 2024, along with clinical trial registries and Google.com.

Study eligibility criteria: Study eligibility criteria include randomized controlled trials (RCTs) and cohort studies.

Participants: Participants include patients with bacteraemia and sepsis.

Interventions: Interventions include early transition to oral antibiotics vs. continued IV antibiotics. Early oral switch was defined as 5-9 days for uncomplicated *Staphylococcus aureus* bacteraemia, <4 weeks for complicated *S. aureus* bacteraemia, 3-7 days for uncomplicated *Streptococcus* bacteraemia, and 3-5 days for uncomplicated *Enterobacterales* bacteraemia.

Assessment of risk of bias: Assessment of risk of bias includes Cochrane risk of bias tool and Newcastle-Ottawa Scale.

Methods of data synthesis: Random-effect models were used to pool the data. The primary outcome was treatment failure. The non-inferiority margin for treatment failure was 10%. The Grading of Recommendations Assessment, Development, and Evaluation approach was used to rate the certainty of the evidence.

Results: In total, 38 studies (6 RCTs, 10 adjusted cohorts, and 22 unadjusted cohorts) involving 11 566 patients were included. A primary analysis of 6 RCTs and 10 adjusted cohorts comprised 7102 patients. High-certainty evidence from six RCTs showed that early transition to oral antibiotics was non-inferior to continued IV therapy for treatment failure ($n = 529$; OR 0.89; 95% CI: 0.54-1.48). Low-certainty evidence from five adjusted cohorts also found no significant difference in treatment failure between the two groups ($n = 929$; OR 0.60; 95% CI: 0.29-1.72). Moderate-certainty evidence showed that oral switch therapy significantly reduced hospital stay ($n = 2041$; mean difference: -5.19 days; 95% CI: -8.16 to -2.22).

Conclusions: Early transition to oral antibiotics was non-inferior to continued IV antibiotic treatment for bacteraemia and sepsis.

BMJ Paediatr Open. 2025 Mar 5;9(1):e003148.

doi: 10.1136/bmjpo-2024-003148.

Comparison of methylprednisolone alone versus intravenous immunoglobulin plus methylprednisolone for multisystem inflammatory syndrome in children (MIS-C)

Phuc Huu Phan¹, Canh Ngoc Hoang², Ha Thu T Nguyen³, Tung Viet Cao⁴, Chi Quynh Le³, Dien Minh Tran^{5,6}

Abstract

Background: As a first-line therapeutic option for multisystem inflammatory syndrome in children (MIS-C) with surging demand, intravenous immunoglobulin (IVIG) is associated with escalating costs and supply shortages, particularly in low-income and middle-income countries. This study compares the effectiveness of methylprednisolone alone versus IVIG combined with methylprednisolone for managing MIS-C.

Methods: We conducted a retrospective cohort study from January 2022 to June 2023 at Vietnam National Children's Hospital. We used propensity score matching to compare the short-term outcomes based on immunomodulatory therapy with methylprednisolone alone or IVIG plus methylprednisolone.

Results: We included 391 patients, comprising 255 boys and 136 girls, who fulfilled the MIS-C case definition of the US Centers for Disease Control and Prevention. Most patients (80.8%) received intravenous methylprednisolone monotherapy, and 19.2% were administered IVIG

in addition to methylprednisolone. In general, the laboratory values indicative of hyperinflammatory and hyperthrombotic states displayed significant early response within 2-3 days after initial treatment, including white cell count (SE=1.77, $p<0.001$), NEU (SE=0.76, $p=0.03$), C reactive protein (SE=-46.51, $p<0.001$), PLT (SE=38.05, $p=0.002$), fibrinogen (SE=-0.37, $p=0.002$), d-dimer (SE=-849.8, $p=0.02$); while subsequent improvement in cardiac markers was also observed, with pro-B-type natriuretic peptide (SE=-165.2, $p<0.001$) on day 5 and troponin I (SE=-0.05, $p=0.004$) on day 7. After propensity score weighting, there were 41 patients in each treatment group. Notably, there were no significant differences in the incidence of cardiac events between treatment groups regarding left ventricular dysfunction and coronary artery dilation or aneurysms (10.3% vs 20.7%, $p=0.074$ and 63.4% vs 56.1%, $p=0.653$, respectively). While the median paediatric intensive care unit length of stay (LOS) and hospital LOS were slightly lengthier in the IVIG and methylprednisolone group compared with those of the methylprednisolone group, these differences were not statistically significant ((5 vs 4, $p=0.782$) and (9 vs 7, $p=0.725$), respectively).

Conclusions: Initial treatment with methylprednisolone monotherapy appears not inferior in effectiveness to adjunctive IVIG plus methylprednisolone in MIS-C. Further investigations in randomised controlled trials deserve to be undergone to clarify if IVIG-sparing glucocorticoids are a viable option for achieving favourable outcomes in MIS-C, particularly in resource-limited settings with barriers approaching IVIG therapy.

Front Pediatr. 2024 Oct 3;12:1443990.

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A pilot randomized controlled trial comparing noradrenaline and adrenaline as a first-line vasopressor for fluid-refractory septic shock in neonates

[Reema Garegrat¹](#), [Suprabha Patnaik¹](#), [Sonali Suryawanshi²](#), [Chinmay Chetan³](#), [Nishant Banait⁴](#), [Pari Singh¹](#), [Aditya Kallimath¹](#), [Naharmal B Soni⁵](#), [Yogen Singh⁶](#), [Pradeep Suryawanshi¹](#)

Abstract

Background and study design: Limited data exists on noradrenaline therapy in neonatal septic shock. We compared the efficacy of noradrenaline with adrenaline in neonatal septic shock. This single center, open label, pilot randomized controlled trial included neonates with clinical evidence of sepsis and shock.

Study outcomes: Primary outcomes were: 1) resolution of shock one hour after treatment, and 2) mortality during hospital stay. Secondary outcomes included: need for additional vasopressors; hemodynamic stability without further administration of vasopressors for ≥ 2 h; changes in blood pressure and heart rate after 1 h of vasopressor treatment; and morbidities during the hospital stay.

Results: Of 65 eligible neonates, 42 were randomized (21 each in adrenaline and noradrenaline treatment arms) between August 2020 and January 2022, at level III neonatal intensive care unit (NICU) of Bharati Vidyapeeth Deemed University Medical College and Hospital (BVDUMCH). The mean (SD) gestational age and mean (SD) birth weight were 36.1(4.2) weeks and 1.8 (0.2) kilograms birth weight for noradrenaline and 36.9 (4.1) weeks and 1.7 (0.7) kilograms for adrenaline. Shock resolved within 1 h of vasopressor therapy in 76.2% neonates in the noradrenaline arm and 61.9% in adrenaline arm (p value-0.53). Mortality during hospital stay was 28.6% (6/21) in noradrenaline group and 33.3% (7/21) in

adrenaline group (p value- 0.58). Additional vasopressors were required in 23.8% neonates of the noradrenaline group compared to 38.1% neonates in adrenaline arm (p value-0.53). Median (SD) duration of intensive care stay was 6 (SD) days in the noradrenaline group and 10 (SD) days in the adrenaline group (p value-0.045).

Conclusion: Among neonates with septic shock, the efficacy of noradrenaline was comparable to adrenaline in resolving septic shock after one hour of infusion and on the mortality during hospital stay.

J Pediatr. 2025 Jul;282:114599.

doi: 10.1016/j.jpeds.2025.114599. Epub 2025 Apr 17.

Norepinephrine versus Dopamine for Septic Shock in Neonates: A Randomized Controlled Trial

[Mohammad Yusuf Ali Mazhari¹](#), [Mayank Priyadarshi²](#), [Poonam Singh¹](#), [Suman Chaurasia¹](#), [Sriparna Basu¹](#)

Abstract

Objective: To assess the effect of norepinephrine (NE) vs dopamine (DA) as first-line vasoactive agent in neonates with fluid-refractory septic shock.

Study design: In this randomized controlled trial, 80 neonates with fluid-refractory septic shock were allocated to receive either NE ($n = 41$) or DA ($n = 39$) as the first-line vasoactive drug. NE and DA were initiated at a dose of 0.2 and 10 $\mu\text{g/kg/min}$ and escalated to a maximum dose of 0.3 and 15 $\mu\text{g/kg/min}$, respectively. The primary outcome was the proportion of neonates with shock reversal at 30 minutes of initiation of vasoactive support. Other outcomes included time to shock reversal, requirement of additional vasoactive drugs and steroids, changes in cerebral tissue oxygen saturation, and acid-base parameters and lactate levels at 6-8 and 24 hours. Incidence of mortality, hyperglycemia, tachycardia, and other morbidities were recorded.

Results: Baseline characteristics were comparable between the 2 groups. The proportion of neonates with shock reversal at 30 minutes was 32% (13/41) and 46% (18/39) in NE and DA groups, respectively (relative risk 0.69, 95% CI 0.39-1.20, $P = .19$). Time to reversal of shock, need for additional vasoactive drugs and steroids, lactate levels, hyperglycemia, mortality, and other morbidities were comparable. However, neonates in the DA group had a higher incidence of tachycardia, lower cerebral tissue oxygen saturation, and lower pH at 24 hours of recruitment.

Crit Care Med. 2025 Jun 13.

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Fifth Centile Versus 50th Centile Mean Blood Pressure Targets in Pediatric Septic Shock: A Randomized Controlled Trial

[Sachin Shah¹](#), [Amita Kaul](#), [Ganesh Shiwarkar](#), [Rajesh Nare](#), [Jayant Khandare](#)

Abstract

Objectives: Hypotension is common in septic children, mean blood pressure (MBP) guides vasoactive agent titration. However, the Surviving Sepsis Guidelines for children were unable to recommend whether to target the 5th or 50th MBP percentile for septic shock. We aim to

compare two MBP targets (5th vs. 50th percentile) for titrating vasoactive agents in septic shock patients.

Design: Single-center, open-label, randomized noninferiority trial.

Setting: It was conducted in a tertiary care PICU in India from April 2021 to March 2024.

Patients: Patients 1 month to 16 years old with septic shock unresponsive to fluids and requiring vasopressors.

Interventions: Children with septic shock were randomly assigned to either the 5th or 50th percentile MBP group, with vasopressor treatment adjusted to maintain the target blood pressure (BP) for each group.

Measurements and main results: The primary outcome was 28-day all-cause mortality. Secondary outcomes included PICU/hospital stay, duration of vasoactive use, vasopressor-related adverse events, need for continuous renal replacement therapy (CRRT), invasive ventilation, and prevalence of acute respiratory distress syndrome (ARDS). A total of 144 children were enrolled. At 28 days, mortality did not differ significantly between groups: 16.9% (12/71) in the 5th centile group vs. 23.2% (17/73) in the 50th centile group ($p = 0.41$; risk difference, 6.3; 95% CI, -6.9 to 19.2). Norepinephrine use was higher in the 50th centile group (85% vs. 67%; $p = 0.04$). Vasoactive duration was longer in the 50th centile group (30.4 ± 13.3 vs. 18.8 ± 10.8 ; $p = 0.001$). The Vasoactive-Inotropic Score was also higher (64.0 ± 35.7 vs. 45.2 ± 29.6 ; $p = 0.001$). ARDS prevalence was significantly higher in the 50th centile group (32.8% vs. 16.9%; $p = 0.02$). No significant differences were found in other secondary outcomes like length of stay, ventilation duration, need for CRRT, or adverse events.

Conclusions: Targeting a lower MBP (5th vs. 50th centile) in septic shock showed no significant difference in 28-day mortality. This suggests a lower BP target may be safe, reducing vasoactive drug use and related side effects.

Crit Care Explor. 2025 Mar 31;7(4):e1242.

doi: 10.1097/CCE.0000000000001242. eCollection 2025 Apr 1.

[Electrocardiometry for the Management of Pediatric Septic Shock: A Pilot Randomized Controlled Trial](#)

[Suman Sudha Moharana](#)¹, [Lalitha Av](#)², [Santu Ghosh](#)³

Abstract

Objectives: To evaluate the difference in the resuscitation fluid volume in the initial 6 hours in pediatric septic shock between those undergoing noninvasive continuous hemodynamic monitoring with electrocardiometry in addition to clinical monitoring vs. clinical monitoring alone.

Design: Randomized control trial.

Setting: PICU in a tertiary care hospital.

Patients: Children from 2 months to 18 years with sepsis and unresolved shock after the initial fluid bolus (FB).

Interventions: Children were randomized to one of the two groups, that is, electrocardiometry with clinical monitoring group (group B) and clinical monitoring alone group (group A). In group B, electrocardiometry variables (cardiac index and systemic vascular resistance index) along with clinical monitoring were used to guide FB, as well as

selection and titration of vasoactive agents. Clinical parameters were used to initiate and titrate fluid resuscitation and vasoactive therapy in group A as per standard guidelines.

Measurements and main results: One hundred nineteen children were enrolled in the study: 60 in group A and 59 in group B. There was a significantly higher requirement for resuscitation fluid volume (mean $\pm$ sd) within the initial 6 hours in the group A (30 ± 8.2 mL/kg) as compared with group B (22 ± 9.2 mL/kg). Similarly, maintenance along with resuscitation fluid volume (mean $\pm$ sd) administration (56 ± 13 vs. 46 ± 10.7 , $p < 0.001$) was higher in group A in the first 24 hours of enrollment. Vasoactive therapy initiation was earlier in group B as compared with group A (37 ± 10.14 vs. 47.33 ± 12.41 min) with lower fluid overload percentage (2.98% vs. 1.7%) in this group. However, there was no difference in time to shock resolution, 28-day ICU-free days, hospital-free days, and mortality.

Conclusions: Advanced hemodynamic monitoring with electrocardiometry along with clinical assessment led to a restrictive fluid strategy in addition to minimizing the risk of fluid overload.

Skin and hair disease

Snake bite and envenomation

Am J Trop Med Hyg. 2024 Aug 6;111(4):904-910.

doi: 10.4269/ajtmh.24-0222. Print 2024 Oct 2.

[A Randomized Controlled Trial to Optimize Antivenom Therapy for Carpet Viper \(*Echis romani*\)-Envenomed Children in Nigeria](#)

[Nicholas A Hamman](#)¹, [Agom D Ibrahim](#)², [Muhammad Hamza](#)³, [Mahmoud G Jahun](#)⁴, [Musa Micah](#)¹, [Hadiza A Lawal](#)⁵, [Saidu B Abubakar](#)¹, [Garba Iliyasu](#)³, [Basheer A Z Chedi](#)⁶, [Idris Mohammed](#)⁷, [Robert A Harrison](#)⁸, [José-María Gutiérrez](#)⁹, [Abdulrazaq G Habib](#)³

Abstract

In an open randomized controlled trial, we compared one vial (10 mL) to two vials (20 mL) of EchiTab-plus-ICP (EPI) antivenom among children with systemic carpet viper (*Echis romani*) envenoming of moderate severity in northeastern Nigeria. Systemic envenoming, presenting with incoagulable blood, was diagnosed using the 20-minute whole blood clotting test (20WBCT). Eligible patients with positive 20WBCT whose guardians assented were recruited and randomly allocated to receive either one vial or two vials of EPI administered either as a bolus or as a slow continuous infusion. The primary outcome was permanent restoration of blood coagulability 6 hours after the start of treatment, assessed by the 20WBCT and repeated at 6, 12, 24, and 48 hours after treatment. Secondary outcomes were the incidences of early adverse reactions to antivenom treatment. Initial doses permanently restored blood coagulability at 6 hours in 34/39 (87.2%) of those treated with one vial and 39/41 (95.1%) of those treated with two vials of EPI ($P = 0.258$). However, the proportion with permanent restoration of clotting at 6 hours among patients randomized to bolus administration was 41 of 42 (97.6%) patients compared with 32 of 38 (84.2%) patients randomized to slow infusion of EPI antivenom ($P = 0.049$); however, the difference was not sustained through the

remaining time points. There was no difference in early adverse reactions between those treated with the two different doses or modes of delivery. We conclude that the one-vial dose compared favorably to two vials of EPI antivenom with regards to effectiveness and safety among children with carpet viper envenoming of moderate severity in Nigeria.

BMJ Glob Health. 2024 Oct 22;9(10):e015985.

doi: 10.1136/bmjgh-2024-015985.

Oral varespladib for the treatment of snakebite envenoming in India and the USA (BRAVO): a phase II randomised clinical trial

[Charles J Gerardo^{#1}](#), [Rebecca W Carter^{#2}](#), [Surendra Kumar³](#), [Farshad M Shirazi⁴](#), [Suneetha D Kotehal⁵](#), [Peter D Akpunonu⁶](#), [Ashish Bhalla⁷](#), [Richard B Schwartz⁸](#), [Chanaveerappa Bammigatti⁹](#), [Neeraj Manikath¹⁰](#), [Partha P Mukherjee¹¹](#), [Thomas C Arnold¹²](#), [Brian J Wolk¹³](#), [Sophia S Sheikh¹⁴](#), [Dawn R Sollee¹⁵](#), [David J Vearrier¹⁶](#), [Samuel J Francis¹](#), [Adiel Aizenberg⁴](#), [Harish Kumar³](#), [Madhu K Ravikumar⁵](#), [Sujoy Sarkar¹¹](#), [Taylor Haston⁸](#), [Andrew Micciche⁶](#), [Suraj C Oomman²](#), [Jeffery L Owen²](#), [Brandi A Ritter²](#), [Stephen P Samuel²](#), [Matthew R Lewin¹⁷](#), [Timothy F Platts-Mills²](#)

Abstract

Introduction: Snakebite envenoming (SBE) results in over 500 000 deaths or disabling injuries annually. Varespladib methyl, an oral inhibitor of secretory phospholipase A2, is a nearly ubiquitous component of snake venoms. We conducted a phase II clinical trial to assess efficacy and safety of oral varespladib methyl in patients bitten by venomous snakes.

Methods: This double-blind, randomised, placebo-controlled trial enrolled patients in emergency departments in India and the USA. Patients with SBE were randomly assigned (1:1) to receive varespladib methyl or placebo two times per day for 1 week. All patients received standard of care, including antivenom. The primary outcome was change in the composite Snakebite Severity Score (SSS) measuring the severity of envenoming, from baseline to the average composite SSS at 6 and 9 hours.

Results: Among 95 patients randomised August 2021 through November 2022, the most common snakebites were from Russell's vipers (n=29), copperheads (n=18) and rattlesnakes (n=14). The SSS improved from baseline to the average at 6 and 9 hours by 1.1 (95% CI, 0.7 to 1.6) in the varespladib group versus 1.5 (95% CI, 1.0 to 2.0) in the placebo group (difference - 0.4, 95% CI, -0.8 to 0.1, p=0.13). While key secondary outcomes were not statistically different by treatment group, benefit was seen in the prespecified subgroup initiating study drug within 5 hours of bite (n=37). For this early treatment group, clinically important differences were observed for illness severity over the first week, patient-reported function on days 3 and 7 and complete recovery. No death or treatment emergent serious adverse event occurred.

Conclusion: For emergency department treatment of snakebites, the addition of varespladib to antivenom did not find evidence of difference for the primary outcome based on the SSS. A potentially promising signal of benefit was observed in patients initiating treatment within 5 hours of snakebite.

Surgical problems

J Neurosurg Pediatr. 2025 May 2:1-10.

doi: 10.3171/2025.1.PEDS24417. Online ahead of print.

[Five-year outcomes after surgical treatment of infant postinfectious hydrocephalus in sub-Saharan Africa: results of a randomized trial](#)

[Edith Mbabazi-Kabachelor^{#1,2}](#), [Mallory R Peterson^{#3}](#), [John Mugamba^{#1}](#), [Peter Ssenyonga^{#1,4}](#), [Justin Onen^{1,4}](#), [Esther Nalule¹](#), [Joshua Magombe^{1,4}](#), [Venkateswararao Cherukuri⁵](#), [Vishal Monga⁵](#), [Steven J Schiff^{#2}](#), [Abhaya V Kulkarni^{#6,7}](#), [Benjamin C Warf^{#8,9}](#)

Abstract

Objective: Postinfectious hydrocephalus (PIH) in infants is a major public health burden in sub-Saharan Africa. In a previously reported randomized trial, the authors found no significant differences in outcome between endoscopic versus shunt treatment, with stagnation in brain growth at 2 years after treatment. They now present the 5-year follow-up results of this cohort, assessing detailed developmental, quality of life, and brain volume outcomes.

Methods: The authors performed a trial at a single center in Mbale, Uganda, involving 100 infants (< 180 days of age) with PIH randomized to endoscopic third ventriculostomy plus choroid plexus cauterization (ETV/CPC) or ventriculoperitoneal shunt (VPS) treatment. After 5 years, they assessed developmental outcomes with the Vineland Adaptive Behavior Scales, Third Edition (VABS-3), quality of life with the Health Utilities Index Mark 3 (HUI-3) and Hydrocephalus Outcome Questionnaire (HOQ), and brain volume derived from CT scans.

Results: Sixty-three infants were assessed for 5-year outcomes (35 ETV/CPC and 28 VPS, by intention to treat). There were no significant differences between the two surgical treatment arms in treatment failure ($p = 0.39$), VABS-3 scores ($p > 0.52$), HUI-3 utility scores ($p > 0.37$), HOQ scores ($p > 0.18$), or brain volume (raw $p = 1.0$, adjusted $p = 0.24$). There were strong correlations between VABS-3, HUI-3, and HOQ scores with brain volume adjusted for age and sex, and weaker correlations when adjusted for anthropometric measurements.

Conclusions: These results suggest that ETV/CPC and VPS treatment have comparable long-term outcomes for infants in medically resource-constrained environments. Furthermore, brain volume strongly correlates with developmental and quality of life metrics, emphasizing the need to focus on optimizing brain volume growth potential in infants with severe perinatal neurological insults such as infection and hydrocephalus.

Telemedicine

Trypanosomiasis

Tuberculosis

(See also Vaccines: Tuberculosis vaccine)

Treatment of tuberculosis

BMJ Glob Health. 2024 Dec 18;9(12):e016416.

doi: 10.1136/bmjgh-2024-016416.

[Cost-effectiveness of integrating paediatric tuberculosis services into child healthcare services in Africa: a modelling analysis of a cluster-randomised trial](#)

[Nyashadzaishe Mafirakureva¹](#), [Lise Denoeud-Ndam²](#), [Boris Kevin Tchounga³](#), [Rose Otieno-Masaba⁴](#), [Nicole Herrera⁵](#), [Sushant Mukherjee⁵](#), [Martina Casenghi⁶](#), [Appolinaire Tiam^{5,7}](#), [Peter J Dodd⁸](#); [INPUT study group](#)

Abstract

Background: In 2021, over one million children developed tuberculosis, resulting in 214 000 deaths, largely due to inadequate diagnosis and treatment. The diagnosis and treatment of tuberculosis is limited in most high-burden countries because services are highly centralised at secondary/tertiary levels and are managed in a vertical, non-integrated way. To improve case detection and treatment among children, the World Health Organisation (WHO) recommends decentralised and integrated tuberculosis care models. The Integrating Paediatric TB Services Into Child Healthcare Services in Africa (INPUT) stepped-wedge cluster-randomised trial evaluated the impact of integrating tuberculosis services into healthcare for children under five in Cameroon and Kenya, compared with usual care, finding a 10-fold increase in tuberculosis case detection in Cameroon but no effect in Kenya.

Methods: We estimated intervention impact on healthcare outcomes, resource use, health system costs and cost-effectiveness relative to the standard of care (SoC) using a decision tree analytical approach and data from the INPUT trial. INPUT trial data on cascades, resource use and intervention diagnostic rate ratios were used to parametrise the decision tree model. Health outcomes following tuberculosis treatment were modelled in terms of mortality and disability-adjusted life-years (DALYs).

Findings: For every 100 children starting antituberculosis treatment under SoC, an additional 876 (95% uncertainty interval (UI) -76 to 5518) in Cameroon and -6 (95% UI -61 to 96) in Kenya would start treatment under the intervention. Treatment success would increase by 5% in Cameroon and 9% in Kenya under the intervention compared with SoC. An estimated 350 (95% UI -31 to 2204) and 3 (95% UI -22 to 48) deaths would be prevented in Cameroon and Kenya, respectively. The incremental cost-effectiveness ratio for the intervention compared with SoC was US\$506 and US\$1299 per DALY averted in Cameroon and Kenya, respectively.

Interpretation: Although likely to be effective, the cost-effectiveness of integrating tuberculosis services into child healthcare services depends on baseline service coverage, tuberculosis detection and treatment outcomes.

Int J Antimicrob Agents. 2024 Jul;64(1):107197.

doi: 10.1016/j.ijantimicag.2024.107197. Epub 2024 May 14.

[Pharmacokinetics of standard versus high-dose rifampin for tuberculosis preventive treatment: A sub-study of the 2R² randomized controlled trial](#)

[Fajri Gafar¹](#), [Vycke Yunivita²](#), [Federica Fregonese³](#), [Lika Apriani⁴](#), [Rob E Aarnoutse⁵](#), [Rovina Ruslami⁶](#), [Dick Menzies⁷](#)

Abstract

Background: Pharmacokinetic data of rifampin, when used for tuberculosis preventive treatment (TPT) are not available. We aimed to describe the pharmacokinetics of rifampin used for TPT, at standard and higher doses, and to assess predictors of rifampin exposure.

Methods: A pharmacokinetic sub-study was performed in Bandung, Indonesia among participants in the 2R² randomized trial, which compared TPT regimens of 2 months of high-dose rifampin at 20 mg/kg/day (2R₂₀) and 30 mg/kg/day (2R₃₀), with 4 months of standard-dose rifampin at 10 mg/kg/day (4R₁₀) in adolescents and adults. Intensive pharmacokinetic sampling was performed after 2-8 weeks of treatment. Pharmacokinetic parameters were assessed non-compartmentally. Total exposure (AUC₀₋₂₄) and peak concentration (C_{max}) between arms were compared using one-way ANOVA and Tukey's post-hoc tests.

Multivariable linear regression analyses were used to assess predictors of AUC₀₋₂₄ and C_{max}.

Results: We enrolled 51 participants in this study. In the 4R₁₀, 2R₂₀, and 2R₃₀ arms, the geometric mean AUC₀₋₂₄ was 68.0, 186.8, and 289.9 h·mg/L, and C_{max} was 18.4, 36.7, and 54.4 mg/L, respectively; high interindividual variabilities were observed. Compared with the 4R₁₀ arm, AUC₀₋₂₄ and C_{max} were significantly higher in the 2R₂₀ and 2R₃₀ arms (P < 0.001). Drug doses, body weight, and female sex were predictors of higher rifampin AUC₀₋₂₄ and C_{max} (P < 0.05). AUC₀₋₂₄ and C_{max} values were much higher than those previously reported in persons with TB disease.

Conclusions: Doubling and tripling the rifampin dose led to three- and four-fold higher exposure compared to standard dose. Pharmacokinetic/pharmacodynamic modelling and simulations are warranted to support trials of shortening the duration of TPT regimens with high-dose rifampin.

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Long-term efficacy and safety of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): extended follow-up of an open-label, multicentre, randomised, non-inferiority trial

Ruth L Goodall¹, Andrew J Nunn², Sarah K Meredith², Adamu Bayissa³, Anuj K Bhatnagar⁴, Chen-Yuan Chiang⁵, Francesca Conradie⁶, Narendran Gopalan⁷, Meera Gurumurthy⁸, Bruce Kirenga⁹, Nana Kiria¹⁰, Daniel Meressa¹¹, Ronelle Moodliar¹², Nosipho Ngubane¹³, Mohammed Rassool¹⁴, Karen Sanders², Rajesh Solanki¹⁵, S Bertel Squire¹⁶, Mekonnen Teferi³, Gabriela Torrea¹⁷, Bazarragchaa Tsogt¹⁸, Elena Tudor¹⁹, Armand Van Deun¹⁷, I D Rusen²⁰; STREAM study collaborators

Abstract

Background: STREAM stage 2 showed that two bedaquiline-containing regimens (a 9-month all-oral regimen and a 6-month regimen with 8 weeks of aminoglycoside) had superior efficacy to a 9-month injectable-containing regimen for rifampicin-resistant tuberculosis up to 76 weeks after randomisation. Our objective in this follow-up analysis was to assess the durability of efficacy and safety, including mortality, at 132 weeks.

Methods: We report the long-term outcomes from STREAM stage 2, a randomised, phase 3 non-inferiority (10% margin) trial in participants (aged ≥15 years) with rifampicin-resistant tuberculosis without fluoroquinolone or aminoglycoside resistance at 13 clinical sites in seven countries (Ethiopia, Georgia, India, Moldova, Mongolia, South Africa, and Uganda).

Participants were randomly assigned 1:2:2:2 (via permuted blocks and stratified by site and HIV status plus CD4 cell count) to the 2011 WHO long regimen (terminated early), a 9-month control regimen, a 9-month oral regimen with bedaquiline (primary comparison), or a 6-month regimen with bedaquiline and 8 weeks of an injectable antituberculous drug. Participants and clinicians were aware of treatment-group assignments, but laboratory staff were masked. The primary outcome, reported previously, was favourable status (negative cultures for *Mycobacterium tuberculosis* without a preceding unfavourable outcome; any death, bacteriological failure or recurrence, and major treatment change were considered unfavourable) at week 76. Here we report efficacy outcomes at week 132, analysed in the modified intention-to-treat (mITT) population. Safety assessments continued to 132 weeks and were in all participants who received at least one dose of the study regimen. All comparisons used concurrently randomised participants. This trial is registered on ISRCTN (ISRCTN18148631) and is now completed.

Findings: Between March 28, 2016, and Jan 28, 2020, 588 participants were randomly assigned to the long (n=32), control (n=202), oral (n=211), or 6-month (n=143) treatment regimens; 352 (60%) were male and 236 (40%) were female. Of the 556 participants on the three shorter regimens, 517 were included in the mITT population (187 in control group, 196 in oral group, and 134 in 6-month group) and 465 in the per-protocol analyses. Six additional participants had an unfavourable outcome that occurred between week 76 and the end of efficacy follow-up (one in control group, four in oral group, one in 6-month group). In the mITT population, the proportion of patients with an unfavourable outcome at the end of follow-up was 19.6% (95% CI 14.3 to 24.9) in the oral group and 29.3% (23.3 to 36.5) in the control group (-9.7 percentage points difference [95% CI -18.7 to -1.8]; $p_{\text{superiority}}=0.024$). An estimated 9.8% (95% CI 4.6 to 14.9) of participants on the 6-month regimen had an unfavourable outcome, which was significantly lower than for those concurrently on the control regimen (32.5% [23.7 to 40.2]; $p_{\text{superiority}}<0.0001$) or the oral regimen (23.8% [16.9 to 31.1]; $p_{\text{superiority}}=0.013$). Few serious or severe adverse events were reported after week 76, with no indication of a difference between the regimens. At week 132, treatment-emergent hearing loss was recorded in significantly fewer participants on the oral regimen (7/205; 3%) than the control regimen (16/198; 8%; $p=0.041$); there was no significant difference in severe hearing loss between the oral regimen (6/139; 4%) and the 6-month regimen (5/143; 4%; $p=0.72$). Death rates were low: 1.01 (95% CI 0.48 to 2.12) per 100 person-years in participants allocated to bedaquiline (ie, oral and 6-month regimen, n=287) compared with 1.52 (0.63 to 3.66) in participants on the control regimen (n=140; $p=0.49$).

Interpretation: Both of the bedaquiline-containing regimens maintained superiority to the control regimen, without evidence of increased mortality, providing two additional evidence-based treatment options for patients; previous mortality concerns for bedaquiline were not substantiated.

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Oral Regimens for Rifampin-Resistant, Fluoroquinolone-Susceptible Tuberculosis
[Lorenzo Guglielmetti¹](#), [Uzma Khan¹](#), [Gustavo E Velásquez¹](#), [Maelenn Gouillou¹](#), [Amanzhan Abubakirov¹](#), [Elisabeth Baudin¹](#), [Elmira Berikova¹](#), [Catherine Berry¹](#), [Maryline Bonnet¹](#), [Matteo Cellamare¹](#), [Vijay Chavan¹](#), [Vivian Cox¹](#), [Zhanna Dakenova¹](#), [Bouke](#)

[Catherine de Jong¹](#), [Gabriella Ferlazzo¹](#), [Aydarkhan Karabayev¹](#), [Ohanna Kirakosyan¹](#), [Nana Kiria¹](#), [Mikanda Kunda¹](#), [Nathalie Lachenal¹](#), [Leonid Lecca¹](#), [Helen McIlleron¹](#), [Ilaria Motta¹](#), [Sergio Mucching Toscano¹](#), [Hebah Mushtaque¹](#), [Payam Nahid¹](#), [Lawrence Oyewusi¹](#), [Samiran Panda¹](#), [Sandip Patil¹](#), [Patrick P J Phillips¹](#), [Jimena Ruiz¹](#), [Naseem Salahuddin¹](#), [Epifanio Sanchez Garavito¹](#), [Kwonjune J Seung¹](#), [Eduardo Ticona¹](#), [Lorenzo Trippa¹](#), [Dante E Vargas Vasquez¹](#), [Sean Wasserman¹](#), [Michael L Rich¹](#), [Francis Varaine¹](#), [Carole D Mitnick¹](#); [endTB Clinical Trial Team](#)

Abstract

Background: For decades, poor treatment options and low-quality evidence plagued care for patients with rifampin-resistant tuberculosis. The advent of new drugs to treat tuberculosis and enhanced funding now permit randomized, controlled trials of shortened-duration, all-oral treatments for rifampin-resistant tuberculosis.

Methods: We conducted a phase 3, multinational, open-label, randomized, controlled noninferiority trial to compare standard therapy for treatment of fluoroquinolone-susceptible, rifampin-resistant tuberculosis with five 9-month oral regimens that included various combinations of bedaquiline (B), delamanid (D), linezolid (L), levofloxacin (Lfx) or moxifloxacin (M), clofazimine (C), and pyrazinamide (Z). Participants were randomly assigned (with the use of Bayesian response-adaptive randomization) to receive one of five combinations or standard therapy. The primary end point was a favorable outcome at week 73, defined by two negative sputum culture results or favorable bacteriologic, clinical, and radiologic evolution. The noninferiority margin was -12 percentage points.

Results: Among the 754 participants who underwent randomization, 699 were included in the modified intention-to-treat analysis, and 562 in the per-protocol analysis. In the modified intention-to-treat analysis, 80.7% of the patients in the standard-therapy group had favorable outcomes. The risk difference between standard therapy and each of the four new regimens that were found to be noninferior in the modified intention-to-treat population was as follows: BCLLfxZ, 9.8 percentage points (95% confidence interval [CI], 0.9 to 18.7); BLMZ, 8.3 percentage points (95% CI, -0.8 to 17.4); BDLLfxZ, 4.6 percentage points (95% CI, -4.9 to 14.1); and DCMZ, 2.5 percentage points (95% CI, -7.5 to 12.5). Differences were similar in the per-protocol population, with the exception of DCMZ, which was not noninferior in that population. The proportion of participants with grade 3 or higher adverse events was similar across the regimens. Grade 3 or higher hepatotoxic events occurred in 11.7% of participants overall and in 7.1% of those receiving standard therapy.

Conclusions: Consistent results across all the analyses support the noninferior efficacy of three all-oral shortened regimens for the treatment of rifampin-resistant tuberculosis.

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[Clinical Outcomes in Children With Human Immunodeficiency Virus Treated for Nonsevere Tuberculosis in the SHINE Trial](#)

[Chishala Chabala^{1,2,3}](#), [Eric Wobudeya⁴](#), [Marieke M van der Zalm⁵](#), [Monica Kapasa²](#), [Priyanka Raichur⁶](#), [Robert Mboizi⁴](#), [Megan Palmer⁵](#), [Aarti Kinikar⁶](#), [Syed Hissar⁷](#), [Veronica Mulenga^{1,2}](#), [Vidya Mave⁶](#), [Philippa Musoke⁴](#), [Anneke C Hesselink⁵](#), [Helen McIlleron³](#), [Diana Gibb⁸](#), [Angela Crook⁸](#), [Anna Turkova⁸](#); [SHINE Trial Team](#)

Abstract

Background: Children with human immunodeficiency virus (HIV, CWH) are at high risk of tuberculosis (TB) and face poor outcomes, despite antiretroviral therapy (ART). We evaluated outcomes in CWH and children not living with HIV treated for nonsevere TB in the SHINE trial.

Methods: SHINE was a randomized trial that enrolled children aged <16 years with smear-negative, nonsevere TB who were randomized to receive 4 versus 6 months of TB treatment and followed for 72 weeks. We assessed TB relapse/recurrence, mortality, hospitalizations, grade ≥ 3 adverse events by HIV status, and HIV virological suppression in CWH.

Results: Of 1204 children enrolled, 127 (11%) were CWH, of similar age (median, 3.6 years; interquartile range, 1.2, 10.3 versus 3.5 years; 1.5, 6.9; $P = .07$) but more underweight (weight-for-age z score, -2.3; (3.3, -0.8 versus -1.0; -1.8, -0.2; $P < .01$) and anemic (hemoglobin, 9.5 g/dL; 8.7, 10.9 versus 11.5 g/dL; 10.4, 12.3; $P < .01$) compared with children without HIV. A total of 68 (54%) CWH were ART-naïve; baseline median CD4 count was 719 cells/mm³ (241-1134), and CD4% was 16% (10-26). CWH were more likely to be hospitalized (adjusted odds ratio, 2.4; 1.3-4.6) and to die (adjusted hazard ratio [aHR], 2.6; 95% confidence interval [CI], 1.2 to 5.8). HIV status, age <3 years (aHR, 6.3; 1.5, 27.3), malnutrition (aHR, 6.2; 2.4, 15.9), and hemoglobin <7 g/dL (aHR, 3.8; 1.3, 11.5) independently predicted mortality. Among children with available viral load (VL), 45% and 61% CWH had VL <1000 copies/mL at weeks 24 and 48, respectively. There was no difference in the effect of randomized treatment duration (4 versus 6 months) on TB treatment outcomes by HIV status (P for interaction = 0.42).

Conclusions: We found no evidence of a difference in TB outcomes between 4 and 6 months of treatment for CWH treated for nonsevere TB. Irrespective of TB treatment duration, CWH had higher rates of mortality and hospitalization than their counterparts without HIV

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Treatment adherence and clinical outcomes amongst in people with drug-susceptible tuberculosis using medication monitor and differentiated care approach compared with standard of care in South Africa: a cluster randomized trial

[Salome Charalambous^{1,2}](#), [Noriah Maraba¹](#), [Lauren Jennings³](#), [Israel Rabothata¹](#), [Dolphina Cogill³](#), [Rachel Mukora^{1,2}](#), [Piotr Hippner¹](#), [Pren Naidoo⁴](#), [Nokhanyo Xaba⁴](#), [Lihle Mchunu¹](#), [Kavindhran Velen¹](#), [Catherine Orrell^{3,5}](#), [Katherine L Fielding^{6,7}](#)

Abstract

Background: Poor treatment adherence contributes to lower treatment completion and higher loss to follow-up among people with tuberculosis (PWTB). Medication monitors have shown some evidence of improved adherence.

Methods: We conducted a cluster randomised trial in 18 primary health clinics in South Africa between May 2019-February 2022. Persons (aged ≥ 2 years) with drug-sensitive tuberculosis (DS-TB) were enrolled. All participants were provided with monitors which were silent in the standard of care (SoC) arm. In the intervention arm, weekly adherence reports were reviewed and participants received intensified support as appropriate (text, phone call, home visit, motivational counselling). The primary outcome was adherence, which was calculated as days box was opened (proxy for drug taken)/total expected treatment days as a binary variable (<80% versus $\geq 80\%$). Analysis took into account clustered design. The trial was registered with the Pan African Trial Registry PACTR20190268115772.

Findings: We enrolled 2727 participants (38% women, median age 36 (IQR 27-45 years), of whom 2584 had available adherence data. The primary outcome (measured as $\geq 80\%$ adherence) was higher in intervention versus SoC arm (81.0% versus 50.8%, adjusted risk ratio (ARR) 1.51 (1.36-1.66). Similarly, overall percentage adherence was higher in intervention versus SoC arm (88.5% versus 69.7%, adjusted risk difference 16.8% (13.3%-20.4%)).

Interpretation: People with DS-TB had improved treatment adherence in the intervention arm. We believe the effect on adherence is important and warrants continued use and evaluation of these technologies.

Prevention of tuberculosis, treatment of latent tuberculosis

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Effectiveness of a Home-based Approach to Child Contact Investigation and TPT Management by Community Health Workers in Ethiopia: A Pragmatic Cluster-randomized Trial

[Nicole Salazar-Austin](#)^{1,2}, [Silvia Cohn](#)³, [Bareng A S Nonyane](#)², [Christiaan Mulder](#)^{4,5}, [Fiseha Mulatu](#)⁶, [Samuel Bayu](#)⁶, [Moges Bizuayehu](#)⁶, [Gidea Conradie](#)⁷, [Akash Malhotra](#)^{8,9}, [Paul Phan](#)³, [Natalia Hernandez Morfin](#)¹, [Stephanie Borsboom](#)⁴, [Petros Mitiku](#)⁶, [Demissu Fulas](#)¹⁰, [Mulunesh Tulema](#)¹⁰, [Jonathan E Golub](#)³, [Richard E Chaisson](#)³, [Gavin Churchyard](#)^{7,11,12}, [Ahmed Bedru](#)⁶

Abstract

Background: Tuberculosis preventive treatment (TPT) is highly effective at preventing tuberculosis (TB) disease but is poorly implemented. We aimed to determine whether home-based contact management improves TPT uptake among close child contacts compared to the facility-based standard of care.

Methods: We conducted a pragmatic cluster-randomized trial among close contacts of TB clients aged <15 years in 18 primary health facilities in Oromia, Ethiopia. Facilities were randomized 1:1 to home-based or facility-based contact management. The intervention was conducted by community health workers (CHWs) and task-shared with TB focal persons. The primary endpoint was the cluster-level ratio of the number of contacts aged <15 years initiated on TPT per TB client.

Results: The cluster-level mean number of child contacts initiated on TPT per TB client was 40% higher in the home-based (1.7 contacts per TB client) versus facility-based arm (1.3 contacts per TB client; rate ratio 1.4, 95% confidence interval [CI]: .7-2.7). In the care continuum, assuming 2.1 children <15 years per household, 73% and 63% of children completed TPT in the 2 arms, respectively. One child failed TPT and 2 children discontinued TPT due to drug-related adverse reactions in the home-based and facility-based arms, respectively.

Conclusions: Home-based contact management by CHWs increased the number of children initiated on TPT by 40% without negative effects on treatment outcomes. Though not statistically significant, on a larger scale, the increased number of children identified and

initiated on TPT has the potential to substantially reduce the burden of pediatric TB in Ethiopia and elsewhere.

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Safety of 3-month rifampicin-isoniazid TPT in child household contacts in a community-based intervention

[B Tchakounte Youngui¹](#), [B K Tchounga²](#), [D Atwine³](#), [A Vasiliu⁴](#), [B Cuer⁵](#), [L Simo²](#), [R Okello⁶](#), [P Tchendjou²](#), [A Kuate Kuate⁷](#), [S Turyahabwe⁸](#), [J Cohn⁹](#), [S M Graham¹⁰](#), [M Casenghi¹¹](#), [M Bonnet⁵](#)

Abstract

The WHO recommends shorter TB preventive treatment (TPT) regimens and decentralised delivery models to improve effectiveness. This study evaluated the safety of a 3-month rifampicin-isoniazid (3RH) regimen administered by community health workers (CHWs) in households in Cameroon and Uganda

METHODS. A cluster-randomised trial was conducted among child contacts of TB patients. We compared the safety of 3RH delivered by CHWs at home (intervention) vs standard-of-care, facility-based administration of 3RH. Safety outcomes included adverse events (AEs), serious adverse events (SAEs), and adverse reactions (ARs). We described the steps from symptom identification by CHWs to classification by a clinician.

Of 1,316 children initiated on 3RH, AEs were reported in 8.7% (81/936) in the intervention arm versus 11.3% (43/380) in the standard-of-care arm, $P = 0.15$. Overall, 37 SAEs occurred in 36 children, all non-medication related. There were 16 ARs reported, occurring in 1.0% (9/936) of children in the intervention arm and 1.6% (6/380) in the standard-of-care arm, $P = 0.22$. During 4,608 follow-up visits, 21 children reporting AR symptoms were identified by CHWs, 16 were assessed by clinicians, and 4 ARs were confirmed.

The 3RH regimen was safe, including when administered by trained CHWs in community settings, supporting its use in decentralised healthcare models.

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Levofloxacin Preventive Treatment in Children Exposed to MDR Tuberculosis

[Anneke C Hesselink¹](#), [Susan E Purchase¹](#), [Neil A Martinson¹](#), [Lee Fairlie¹](#), [H Simon Schaaf¹](#), [Joanna Brigden¹](#), [Suzanne Staples¹](#), [Diana M Gibb¹](#), [Anthony Garcia-Prats¹](#), [Francesca Conradie¹](#), [Charlotte McGowan¹](#), [Charlotte Layton¹](#), [Elize Batist¹](#), [Anne-Marie Demers¹](#), [Samukelisiwe Nyamathe¹](#), [Lisa Frigati¹](#), [Rebecca Turner¹](#), [Trinh Duong¹](#), [James A Seddon¹](#)

Abstract

Background: Worldwide, approximately 2 million children younger than 15 years of age are infected with multidrug-resistant (MDR) *Mycobacterium tuberculosis*, with MDR tuberculosis developing in approximately 30,000 annually. Evidence from randomized, controlled trials on tuberculosis preventive treatment in persons exposed to MDR tuberculosis is lacking.

Methods: In this community-based, multisite, double-blind, cluster-randomized, placebo-controlled trial in South Africa, we assessed the efficacy and safety of levofloxacin as preventive treatment in children with household exposure to an adult with bacteriologically confirmed MDR pulmonary tuberculosis. Children younger than 5 years of age were eligible for inclusion regardless of interferon- γ release assay result or human immunodeficiency virus (HIV) status, and children 5 to 17 years of age were eligible if they had a positive interferon- γ release assay or HIV infection. Households were randomly assigned to a trial regimen, and children in the household received levofloxacin or placebo once daily for 24 weeks. The primary efficacy end point was incident tuberculosis, which included death from tuberculosis, by week 48 after randomization. The primary safety end point was any adverse event of grade 3 or higher during the treatment period that was at least possibly related to the trial regimen.

Results: Of 922 participants from 497 households, 453 were assigned to receive levofloxacin and 469 to placebo; 91.0% of the participants were younger than 5 years of age. At least 80% of the assigned doses of levofloxacin or placebo were received by 86% of the participants in each trial group. By week 48, tuberculosis had developed in 5 participants (1.1%) in the levofloxacin group and in 12 participants (2.6%) in the placebo group (hazard ratio, 0.44; 95% confidence interval [CI], 0.15 to 1.25). The results of sensitivity analyses were consistent with those of the primary analysis. Grade 3 or higher adverse events during the treatment period that were considered to be at least possibly related to the trial regimen occurred in 4 participants in the levofloxacin group and in 8 participants in the placebo group (hazard ratio, 0.52; 95% CI, 0.16 to 1.71). Grade 2 tendonitis occurred in 1 child in the levofloxacin group.

Conclusions: Although preventive treatment with levofloxacin led to a lower incidence of tuberculosis than placebo among children with household exposure to MDR tuberculosis, the difference was not significant.

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Levofloxacin for the Prevention of Multidrug-Resistant Tuberculosis in Vietnam

[Greg J Fox¹](#), [Nguyen Viet Nhung¹](#), [Nguyen Cam Binh¹](#), [Nguyen Binh Hoa¹](#), [Frances L Garden¹](#), [Andrea Benedetti¹](#), [Pham Ngoc Yen¹](#), [Nguyen Kim Cuong¹](#), [Emily L MacLean¹](#), [H Manisha Yapa¹](#), [David W Dowdy¹](#), [Nguyen Huu Lan¹](#), [Elyse Guevara-Rattray¹](#), [Pham Duc Cuong¹](#), [Ori Solomon¹](#), [Marcel A Behr¹](#), [Ben J Marais¹](#), [Steven M Graham¹](#), [Dick Menzies¹](#), [Nguyen Thu Anh¹](#), [Guy B Marks¹](#)

Abstract

Background: Prevention of drug-resistant tuberculosis is a global health priority. However, trials evaluating the effectiveness of treating *Mycobacterium tuberculosis* infection among contacts of persons with drug-resistant tuberculosis are lacking.

Methods: We conducted a double-blind, randomized, controlled trial comparing 6 months of daily levofloxacin (weight-based doses) with placebo to treat *M. tuberculosis* infection. The trial population comprised household contacts of persons with bacteriologically confirmed rifampicin-resistant or multidrug-resistant (MDR) tuberculosis in Vietnam. Contacts of any age with a positive tuberculin skin test or immunologic impairment were eligible. The primary end point was bacteriologically confirmed tuberculosis within 30 months.

Secondary end points included grade 3 or 4 adverse events, death from any cause, and acquired drug resistance.

Results: Of 3948 persons screened for eligibility, 61 (1.5%) had coprevalent tuberculosis (defined as active tuberculosis disease diagnosed before randomization) and 2041 underwent randomization. Of these 2041 participants, 1995 (97.7%) completed 30 months of follow-up, had a primary end-point event, or died. Confirmed tuberculosis occurred in 6 participants (0.6%) in the levofloxacin group and 11 (1.1%) in the placebo group (incidence rate ratio, 0.55; 95% confidence interval [CI], 0.19 to 1.62); this difference was not significant. There was little difference in grade 3 or 4 adverse events between the two groups (risk difference, 1.0 percentage point; 95% CI, -0.3 to 2.4). Adverse events of any grade were reported in 306 participants (31.9%) taking levofloxacin and 125 (13.0%) taking placebo (risk difference, 18.9 percentage points; 95% CI, 14.2 to 23.6). No acquired fluoroquinolone resistance was observed.

Conclusions: Although the incidence of tuberculosis was lower in the levofloxacin group than in the placebo group at 30 months, the difference was not significant.

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A Meta-Analysis of Levofloxacin for Contacts of Multidrug-Resistant Tuberculosis

[Trinh Duong¹](#), [Joanna Brigden¹](#), [H Simon Schaaf²](#), [Frances Garden³](#), [Ben J Marais⁴](#), [Thu Anh Nguyen^{4,5,6}](#), [Ian R White¹](#), [Diana M Gibb¹](#), [Nguyen Viet Nhung⁷](#), [Neil A Martinson^{8,9}](#), [Lee Fairlie¹⁰](#), [Leonardo Martinez¹¹](#), [Charlotte Layton¹](#), [Andrea Benedetti^{12,13}](#), [Guy B Marks^{3,5}](#), [Rebecca M Turner¹](#), [James A Seddon^{2,14}](#), [Anneke C Hesselink²](#), [Greg J Fox^{4,5,15}](#)

Abstract

Background: Data from randomized trials evaluating the effectiveness of tuberculosis (TB) preventive treatment for contacts of multidrug-resistant (MDR)-TB are lacking. Two recently published randomized trials that did not achieve statistical significance provide the opportunity for a meta-analysis.

Methods: We conducted combined analyses of two phase 3 trials of levofloxacin MDR-TB preventive treatment - Levofloxacin for the Prevention of Multidrug-Resistant Tuberculosis (VQUIN) trial and the Levofloxacin preventive treatment in children exposed to MDR-TB (TB-CHAMP) trial. Following MDR-TB household exposure, VQUIN enrolled mainly adults in Vietnam; TB-CHAMP enrolled mainly young children in South Africa. Random assignment in both trials was 1:1 at the household level to daily levofloxacin or placebo for 6 months. The primary outcome was incident TB by 54 weeks. We estimated the treatment effect overall using individual participant data meta-analysis.

Results: The VQUIN trial (n=2041) randomly assigned 1023 participants to levofloxacin and 1018 participants to placebo; TB-CHAMP (n=922) assigned 453 participants to levofloxacin and 469 participants to placebo. Median age was 40 years (interquartile range 28 to 52 years) in VQUIN and 2.8 years (interquartile range 1.3 to 4.2 years) in TB-CHAMP. Overall, 8 levofloxacin-group participants developed TB by 54 weeks versus 21 placebo-group participants; the relative difference in cumulative incidence was 0.41 (95% confidence interval [CI] 0.18 to 0.92; P=0.03). No association was observed between levofloxacin and grade 3 or above adverse events (risk ratio 1.07, 95% CI 0.70 to 1.65). Musculoskeletal events of any grade occurred more frequently in the levofloxacin group (risk ratio 6.36, 95% CI 4.30

to 9.42), but not among children under 10 years of age. Overall, four levofloxacin-group participants and three placebo-group participants had grade 3 events.

Conclusions: In this meta-analysis of two randomized trials, levofloxacin was associated with a 60% relative reduction in TB incidence among adult and child household MDR-TB contacts, but with an increased risk of musculoskeletal adverse events.

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Update on multidrug-resistant tuberculosis preventive therapy toward the global tuberculosis elimination

[Alberto Matteelli](#)¹, [Sofia Lovatti](#)², [Benedetta Rossi](#)³, [Luca Rossi](#)²

Abstract

Multidrug-resistant tuberculosis (MDR-TB), the deadliest form of tuberculosis (TB), has been included in the 2024 World Health Organization (WHO) priority list of antibiotic-resistant bacterial pathogens owing to its severe public health implications. Almost two billion people worldwide are infected with *Mycobacterium tuberculosis*; however, the share of MDR-*M. tuberculosis* remains uncertain. Mathematical modeling estimates that MDR-TB affects nearly three in every 1000 people worldwide, highlighting the urgent need to address TB preventive treatment (TPT) for contacts of MDR-TB cases. Before 2018, close monitoring of contacts of people with MDR-TB was recommended rather than TPT. However, considering the ethical and public health concerns associated with leaving infected individuals untreated, the WHO updated its guidelines in 2018, 2020, and 2022. Despite the limited evidence at the time, the WHO suggested considering quinolone-based TPT for selected high-risk cases. To close this gap in evidence, two large-scale prospective randomized controlled trials were conducted: VQUIN (VQUIN MDR Australia New Zealand Clinical Trials Registry number, ACTRN12616000215426) and TB-CHAMP (TB-CHAMP ISRCTN Registry number, ISRCTN92634082). Both trials evaluated the efficacy of levofloxacin (Lfx) compared with a placebo for MDR-TB after household exposure in adults and children. A combined meta-analysis of the two trials showed a 60% reduction in TB incidence in the Lfx group, and the difference was statistically significant. Based on these results, in 2024, the WHO recommended the use of 6 months of daily Lfx as a TPT for contacts exposed to MDR/rifampicin-resistant TB. This regimen is cost-effective, safe, demonstrates good efficacy, and does not interact with HIV therapies. Despite these promising results, pre-extensively drug-resistance (XDR)-TB (MDR-TB with documented resistance to quinolones) remains an emerging concern. Two ongoing trials will address this challenge: the PHOENix trial (PHOENix-MDR TB [NCT03568383](#)), which will evaluate the efficacy of delamanid compared with isoniazid for preventing M/XDR-TB after household exposure, and the BRANCH-TB trial ([NCT0656848](#)), which will assess the efficacy and safety of 1 month of bedaquiline regimen compared with WHO-recommended TPT regimens. Preventing MDR/rifampicin-resistant TB remains a significant challenge for the global elimination of TB. Although the recent WHO recommendation for 6 months of daily Lf is a promising step, expanding the TPT options for pre-XDR TB and addressing drug intolerance are critical. Ongoing and new trials are essential to develop alternative treatment and achieve TB elimination.

Int J Infect Dis. 2024 Oct;147:107196.

doi: 10.1016/j.ijid.2024.107196. Epub 2024 Jul 27.

Adherence to preventive treatment for latent tuberculosis infection in close contacts of pulmonary tuberculosis patients: A cluster-randomized controlled trial in China

[Hui Chen¹](#), [Hui Zhang¹](#), [Jun Cheng¹](#), [Dingyong Sun²](#), [Qiaozhi Wang³](#), [Chengguo Wu⁴](#), [Yushu Liu¹](#), [Yinyin Xia¹](#), [Caihong Xu¹](#), [Canyou Zhang⁵](#)

Abstract

Objectives: This study examined adherence rates to tuberculosis preventive treatment (TPT) among close contacts of individuals with pulmonary tuberculosis (PTB) and identified factors associated with TPT adherence in China.

Methods: A multicenter, cluster-randomized, open-label control trial was carried out across three sites involving 34 counties in China. Close contacts of bacteriologically confirmed rifampin and isoniazid-susceptible PTB cases were identified and screened for latent tuberculosis infection (LTBI). Eligible participants were randomly assigned to either the 3H₂P₂ group, which consisted of a 3-month, twice-weekly regimen of rifapentine and isoniazid, or the 6H group, which entailed a 6-month daily regimen of isoniazid. To assess the factors influencing adherence, a two-level logistic regression model was utilized.

Results: Out of the 2434 close contacts who initiated TPT, 2121 (87.1%) completed the regimen. Of the 313 individuals who did not complete TPT, 60.1% refused to continue, and 27.8% discontinued due to adverse effects. The two-level logistic regression model revealed several factors associated with enhanced TPT adherence: enrollment in the 3H₂P₂ group (odds ratio [OR] = 2.09), management by a TB dispensary responsible for TPT (OR = 2.55), supervision by healthcare workers (OR = 6.40), and clinician incentives (OR = 2.49). Conversely, the occurrence of any adverse effects (OR = 0.08) was identified as a risk factor for nonadherence.

Conclusion: Administering TPT to individuals with LTBI is feasible among close contacts. Adherence to TPT can be enhanced through shorter, safer treatment regimens and supportive interventions, such as directly supervised therapy for TPT recipients and incentives for healthcare providers managing TPT.

Clin Microbiol Infect. 2024 Nov;30(11):1410-1417.

doi: 10.1016/j.cmi.2024.06.024. Epub 2024 Jul 10.

One-month daily and three-month weekly rifapentine plus isoniazid are comparable in completion rate and safety for latent tuberculosis infection in non-HIV Population: a randomized controlled trial

[Hung-Ling Huang¹](#), [Meng-Rui Lee²](#), [Chih-Hsin Lee³](#), [Meng-Hsuan Cheng⁴](#), [Po-Liang Lu⁵](#), [Chau-Chyun Sheu⁶](#), [Jann-Yuan Wang⁷](#), [Inn-Wen Chong⁸](#), [Jinn-Moon Yang⁹](#)

Abstract

Objectives: The weekly rifapentine plus isoniazid for 3 months (3HP) improves completion rate of latent tuberculosis infection treatment, but flu-like symptoms are common. The novel 1HP regimen, involving daily rifapentine plus isoniazid for 28 days, has demonstrated low toxicity in HIV-infected populations. We aimed to investigate whether 1HP has a lower incidence rate of systemic drug reaction (SDR) compared with 3HP during treatment in non-HIV populations.

Methods: This randomized, multicentre trial compared the completion rate and risks of SDRs of 1HP and 3HP in aged ≥13 years non-HIV subjects with latent tuberculosis infection

between September 2019 and September 2023 (ClinicalTrials.gov: [NCT04094012](#)). We also investigated associations between SDRs and plasma levels of drugs and their metabolites.

Results: A total of 251 and 239 individuals were randomly assigned to 1HP and 3HP groups, respectively, with completion rates of 82.9% (208/251) and 84.5% (202/239), respectively. Among them, 12.7% (32/251) and 10.9% (26/239) of 1HP and 3HP groups experienced SDRs, respectively (p 0.522), predominantly urticaria in 1HP group (59.4% [19/32]) and flu-like syndrome in 3HP group (80.8% [21/26]). Among participants experiencing SDRs, 43.8% (14/32) and 34.6% (9/26) in 1HP and 3HP groups, respectively, completed treatment (p 0.470). Cutaneous reactions were more common in 1HP than 3HP group (32.7% [82/251] vs. 13.0% [31/239], p < 0.001). In 1HP group, urticaria was associated with a higher plasma desacetyl-rifapentine level (ug/mL) at both 2 (median [interquartile range]: 36.06 [17.46-50.79] vs. 22.94 [14.67-31.65], p 0.018) and 6 hours (26.13 [15.80-53.06] vs. 29.83 [18.13-34.01], p 0.047) after dosing.

Discussion: In non-HIV population, the incidence rate of SDR under 1HP is not lower than 3HP. Notably, urticaria, rather than flu-like syndrome, was the predominant SDR associated 1HP. The findings of this study underscore the feasibility of 1HP regimen in non-HIV populations with a high-completion rate exceeding 80%.

EClinicalMedicine. 2025 May 26;84:103259.

doi: 10.1016/j.eclim.2025.103259. eCollection 2025 Jun.

Innovative timing strategies for tuberculosis household contact investigation: cost-effectiveness analysis from a randomized trial in rural and urban South Africa (Kharituwe Study)

[Neenah Young¹](#), [Patrick Biché¹](#), [Mbali Mohlamonyane²](#), [Matshidiso Morolo³](#), [Babalwa Maholwana³](#), [Khatija Ahmed^{3,4,5}](#), [Neil Martinson^{2,6}](#), [Colleen F Hanrahan¹](#), [David W Dowdy¹](#)

Abstract

Background: Household contact investigation (HCI) for tuberculosis (TB) is recommended but often limited by resource constraints, particularly for individuals unavailable during business hours.

Methods: We conducted an economic evaluation from January 1, 2022, through December 31, 2022, nested within a randomized trial in South Africa ("Kharituwe") comparing standard HCI for TB and two novel strategies: HCI during holiday periods in a rural setting and off-peak HCI during weekends and evenings in an urban setting. Costs were derived from 2022 expenditures, and secondary TB cases were defined by positive sputum cultures. As a secondary outcome of the Kharituwe Study, we assessed the incremental cost-effectiveness ratio (ICER) of each strategy against a hypothetical no-HCI scenario from the health system perspective in 2022 US dollars. Cost-effectiveness was assessed using a country-specific willingness-to-pay threshold of US\$3015 per disability-adjusted life year (DALY) averted. The trial is registered with clinicaltrials.gov ([NCT04520113](#)).

Findings: Relative to a hypothetical no-HCI approach, standard HCI was estimated to cost US\$1400 [95% uncertainty interval (UI): \$1000-\$2100] per DALY averted in the urban setting and US\$3600 [95% UI: \$2500-\$5400] in the rural setting. Corresponding cost-effectiveness ratios were US\$1900 [95% UI: \$1300-\$2800] for off-peak (urban) and US\$6400 [\$3900-\$10,000] for holiday-based (rural) HCI. Personnel costs, travel costs (in the rural setting), and TB prevalence among contact persons were primary drivers of cost-effectiveness.

Interpretation: HCI for TB is likely cost-effective in urban South Africa and may be cost-effective in rural settings, which face barriers including long travel times and lower TB prevalence. Holiday-based HCI was not found to be cost-effective. Integrating HCI for TB into broader home-based interventions may improve cost-effectiveness.

Diagnosis of tuberculosis

Indian J Tuberc. 2024 Jul;71(3):269-275.

doi: 10.1016/j.ijtb.2023.05.006. Epub 2023 May 13.

[Impact of fine needle aspiration cytology strategy implemented at the microscopy center level for diagnosis of tuberculous lymphadenitis](#)

[Kalyan Khan](#)¹

Abstract

Introduction: In India, EPTB accounts for about 50% of TB cases especially in people living with HIV/AIDS. Microbiological confirmation is present in only about 15% of EPTB cases. Tuberculous Lymphadenitis is the most common form of EPTB in India, accounting for around 35% of EPTB cases. Fine needle aspiration cytology has been found to be highly sensitive and specific in the diagnosis of tuberculous lymphadenitis with 83-94% accuracy. The procedure of AFB detection is exactly the same for the FNAC obtained smears as for the presently examined sputum smears at the DMCs. The aim of the present study was to determine the feasibility and effectiveness of FNAC strategy implemented at DMC level for detection of tuberculous lymphadenitis cases.

Methods: The present study was a randomized cluster trial with one control and one intervention arm. At the intervention units (DMCs) all suspected tuberculous lymphadenitis cases was subjected to FNAC of the suspected superficial lymph nodes by the trained Medical Officers. The control group was free from any such intervention. Effectiveness and feasibility of FNAC strategy in the intervention group was determined by relevant indicators.

Results: At the seven intervention DMCs, FNAC was performed on a total number of 1298 suspected cases of Tuberculous Lymphadenitis. Among them 294 cases were selected in the intervention arm and 196 cases in the control arm. Intervals between advice of FNAC and performance of FNAC as well as start of therapy was significantly low in the intervention arm. Complication was insignificant. The concordance between FNAC reports generated at the DMCs and that at Medical College estimated by agreement measurement kappa (0.970) suggested a high level of agreement.

Conclusion: Implementation of FNAC strategy at the DMC level for detection of tuberculous lymphadenitis cases was found to be feasible as well as effective.

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[Molecular epidemiology of Mycobacterium tuberculosis across three distinct geographic sites in South Africa](#)

[Theresa S Ryckman^{1,2}](#), [Lincoln Hopkins³](#), [Linrui Tang⁴](#), [Patrick Biche^{2,3}](#), [Mbali Mohlamonyane⁵](#), [Matshidiso Morolo⁶](#), [Bareng Aletta Sanny Nonyane^{2,7}](#), [Khatija Ahmed^{6,8,9}](#), [Neil Martinson^{2,5,10}](#), [Colleen F Hanrahan^{2,3}](#), [Shaheed V Omar¹¹](#), [Barun Mathema⁴](#), [David W Dowdy^{2,3}](#)

Abstract

Background: Whole genome sequence (WGS) data can generate insights about Mycobacterium tuberculosis (Mtb) transmission. We used WGS and linked epidemiology data from a recent randomized trial to characterize Mtb relatedness across three geographically distinct South African sites.

Methods: We sequenced culture isolates from participants with culture-positive TB in the Kharituwe study, which evaluated household contact investigation strategies in one urban and two rural sites. We adapted a previous bioinformatic pipeline to clean, extract, and filter Mtb reads, perform reference alignment, calculate single nucleotide polymorphism (SNP) distances between isolates, and group isolates into clusters linked by recent transmission, based on three SNP-based cutoffs. Sequence data were linked to individual data on demographics and risk factors. We analyzed clustering across and within study sites and used log binomial regression to assess characteristics associated with clustering.

Results: At a cutoff of 12 SNPs, 213 out of 714 sequenced isolates passing quality control filters were clustered. While only 3 out of 45 pairs included participants from different sites, the majority of clusters with ≥ 4 participants included representation from at least 2 sites. Expanding to a 20-SNP cutoff revealed a large cluster containing 10% of isolates, with urban/rural representation mirroring that of all the isolates (61% urban, 39% rural). Participants from the urban site, TB household contacts, and participants reporting a history of incarceration were more likely to be in a cluster.

Conclusions: Observed clustering and strain diversity across sites indicate the presence of multiple ongoing and geographically dispersed outbreaks in this setting.

Tungiasis

PLoS Negl Trop Dis. 2024 Jul 23;18(7):e0012341.

doi: 10.1371/journal.pntd.0012341. eCollection 2024 Jul.

[A pilot study of dimeticone oils versus sodium carbonate treatment for tungiasis: A randomized cohort trial in Homa Bay County, Kenya](#)

[Kana Suzuki¹](#), [Yasuhiko Kamiya¹](#), [Chris Smith^{1,2}](#), [Satoshi Kaneko^{1,3}](#), [Gordon Okomo⁴](#), [Asiko Ongaya⁵](#), [Evans Amukoye⁵](#)

Abstract

Background: Tungiasis is a cutaneous parasitosis caused by the female flea *Tunga penetrans*. Two-component dimeticone (NYDA) is the only treatment for tungiasis recommended by the World Health Organization; however, this topical drug is not available in Kenya. In Western Kenya, sodium carbonate is commonly used in the treatment of tungiasis. This study evaluated the 7-day cure rates for tungiasis by comparing sodium carbonate and NYDA treatments in Homa Bay County, Kenya.

Methodology/principal findings: This was a randomized, observer-blinded, parallel-treatment cohort trial. Twenty-three eligible children with 126 flea infections were matched

and randomized. All participants received both treatments, with one treatment on each foot. We recorded all health conditions/information, including inflammation scores and adverse events. Observations were performed on days 3, 5, and 7 using a digital microscope to confirm dead or live fleas based on the viability signs. Twenty-three children aged 3-13 years were analyzed. The proportion of dead fleas on day 7 was higher after NYDA treatment than after 5% sodium carbonate treatment (87% versus 64%, respectively, $P = 0.01$). NYDA. Median survival was 5 days for both treatments; NYDA had significantly higher trend of flea non-viability rate than 5% sodium carbonate ($P < 0.01$). There were no significant differences in the inflammation score or pain/itchiness between the two treatments. On the last day, 14 children indicated their preference for NYDA in future treatment of tungiasis, whereas nine children preferred the 5% sodium carbonate solution.

Conclusions/significance: NYDA was significantly more effective than 5% sodium carbonate for tungiasis treatment. Both treatments were safe but the children preferred NYDA more. Future studies with more participants and an extended observation period are warranted to confirm our findings. The findings suggest that NYDA should be made more available in tungiasis endemic area.

Typhus

Ultrasound

Urinary tract infection

Urology

Vaccines and immunization

(see also deworming)

Vaccine coverage and administration

Indian Pediatr. 2024 Jul 23:S097475591600669.

Online ahead of print.

[Enhancing Coverage of Second Booster Dose of DPT Vaccine Coverage With Parental Education: A Cluster Randomized Approach](#)

[Rangasai Anirudh Neeli](#)¹, [Amit Kumar Satapathy](#)¹, [Arvind Kumar Singh](#)², [Bhagirathi Dwibedi](#)³

Abstract

Objectives: To assess the effect of a single clinic-based educational intervention session on parents of children aged 4.5 to 5.5 years on improving the coverage of a second booster dose

of the DPT vaccine. The secondary objective was to assess the coverage of second booster dose of the DPT vaccine among children aged > 6 years and to learn about the reasons behind such dropouts, if any.

Methods: The study was conducted in two phases. In the first phase, a cross-sectional study was conducted among children aged > 6 years who were attending pediatric OPD or IPD to determine the coverage of the second booster dose of DPT vaccine and possible reasons for dropout. This was followed by a clustered randomized trial evaluating the effect of an educational intervention (Clinic-based, single session) among parents of children aged 4.5 to 5.5 years to inform about counselling and audiovisual information for improving second DPT booster coverage.

Results: A total of 384 children were enrolled in the first phase, of which 233 (60.68%) were vaccinated. Subgroup analysis showed significant differences in the vaccine coverage between children from tribal dominant and non-tribal dominant districts (45.10% vs 63.06%, $P = 0.01$). Educational intervention resulted in higher vaccination coverage (77.24%) compared to 71.43% in the control arm ($P = 0.300$).

Conclusion: The current study showed low coverage for second booster of DPT vaccine. With educational intervention, the target immunization coverage could be attained early which has implications for reducing childhood morbidity due to vaccine-preventable diseases.

Vaccine. 2025 May 10:55:127039.

doi: 10.1016/j.vaccine.2025.127039. Epub 2025 Mar 25.

Refresher training in administering intradermal BCG-vaccine increased BCG-scarring rates in rural Guinea-Bissau

Julie Odgaard Vedel¹, Oides Furtado², Laerte Lima Almeida², Jailson Sydenei Dias Martins², Sanne Møller Thysen³, Andreas Møller Jensen⁴, Igualdino Da Silva Borges², Ane Bærent Fisker⁵

Abstract

Background: A correct vaccination technique is important for developing BCG scars. Having a BCG scar is associated with lower mortality among BCG-vaccinated children.

Aim: To compare BCG-scar prevalences among children vaccinated before and after refresher training in BCG vaccination technique.

Methods: BCG-scar prevalence is assessed through a health and demographic surveillance system in rural Guinea-Bissau. In the context of a randomised trial, staff at health facilities in three regions (intervention area) received refresher training on BCG vaccination technique. In a fourth region (control area) no training was implemented. In logistic regression models, we compared scar prevalence among children vaccinated before and after the training.

Results: BCG-scar prevalence increased from 75 % to 92 % (odds ratio (OR) = 4.19, 95 %CI 2.92-6.01) in the intervention area and from 71 % to 78 % (OR = 1.43, 95 %CI 0.89-2.29) in the control area (p-value for same increase: <0.001).

Conclusion: BCG scarring rates increased after training in vaccination technique.

Lancet Glob Health. 2024 Nov;12(11):e1860-e1870.

doi: 10.1016/S2214-109X(24)00340-1.

Schistosome and malaria exposure and urban-rural differences in vaccine responses in Uganda: a causal mediation analysis using data from three linked randomised controlled trials

[Agnes Natukunda¹](#), [Gyaviira Nkurunungi²](#), [Ludoviko Zirimenya³](#), [Jacent Nassuuna⁴](#), [Christopher Zziwa⁴](#), [Caroline Ninsiima⁴](#), [Josephine Tumusiime⁴](#), [Ruth Nyanzi⁴](#), [Milly Namutebi⁴](#), [Fred Kiwudhu⁴](#), [Govert J van Dam⁵](#), [Paul L A M Corstjens⁶](#), [Robert Kizindo⁴](#), [Ronald Nkangi⁴](#), [Joyce Kabagenyi⁴](#), [Beatrice Nassanga⁷](#), [Stephen Cose³](#), [Anne Wajja⁸](#), [Pontiano Kaleebu⁴](#), [Alison M Elliott³](#), [Emily L Webb⁹](#); [POPVAC trial team](#)

Abstract

Background: Vaccine immunogenicity and effectiveness vary geographically. Chronic immunomodulating parasitic infections including schistosomes and malaria have been hypothesised to be mediators of geographical variations.

Methods: We compared vaccine-specific immune responses between three Ugandan settings (schistosome-endemic rural, malaria-endemic rural, and urban) and did causal mediation analysis to assess the role of *Schistosoma mansoni* and malaria exposure in observed differences. We used data from the control groups of three linked randomised trials investigating the effects of intensive parasite treatment among schoolchildren. All participants received the BCG vaccine (week 0); yellow fever (YF-17D), oral typhoid (Ty21a), human papillomavirus (HPV; week 4); and HPV booster and tetanus-diphtheria (week 28). Primary outcomes were vaccine responses at week 8 and, for tetanus-diphtheria, week 52. We estimated the total effect (TE) of setting on vaccine responses and natural indirect effect (NIE) mediated through current or previous infection with *S. mansoni* or malaria, and baseline vaccine-specific responses.

Findings: We included 239 (43%) participants from the schistosomiasis-endemic setting, 171 (30%) from the malaria-endemic setting, and 151 (27%) from the urban setting. At week 8, vaccine responses were lower in rural settings: schistosomiasis-endemic versus urban settings (TE geometric mean ratio for YF-17D plaque reduction neutralisation at 50% (PRNT₅₀) titres 0.58 [95% CI 0.37 to 0.91], for S Typhi O-lipopolysaccharide-specific IgG 0.61 [0.40 to 0.93], and for tetanus-specific IgG 0.33 [0.22 to 0.51]); malaria-endemic versus urban settings (YF-17D 0.70 [0.49 to 0.99], S Typhi O-lipopolysaccharide-specific IgG 0.29 [0.20 to 0.43], and tetanus-specific IgG 0.53 [-0.35 to 0.80]). However, we found higher BCG-specific IFN γ responses in the malaria-endemic versus urban setting (1.54 [1.20 to 1.98]). The estimated NIEs of setting on vaccine responses mediated through previous and current *S. mansoni* and malaria were not statistically significant. For malaria-endemic versus urban settings, baseline vaccine-specific responses contributed to some but not all differences: S Typhi O-lipopolysaccharide-specific IgG at week 8 (57.9% mediated [38.6 to 77.2]) and week 52 (70.0% mediated [49.4 to 90.6]) and BCG at week 52 (46.4% mediated [-4.8 to 97.7]).

Interpretation: We found significant variation in vaccine response between urban and rural settings but could not confirm a causal role for schistosome or malaria exposure. Other exposures require consideration.

Comparison of Sucrose vs. Swaddling in Pain Management during Birth Dose of Hepatitis B Vaccine: A Randomized Control Trial

[Somashekhar M Nimbalkar¹](#), [Fenil A Thakkar²](#), [Jigar P Thacker²](#), [Ajay G Phatak³](#), [Mayur K Shinde³](#)

Abstract

Objectives: To evaluate the efficacy of pain management of 1 ml of 24% sucrose given orally compared to routine care given one minute before vaccination for reduction of pain.

Methods: This double-blind randomized controlled trial included term neonates visiting Pediatric OPD for immunization. Neonates were randomly assigned into two groups (Group A- Sucrose, Group B- Swaddling). Commercially available sucrose solution (StayHappy solution 24%) was given in a dose of 1 ml to the neonates. Video recording of the neonate's facial expression was done during the procedure. Duration of cry, latency of onset of cry as well Modified Neonatal Facial Coding Score (MFCS) were the outcome variables.

Results: The mean (SD) of birth weight and gestational age was 2729 (321.6) g and 38.24 (0.84) d, respectively. Analysis showed significant difference in total MFCS across the groups ($P < 0.001$). Total MFCS was significantly lower in sucrose group [4.88 (1.07) vs. 7.17 (0.95)]. The duration of cry (in seconds) was also found to be significantly lower in sucrose group.

Conclusions: Administration of 1 ml 24% sucrose one minute prior to immunization is efficacious in pain management during injectable immunization.

Vaccine demand and education

EBioMedicine. 2024 Dec 21;111:105520.

doi: 10.1016/j.ebiom.2024.105520. Online ahead of print.

The impact of information and communication technology on immunisation and immunisation programmes in low-income and middle-income countries: a systematic review and meta-analysis

[Mohini Zarekar¹](#), [Hussein Al-Shehabi²](#), [Rita Dörner²](#), [Heide Weishaar²](#), [Tessa Lennemann³](#), [Charbel El Bcheraoui⁴](#), [Andrea Bernasconi⁵](#)

Abstract

Background: Low-income and Middle-income Countries (LMIC) are continually working to ensure everyone can access life-saving vaccines. Recognising the considerable impact of Information and Communication Technology (ICT) in healthcare, we performed a systematic review and meta-analysis to summarise ICT effectiveness in improving vaccine delivery in LMICs.

Methods: A systematic search from January 2010 to August 2023 in MEDLINE, EMBASE, Cochrane Library, BMJ Health & Care Informatics, and grey literature was performed. This search focused on randomised controlled trials (RCTs), non-RCTs, observational, and mixed-methods studies in English, examining ICT's effects on childhood immunisation in LMICs. Risk of bias in RCTs and non-RCTs was assessed using the Joanna Briggs Institute tool, and mixed-methods studies were evaluated with the Mixed Methods Appraisal Tool. A meta-analysis summarised ICT's impact on third pentavalent dose coverage and full immunisation by age one. The study is registered with PROSPERO (CRD42023446062).

Findings: Of 6535 screened studies, 27 involving 354,979 children were included. All apart from one study demonstrated a positive impact on immunisation coverage and timeliness, completeness and accuracy of records, number of adverse events reporting, vaccine stockouts, and cold chain expansion. The meta-analysis demonstrated that reminders effectively improved coverage rate of the third dose of the pentavalent vaccine (OR 2.32, 95% CI 1.34-4.03) and the full immunisation at one year of age (OR 2.61, 95% CI 1.2-5.67) with significant degrees of heterogeneity, respectively I^2 82% and I^2 89%. Main concerns for bias in RCTs included unblinded outcome assessors and intervention providers. Interpreting quasi-experimental studies was more challenging due to the higher risk of baseline differences between study arms, statistical methods, and dropouts. Mixed-methods studies often lacked clarity in integrating qualitative and quantitative data.

Interpretation: This systematic review confirms the benefits of ICT in immunisation programmes by enhancing various stages of vaccine delivery. Specifically, reminders have been shown to enhance childhood immunisation coverage rates.

J Pediatr Health Care. 2024 Sep-Oct;38(5):727-736.

doi: 10.1016/j.pedhc.2024.03.002. Epub 2024 Mar 28.

Utilization of Mobile Reminders in Improving the Completeness and Timeliness of Routine Childhood Immunization in Kano Metropolis, Nigeria: A Randomized Controlled Trial

[Umar Yunusa](#), [Saleh Ngaski Garba](#), [Shannon E MacDonald](#), [Umar Lawal Bello](#), [Abdullahi Haruna Ibrahim](#), [Idris Abdulrashid](#), [Adamu Dalhatu](#), [Muhammad Awwal Ladan](#)

Abstract

Introduction: This study examined the effectiveness of mobile phone reminders in improving the completeness and timeliness of childhood immunization.

Method: We conducted a parallel arm cluster randomized controlled trial in four primary health care facilities in Nigeria. Reminders were sent to eligible participants in the intervention group at specific intervals when their children were scheduled to receive the vaccines administered at the sixth, 10, and 14 weeks after birth. Immunization records of all participants' children were then tracked to assess their immunization status.

Results: The immunization status of the intervention ($n = 275$) and control ($n = 261$) arms was analyzed. Completeness and timeliness of the vaccine series were significantly higher ($p < .001$) among children of participants in the intervention ($n = 169$, 61.5% and $n = 138$, 50.2%) than those in the control group ($n = 35$, 13.4% and $n = 13$, 5%) arm.

Discussion: Mobile phone reminders were established to be effective in increasing the completeness and timeliness of childhood immunization.

Indian Pediatr. 2024 Oct 15;61(10):953-959.

Epub 2024 Jul 23.

Enhancing Coverage of Second Booster Dose of DPT Vaccine Coverage With Parental Education: A Cluster Randomized Approach

[Rangasai Anirudh Neeli](#)¹, [Amit Kumar Satapathy](#)¹, [Arvind Kumar Singh](#)², [Bhagirathi Dwibedi](#)³

Abstract

Objective: To assess the effect of a single clinic-based educational intervention session on parents of children aged 4.5 to 5.5 years on improving the coverage of a second booster dose of the DPT vaccine. The secondary objective was to assess the coverage of second booster dose of the DPT vaccine among children aged > 6 years and to learn about the reasons behind such dropouts, if any.

Methods: The study was conducted in two phases. In the first phase, a cross-sectional study was conducted among children aged > 6 years who were attending the pediatric OPD or IPD to determine the coverage of the second booster dose of DPT vaccine and possible reasons for dropout. This was followed by a clustered randomized trial evaluating the effect of an educational intervention (clinic-based, single session) among parents of children aged 4.5 to 5.5 years for improving second DPT booster coverage.

Results: A total of 384 children were enrolled in the first phase, of which 233 (60.68%) were vaccinated. Subgroup analysis showed significant differences in the vaccine coverage between children from tribal-dominant and non-tribal-dominant districts (45.10% vs 63.06%, $P = 0.01$). Educational intervention resulted in higher vaccination coverage (77.24%) compared to 71.43% in the control arm ($P = 0.300$).

Conclusion: The current study showed low coverage for second booster of DPT vaccine. With educational intervention, the target immunization coverage could be attained early which has implications for reducing childhood morbidity due to vaccine-preventable diseases.

Am J Infect Control. 2024 Oct;52(10):1170-1175.

doi: 10.1016/j.ajic.2024.05.008. Epub 2024 May 18.

Predictors on parent's attitudes toward the measles-rubella (MR) vaccine in Jordan: An education program

[Dua'a Al-Maghairah¹](#), [Khitam Alsager²](#), [Mariam Kawafha³](#), [Samar Thabet Jallad⁴](#), [Abdelkader Al Kofahj⁵](#)

Abstract

Background: Vaccine hesitancy is considered 1 of the top 10 threats to global health. This study aims to assess the impact of an education program on parents' attitudes toward the measles-rubella vaccine.

Methods: A study was conducted with 250 parents using a randomized controlled trial design. The intervention group (125 parents) received training, education programs, and video, while the control group (125 parents) only received video. The Parent Attitudes about Childhood Vaccines (PACV) scale, including its behavior, safety and efficacy, and trust subscales, was used for pre-post assessment. This allowed for comparison between the groups and measurement of score differences. The PACV scale (range 0-42) identified vaccine hesitancy, with a score below 21 indicating "non-hesitant" and 21 or higher indicating "hesitant."

Results: The intervention group had a significant decrease in PACV scores after the program (17.54 ± 4.7 , $P = .001$), mainly in behavior, safety, efficacy, and trust (6.4 ± 3.6 , 9.8 ± 4.7 , 3.9 ± 2 ; $P = .001$, $.011$, $.002$). The control group showed no changes (23.6 ± 3.5 ; $P = .402$). Postintervention PACV score differences were significant ($t = 11.562$, $P = .001$).

Discussion: Findings indicate that the education program had a positive effect on changing vaccine hesitancy.

Vaccine-related adverse effects

BCG and other tuberculosis vaccines

(See also Vaccine - Tuberculosis vaccine)

Lancet Microbe. 2024 Dec 19:100961.

doi: 10.1016/j.lanmic.2024.100961. Online ahead of print.

Effectiveness of the primary Bacillus Calmette-Guérin vaccine against the risk of Mycobacterium tuberculosis infection and tuberculosis disease: a meta-analysis of individual participant data

[Puck T Pelzer¹](#), [Logan Stuck²](#), [Leonardo Martinez³](#), [Alexandra S Richards⁴](#), [Carlos Acuña-Villaorduña⁵](#), [Naomi E Aronson⁶](#), [Maryline Bonnet⁷](#), [Anna C Carvalho⁸](#), [Pei-Chun Chan⁹](#), [Li-Min Huang¹⁰](#), [Chi-Tai Fang¹¹](#), [Gavin Churchyard¹²](#), [Helena Del Corral-Londoño¹³](#), [Manjula Datta¹⁴](#), [Marcos A Espinal¹⁵](#), [Katherine Fielding¹⁶](#), [Andrew J Fiore-Gartland¹⁷](#), [Alberto Garcia-Basteiro¹⁸](#), [Willem Hanekom¹⁹](#), [Mark Hatherill²⁰](#), [Phillip C Hill²¹](#), [Helena Huerga²²](#), [Edward C Jones-López²³](#), [Afranio Kritski²⁴](#), [Anna M Mandalakas²⁵](#), [Punam Mangtani¹⁶](#), [Eduardo Martins Netto²⁶](#), [Harriet Mayanja²⁷](#), [Rufaida Mazahir²⁸](#), [Megan Murray²⁹](#), [Molebogeng Rangaka³⁰](#), [Thomas Scriba²⁰](#), [Jitendra Singh³¹](#), [Sarman Singh³²](#), [Catherine M Stein³³](#), [Johan Vekemans³⁴](#), [Lilly M Verhagen³⁵](#), [Julian A Villalba³⁶](#), [Anne Wajja²⁷](#), [Basilea Watson³⁷](#), [Richard G White⁴](#), [Frank G J Cobelens²](#)

Abstract

Background: Tuberculosis vaccine trials using disease as the primary endpoint are large, time consuming, and expensive. An earlier immunological measure of the protection against disease would accelerate tuberculosis vaccine development. We aimed to assess whether the effectiveness of the Bacillus Calmette-Guérin (BCG) vaccine for prevention of Mycobacterium tuberculosis infection was consistent with that for prevention of tuberculosis disease.

Methods: We conducted an individual participant data (IPD) meta-analysis on experimental and observational longitudinal studies before April 6, 2018, identified through systematic reviews, known to us through expert knowledge in the field, reporting on BCG vaccination status, M tuberculosis infection test (QuantiFERON IFN- γ release assay [IGRA] and tuberculin skin test [TST]), and tuberculosis incidence. Cohort studies were included only for countries with a mandatory neonatal BCG vaccination policy. Exclusion criteria were previous or current tuberculosis disease, HIV infection, tuberculosis preventive treatment usage, and for household contacts, a positive baseline IGRA or TST test and young children aged 0-2 years; for randomised controlled trials, TST results within 2 years after random assignment were excluded. We contacted the investigators of the identified studies to provide IPD. We compared the protective efficacy of the BCG vaccine against M tuberculosis infection with that against tuberculosis disease using mixed-effects, multivariable proportional hazards modelling, by study type, M tuberculosis infection test (IGRA and TST), cutoff for defining test positivity, age, sex, and latitude.

Findings: We identified 79 studies eligible for full screening and of these, IPD datasets from 14 studies were included in our analysis: 11 household contact studies (29 147 participants), two adolescent cohort studies (11 368 participants), and one randomised controlled trial

(2963 participants). Among 28 188 participants we found no protection by the BCG vaccine against TST conversion regardless of cutoff in any type of study. Among 1491 household contacts, but not among 5644 adolescents, the BCG vaccine protected against QuantiFERON conversion at the primary cutoff of 0.7 IU/mL or more with the adjusted hazard ratio (0.65, 95% CI 0.51-0.82) being consistent with that for protection against disease (0.68, 0.18-2.59). Protection against QuantiFERON conversion at cutoff of 0.35 IU/mL or more (0.64, 0.51-0.81) was similar.

Interpretation: Protection from the BCG vaccination against M tuberculosis infection, measured as QuantiFERON conversion, is inconsistent across different groups. Among groups with recent household exposure, QuantiFERON conversion is consistent with protection against disease and could be evaluated as a proxy for disease in tuberculosis vaccine trials. We found that TST lacks value for prevention in phase 2b proof-of-concept trials.

J Infect Dis. 2024 Oct 16;230(4):995-1003.

doi: 10.1093/infdis/jiae262.

Maternal Bacille Calmette-Guérin Scars and Mortality Risk for Male and Female Newborns: Observational Study From Guinea-Bissau

[Frederik Scholtz-Buchholzer^{1,2}](#), [Sebastian Nielsen^{1,2}](#), [Marcus Kjær Sørensen¹](#), [Gabriel Marciano Gomes¹](#), [Simon Hoff^{1,3}](#), [Anna Memborg Toft^{1,3}](#), [Elise Brenno Stjernholm¹](#), [Ivan Monteiro¹](#), [Peter Aaby¹](#), [Christine Stabell Benn^{1,2,4}](#)

Abstract

Background: Maternal priming with bacille Calmette-Guérin (BCG) has been associated with reduced mortality in male offspring. We investigated this association in a cohort of healthy BCG-vaccinated neonates.

Methods: This observational study within a randomized controlled trial comparing different BCG strains was conducted in Guinea-Bissau from 2017 to 2020. As part of trial inclusion procedures, on the day of discharge from the maternity ward, maternal BCG scar status was evaluated by visual inspection, followed by offspring BCG and polio vaccination. Through mortality data collected at telephone interviews at 6 weeks and 6 months of age, we assessed all-cause mortality risk in Cox proportional hazards models adjusted for maternal schooling and BCG strain, providing adjusted mortality rate ratios (aMRRs).

Results: In total, 64% (11 070/17 275) of mothers had a BCG scar, which was not associated with admission risk, admission severity, or all-cause mortality for females and the overall sample. By 6 months of age, the mortality rate (MR) was 4.1 (200 deaths/4919 person-years) for the maternal BCG scar cohort and 5.2 (139/2661) for no maternal scar (aMRR, 0.86; 95% Confidence Interval [CI], .69-1.06). In males, 6-month MRs were 4.3 (109 deaths/2531 person-years) for maternal BCG scar vs 6.3 (87/1376) for no scar (aMRR, 0.74; 95% CI, .56-.99). In females, 6-month MRs were 3.8 (91 deaths/2388 person-years) vs 4.0 (52/1286), respectively (aMRR, 1.04; 95% CI, .74-1.47; for interaction with sex, $P = .16$).

Conclusions: While we cannot rule out an association in females, being born to a mother with a BCG scar reduced the risk of death during early infancy for BCG-vaccinated males, reproducing findings from previous studies.

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doi: 10.1016/j.lanmic.2024.100961. Epub 2024 Dec 19.

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[Puck T Pelzer¹](#), [Logan Stuck²](#), [Leonardo Martinez³](#), [Alexandra S Richards⁴](#), [Carlos Acuña-Villaorduña⁵](#), [Naomi E Aronson⁶](#), [Maryline Bonnet⁷](#), [Anna C Carvalho⁸](#), [Pei-Chun Chan⁹](#), [Li-Min Huang¹⁰](#), [Chi-Tai Fang¹¹](#), [Gavin Churchyard¹²](#), [Helena Del Corral-Londoño¹³](#), [Manjula Datta¹⁴](#), [Marcos A Espinal¹⁵](#), [Katherine Fielding¹⁶](#), [Andrew J Fiore-Gartland¹⁷](#), [Alberto Garcia-Basteiro¹⁸](#), [Willem Hanekom¹⁹](#), [Mark Hatherill²⁰](#), [Phillip C Hill²¹](#), [Helena Huerga²²](#), [Edward C Jones-López²³](#), [Afranio Kritski²⁴](#), [Anna M Mandalakas²⁵](#), [Punam Mangtani¹⁶](#), [Eduardo Martins Netto²⁶](#), [Harriet Mayanja²⁷](#), [Rufaida Mazahir²⁸](#), [Megan Murray²⁹](#), [Molebogeng Rangaka³⁰](#), [Thomas Scriba²⁰](#), [Jitendra Singh³¹](#), [Sarman Singh³²](#), [Catherine M Stein³³](#), [Johan Vekemans³⁴](#), [Lilly M Verhagen³⁵](#), [Julian A Villalba³⁶](#), [Anne Wajja²⁷](#), [Basilea Watson³⁷](#), [Richard G White⁴](#), [Frank G J Cobelens²](#)

Abstract

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Interpretation: Protection from the BCG vaccination against M tuberculosis infection, measured as QuantiFERON conversion, is inconsistent across different groups. Among groups with recent household exposure, QuantiFERON conversion is consistent with protection against disease and could be evaluated as a proxy for disease in tuberculosis vaccine trials. We found that TST lacks value for prevention in phase 2b proof-of-concept trials.

Lancet Glob Health. 2024 Nov;12(11):e1849-e1859.

doi: 10.1016/S2214-109X(24)00282-1.

The effect of BCG revaccination on the response to unrelated vaccines in urban Ugandan adolescents (POPVAC C): an open-label, randomised controlled trial

[Jacent Nassuuna¹](#), [Ludoviko Zirimenya²](#), [Gyaviira Nkurunungi³](#), [Agnes Natukunda⁴](#), [Christopher Zziwa¹](#), [Caroline Ninsiima¹](#), [Barbara Apule¹](#), [Caroline Onen¹](#), [Susan Amongi¹](#), [Joel Serubanja¹](#), [Pius Tumwesige¹](#), [Denis Nsubuga¹](#), [Rebecca Amongin¹](#), [Govert J van Dam⁵](#), [Paul L A M Corstjens⁶](#), [John Kayiwa⁷](#), [Joyce Kabagenyi¹](#), [Stephen Cose²](#), [Anne Wajja⁸](#), [Pontiano Kaleebu¹](#), [Emily L Webb⁹](#), [Alison M Elliott²](#); [POPVAC trial team](#)

Abstract

Background: Immune responses induced by several important vaccines differ between populations, with reduced responses in low-income and rural settings compared with high-income and urban settings. BCG immunisation boosts immune responses to some unrelated vaccines in high-income populations. We aimed to test the hypothesis that BCG revaccination can enhance responses to unrelated vaccines in Ugandan schoolchildren.

Methods: We conducted an open-label, randomised controlled trial to compare the effects of BCG revaccination versus no BCG revaccination on the immunogenicity of subsequent unrelated vaccines among adolescents aged 13-17 years who are participants in an urban Ugandan birth cohort study, in which BCG vaccination was documented at birth. Participants were excluded if they had received any of the trial vaccines or related agents when aged 5 years or older. Computer-generated 1:1 randomisation was implemented in REDCap. Participants were excluded if they were concurrently enrolled in other trials; had a clinically significant history of immunodeficiency, or serious psychiatric conditions or moderate to severe acute illnesses; were taking immunosuppressive medications; had allergies to vaccine components, a predisposition towards developing keloid scarring; positive HIV tests or pregnancy tests; were female participants who were lactating; or if they planned to use investigational drugs, vaccines, blood products, or any combination thereof. Trial participants assigned to the BCG revaccination group received the live parenteral BCG-Russia vaccine (Serum Institute of India, Pune, India; 0.1 mL intradermally, right upper arm) at week 0. All participants received yellow fever vaccine (YF-17D; Sanofi Pasteur, Lyon, France; 0.5 mL intramuscularly, left upper arm), live oral typhoid vaccine (Ty21a; PaxVax, London, UK; one capsule per day taken for three alternate days), and quadrivalent virus-like particle human papillomavirus (HPV) vaccine (Merck, Rahway, NJ, USA; 0.5 mL intramuscularly, left upper arm) at week 4; and toxoid vaccines (tetanus-diphtheria; Serum Institute of India; 0.5 mL intramuscularly, left upper arm) and an HPV booster at week 28. An additional HPV vaccination at week 8 was provided to female participants older than 14 years who had not previously been vaccinated. The primary outcomes were yellow fever

neutralising antibody titres at 4 weeks post-YF-17D vaccination, *Salmonella enterica* serovar Typhi (henceforth S Typhi) O-lipopolysaccharide (O:LPS)-specific IgG concentration at 4 weeks post-Ty21a vaccination, and HPV-16 and HPV-18 L1 protein-specific IgG concentration at 4 weeks post-HPV vaccination. Primary outcome assays were conducted at week 8, and at week 52 for tetanus-diphtheria. We conducted an intention-to-treat analysis comparing log-transformed outcomes between trial groups, with results back-transformed to geometric mean ratios (GMRs). The safety population comprised all randomly allocated participants. The trial was registered at the ISRCTN Registry (ISRCTN10482904) and is complete.

Findings: Between Aug 31 and Oct 12, 2020, we screened 376 potential participants for eligibility. We enrolled and randomly allocated 300 participants to the two groups (151 [50%] to the BCG group and 149 [50%] to the no BCG group). 178 (59%) of 300 participants were male and 122 (41%) were female. 142 (91%) of 151 participants in the BCG group and 139 (93%) of 149 in the no BCG group completed follow-up. There was no effect of BCG revaccination, compared with no BCG revaccination, on the response observed for any vaccine. Yellow fever plaque reduction neutralising reference tests (PRNT₅₀) titres (the reciprocal of the last plasma dilution that reduced by 50%) had a GMR of 0.95 (95% CI 0.75-1.19; p=0.62) and PRNT₉₀ (reciprocal of the last plasma dilution that reduced by 90%) had a GMR of 0.94 (0.74-1.19; p=0.60); IgG to S Typhi O:LPS was 0.99 (0.80-1.23; p=0.94); IgG to HPV-16 was 0.97 (0.69-1.35; p=0.85) and to HPV-18 was 1.03 (0.76-1.40; p=0.83); and toxoid-specific IgG for tetanus was 1.13 (0.87-1.47; p=0.36) and was 1.00 (0.87-1.16; p=0.97) for diphtheria. There were no serious adverse events in either group.

Interpretation: We found no evidence that BCG revaccination is an effective strategy to improve immunogenicity of other vaccines in this low-income, urban setting.

EBioMedicine. 2025 Apr;114:105628.

doi: 10.1016/j.ebiom.2025.105628. Epub 2025 Mar 17.

Safety, reactogenicity, and immunogenicity of MTBVAC in infants: a phase 2a randomised, double-blind, dose-defining trial in a TB endemic setting

[Michele Tameris¹](#), [Virginie Rozot¹](#), [Claire Imbratta¹](#), [Hennie Geldenhuys¹](#), [Simon C Mendelsohn¹](#), [Angelique Kany Kany Luabeya¹](#), [Justin Shenje¹](#), [Nicolette Tredoux¹](#), [Michelle Fisher¹](#), [Humphrey Mulenga¹](#), [Nicole Bilek¹](#), [Carly Young¹](#), [Ashley Veldsman¹](#), [Natasja Botes¹](#), [Jelle Thole²](#), [Bernard Fritzell²](#), [Rajat Mukherjee³](#), [Ingrid Murillo Jelsbak²](#), [Ester Rodriguez²](#), [Eugenia Puentes²](#), [Juana Doce²](#), [Dessislava Marinova⁴](#), [Jesús Gonzalo-Asensio⁴](#), [Nacho Aguilo⁴](#), [Carlos Martin⁴](#), [Thomas J Scriba¹](#), [Mark Hatherill⁵](#); [MTBVAC 202 study team](#)

Abstract

Background: Safer and more effective tuberculosis (TB) vaccines than Bacille Calmette Guérin (BCG) are needed. We evaluated the safety, reactogenicity, and immunogenicity of three dose levels of the live-attenuated *Mycobacterium tuberculosis* (Mtb) vaccine, MTBVAC, compared to BCG, in South African infants.

Methods: Healthy, HIV-unexposed, BCG-naïve infants were randomised to receive a single intradermal dose of BCG (2.5×10^5 CFU, n = 24) or MTBVAC (2.5×10^4 , 2.5×10^5 , or 2.5×10^6 CFU, each n = 25). Safety endpoints were solicited systemic, solicited injection site, and unsolicited adverse events (AE), and serious AE (SAE). Immunogenicity was measured using

interferon- γ release assay (IGRA) and whole blood intracellular cytokine staining assay. Follow-up was 12 months post-vaccination.

Findings: Ninety-nine infants were enrolled between 18 February 2019 and 08 March 2021. Seventy-eight infants experienced reactogenicity AE (all mild except one grade 2 erythema). Induration, swelling, and erythema were more frequent as MTBVAC dose increased. All reactogenicity events were less frequent in infants receiving MTBVAC 2.5×10^5 CFU compared with BCG. Twelve infants (three BCG and nine MTBVAC recipients) experienced 14 vaccine-unrelated SAE, including one death due to bronchopneumonia (MTBVAC recipient). Eight infants were treated for unconfirmed pulmonary TB (four BCG and four MTBVAC 2.5×10^4 CFU recipients); one BCG recipient was treated for unconfirmed TB meningitis. MTBVAC was immunogenic at all 3 doses, inducing predominantly Th1-cytokine-expressing CD4 T cells, which peaked at Day 56. The 2.5×10^5 and 2.5×10^6 CFU MTBVAC doses induced similar response magnitudes and were more immunogenic than BCG. Day 56 IGRA conversion was observed in 61 (87.4%) infants receiving any MTBVAC dose, but only 28 (42.4%) remained positive by Day 365.

Interpretation: MTBVAC appeared safe, well-tolerated, and immunogenic at doses between 2.5×10^4 and 2.5×10^6 CFU in South African infants. The 2.5×10^5 CFU MTBVAC dose, being less reactogenic and more immunogenic than BCG, was selected for a multi-centre, phase 3 trial.

Cholera vaccine

Vaccine. 2025 May 10:55:126998.

doi: 10.1016/j.vaccine.2025.126998. Epub 2025 Apr 1.

[A double-blind, randomised phase III clinical trial to evaluate safety, immunogenicity, non-inferiority & lot to lot consistency of single component oral cholera vaccine BBV131 \(Hillchol®\) in comparison to Shanchol™](#)

[Krishna Mohan Vadrevu¹](#), [Abhishek Chavan²](#), [Amit Chawla³](#), [B S Chakravarthy⁴](#), [Chandramani Singh⁵](#), [Sagar Redkar⁶](#), [Savita Verma⁷](#), [Sriharsha Yandapally⁸](#), [M Suma Priya⁹](#), [Vasant Khalatkar¹⁰](#), [Vishal Tripathi¹¹](#), [Brunda Ganneru¹²](#), [Siddharth Reddy¹²](#), [Bhargav Reddy¹²](#), [Jan Holmgren¹³](#), [Badri Patnaik¹²](#), [Sai D Prasad¹²](#), [Raches Ella¹²](#)

Abstract

Background: Cholera is a vaccine-preventable disease that has faced a surge in outbreaks and a shortage of vaccines. The new generation oral cholera vaccine (OCV) BBV131, featuring a simplified single stable O1 Hikojima strain, aims to enhance production efficiency and affordability. This study evaluates BBV131's immune profile, safety, and non-inferiority compared to Shanchol™ in healthy adults and children. Adding BBV131 to the vaccine stockpile could improve supply, simplify logistics, and ease administration efforts.

Methods: In this randomised, modified, double-blind, multi-centre, phase III trial, 1800 participants were recruited across 10 clinical trial sites across India. Participants were stratified into three age groups (adults >18 years, children ≥ 5 to <18 years, and infants ≥ 1 to <5 years) and were randomised in a 3:1 ratio to receive either BBV131 or Shanchol™. All participants received two doses of the vaccine orally on days 0 and 14. Immunogenicity was

assessed through blood samples collected at baseline, two weeks after each dose, and follow-ups at days 28, 56, 90, and 180. The primary endpoint focused on the proportion of participants achieving >4-fold increase in vibriocidal antibody titres against Ogawa and Inaba serotypes 14 days post two doses. While secondary endpoints included Geometric Mean Titre (GMT) measurements and safety. Safety was evaluated throughout the study, reporting solicited and unsolicited adverse events (AEs). Another cohort of 1800 was added to the above study as an addendum to expand the safety database.

Findings: Of the 1800 enrolled participants, 1794 completed the study. Post-vaccination, the percentage of participants in the BBV131 group who exhibited a > 4-fold increase in anti-V. cholerae antibody titres were 68.25 % for Ogawa and 69.52 % for Inaba-demonstrating non-inferiority to Shanchol™, with a lower limit of 95 % CI above the non-inferiority margin. The safety profile revealed 257 AEs among 236 participants (13.1 %), with similar incidence across age groups and between vaccines; common AEs included dry mouth and headache.

Interpretation: The findings indicate that BBV131 demonstrates non-inferior immunogenicity and comparable safety to Shanchol™ in healthy Indian adults and children, supporting its potential as an effective OCV.

Covid-19 vaccine

Hum Vaccin Immunother. 2025 Dec;21(1):2450120.

doi: 10.1080/21645515.2025.2450120. Epub 2025 Jan 27.

Safety and immunogenicity of Ad26.COV2.S in adolescents: Phase 2 randomized clinical trial

[Jelena Tica¹](#), [Veronica V Rezelj²](#), [Benoit Baron³](#), [Vitalija van Paassen³](#), [Javier Zaidman⁴](#), [Lee Fairlie⁵](#), [Gert Scheper⁶](#), [Mathieu Le Gars²](#), [Frank Struyf⁷](#), [Macaya Douguih⁸](#), [Javier Ruiz-Guiñazú⁹](#); [COV3006 study group](#); [COV3006 Study Group Collaborators](#)

Abstract

We conducted a randomized, Phase 2 trial to assess the safety and humoral immunogenicity of reduced doses/dose volume of the standard dose of Ad26.COV2.S COVID-19 vaccine (5×10^{10} viral particles [vp]) in healthy adolescents aged 12-17 years. Participants were randomly assigned to receive Ad26.COV2.S at reduced dose levels of 0.625×10^{10} (0.5 mL), 1.25×10^{10} (0.5 mL) or 2.5×10^{10} (0.5 mL or low volume 0.25 mL) vp in a 1- or 2-dose (56-day interval) primary schedule. Adolescents who received a 1-dose primary schedule received a 2.5×10^{10} vp booster dose 6 months later. Safety and humoral immunogenicity were assessed up to 6 months post-last vaccination. All regimens were well tolerated, with no safety concerns identified. Local and systemic solicited AEs in adolescents were consistent with the known safety profile in adults. All 1- and 2-dose Ad26.COV2.S primary schedules elicited robust peak Spike-binding antibody responses and virus neutralizing titers against the reference strain, in participants with and without preexisting SARS-CoV-2 immunity. Immune responses were durable for at least 6 months. Spike-binding antibody responses were comparable to those elicited in young adults aged 18-25 years who received a standard dose of Ad26.COV2.S in Phase 3 efficacy studies. Reduced doses/dose volume of Ad26.COV2.S had an acceptable safety profile and elicited robust humoral immune responses in adolescents aged 12-17 years. All 1- and 2-dose schedules elicited Spike-binding antibody responses that were

comparable to an adult population in whom efficacy has been demonstrated using a higher vaccine dose.

Chikungunya virus vaccine

Lancet Infect Dis. 2025 Jan;25(1):114-125.

doi: 10.1016/S1473-3099(24)00458-4. Epub 2024 Sep 5.

Safety and immunogenicity of a live-attenuated chikungunya virus vaccine in endemic areas of Brazil: interim results of a double-blind, randomised, placebo-controlled phase 3 trial in adolescents

[Vera Buerger¹](#), [Sandra Hadl²](#), [Martina Schneider²](#), [Michaela Schaden²](#), [Romana Hochreiter²](#), [Annegret Bitzer²](#), [Karin Kosulin²](#), [Robert Mader³](#), [Oliver Zoihs²](#), [Andrea Pfeiffer²](#), [Ana Paula Loch⁴](#), [Eolo Morandi Jr⁴](#), [Mauricio Lacerda Nogueira⁵](#), [Carlos Alexandre Antunes de Brito⁶](#), [Julio Croda⁷](#), [Mauro Martins Teixeira⁸](#), [Ivo Castelo-Branco Coelho⁹](#), [Ricardo Gurgel¹⁰](#), [Allex Jardim da Fonseca¹¹](#), [Marcus Vinícius Guimarães de Lacerda¹²](#), [Edson Duarte Moreira Jr¹³](#), [Ana Paula Rocha Veiga¹⁴](#), [Katrin Dubischar²](#), [Nina Wressnigg²](#), [Susanne Eder-Lingelbach²](#), [Juan Carlos Jaramillo²](#)

Abstract

Background: Chikungunya outbreaks have been reported in Brazil since 2014. Adolescents are a sensitive population who would benefit from a prophylactic vaccine. This study assessed the immunogenicity and safety of the vaccine VLA1553 in adolescents in Brazil. With an overall trial duration of 12 months, we now report data on safety and immunogenicity over a period of 28 days after vaccination.

Methods: In this double-blind, randomised, placebo-controlled phase 3 trial, adolescents aged 12 to <18 years were recruited. The trial was performed at ten trial sites across Brazil. Eligible participants were generally healthy. The main exclusion criteria comprised immune-mediated or chronic arthritis or arthralgia, a known or suspected defect of the immune system, or any live vaccine received within the 4 weeks before trial vaccination.

Randomisation was stratified by baseline serostatus in a 2:1 ratio to receive VLA1553 (at a dose of 1×10^4 TCID₅₀ per 0.5 mL [ie, 50% tissue culture infectious dose]) or placebo. VLA1553 or placebo was administered intramuscularly as a single-dose immunisation on day 1. The primary endpoint was the proportion of baseline seronegative participants with chikungunya virus neutralising antibody levels of 150 or more in μ PRNT₅₀ (a micro plaque reduction neutralisation test), which was considered a surrogate of protection. The safety analysis included all participants receiving a trial vaccination. Immunogenicity analyses were performed in a subset. The trial is registered with ClinicalTrials.gov, [NCT04650399](#).

Findings: Between Feb 14, 2022, and March 14, 2023, 754 participants received a trial vaccination (502 received VLA1553 and 252 received placebo) with a per-protocol population of 351 participants for immunogenicity analyses (303 in the VLA1553 group and 48 in the placebo group). In participants who were seronegative at baseline, VLA1553 induced seroprotective chikungunya virus neutralising antibody levels in 247 of 250 (98.8%, 95% CI 96.5-99.8) participants 28 days after vaccination. In seropositive participants, the baseline seroprotection rate of 96.2% increased to 100% after vaccination with VLA1553. Most (365

[93%] of 393) adverse events were of mild or moderate intensity, VLA1553 was generally well tolerated. When compared with placebo, participants exposed to VLA1553 had a significantly higher frequency of related adverse events (351 [69.9%] of 502 vs 121 [48.0%] of 252; $p < 0.0001$), mostly headache, myalgia, fatigue, and fever. Among four reported serious adverse events (three in the VLA1553 group and one in the placebo group), one was classified as possibly related to VLA1553: a high-grade fever. Among 20 adverse events of special interest (ie, symptoms suggesting chikungunya-like disease), 16 were classified as related to trial vaccination (15 in the VLA1553 group and one in the placebo group), with severe symptoms reported in four participants (fever, headache, or arthralgia). 17 adverse events of special interest resolved within 1 week. Among 85 participants with arthralgia (68 in the VLA1553 group and 17 in the placebo group), eight adolescents had short-lived (range 1-5 days), mostly mild recurring episodes (seven in the VLA1553 group and one in the placebo group). The median duration of arthralgia was 1 day (range 1-5 days). The frequency of injection site adverse events for VLA1553 was higher than in the placebo group (161 [32%] vs 62 [25%]), but rarely severe (two [$<1\%$] in the VLA1553 group and one [$<1\%$] in the placebo group). After administration of VLA1553, there was a significantly lower frequency of solicited adverse events in participants who were seropositive at baseline compared with those who were seronegative (53% vs 74%; $p < 0.0001$) including headache, fatigue, fever, and arthralgia. **Interpretation:** VLA1553 was generally safe and induced seroprotective titres in almost all vaccinated adolescents with favourable safety data in adolescents who were seropositive at baseline. The data support the use of VLA1553 for the prevention of disease caused by the chikungunya virus among adolescents and in endemic areas.

Dengue vaccine

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Efficacy and safety of Butantan-DV in participants aged 2-59 years through an extended follow-up: results from a double-blind, randomised, placebo-controlled, phase 3, multicentre trial in Brazil

[Mauricio L Nogueira¹](#), [Monica A T Cintra²](#), [José A Moreira²](#), [Elizabeth G Patiño²](#), [Patricia Emilia Braga²](#), [Juliana C V Tenório²](#), [Lucas Bassolli de Oliveira Alves²](#), [Vanessa Infante²](#), [Daniela Haydee Ramos Silveira²](#), [Marcus Vínicius Guimarães de Lacerda³](#), [Dhelio Batista Pereira⁴](#), [Allex Jardim da Fonseca⁵](#), [Ricardo Queiroz Gurgel⁶](#), [Ivo Castelo-Branco Coelho⁷](#), [Cor Jesus Fernandes Fontes⁸](#), [Ernesto T A Marques⁹](#), [Gustavo Adolfo Sierra Romero¹⁰](#), [Mauro Martins Teixeira¹¹](#), [André M Siqueira¹²](#), [Viviane Sampaio Boaventura¹³](#), [Fabiano Ramos¹⁴](#), [Erivaldo Elias Júnior¹⁵](#), [José Cassio de Moraes¹⁶](#), [Stephen S Whitehead¹⁷](#), [Alejandra Esteves-Jaramillo¹⁸](#), [Tulin Shekar¹⁸](#), [Jung-Jin Lee¹⁸](#), [Julieta Macey¹⁹](#), [Sabrina Gozlan Kelner¹⁸](#), [Beth-Ann G Collier¹⁸](#), [Fernanda Castro Boulos²⁰](#), [Esper G Kallás²¹](#); [Phase 3 Butantan-DV Working Group](#)

Abstract

Background: A single-dose dengue vaccine that protects individuals across a wide age range and regardless of dengue serostatus is an unmet need. We assessed the safety and efficacy of the live, attenuated, tetravalent Butantan-dengue vaccine (Butantan-DV) in adults, adolescents, and children. We previously reported the primary and secondary efficacy and

safety endpoints in the initial 2 years of follow-up. Here we report the results through an extended follow-up period, with an average of 3·7 years of follow-up.

Methods: In this double-blind, randomised, placebo-controlled, phase 3, multicentre trial in Brazil, healthy participants (aged 2-59 years) who had not previously received a dengue vaccine were enrolled and randomly assigned 2:1 (stratified by age 18-59 years, 7-17 years, and 2-6 years) using a central electronic randomisation system to receive 0·5 mL of Butantan-DV (containing approximately 10^3 plaque-forming units of each of the four vaccine virus strains) or placebo, administered subcutaneously. Syringes containing vaccine or placebo were prepared by an unmasked trial pharmacist who was not involved in any subsequent participant assessments; other site staff and the participants remained unaware of the group allocations. Vaccine efficacy was calculated with the accrual of virologically confirmed dengue (VCD) cases (by RT-PCR) at least 28 days after vaccination up until the cutoff (at least 2 years of follow-up from the last participant enrolled). The primary endpoint was vaccine efficacy against VCD after day 28 by any dengue virus (DENV) serotype regardless of dengue serostatus at baseline in the per-protocol population. The primary and secondary safety endpoints up until day 21 were previously reported; secondary safety endpoints include the frequency of unsolicited vaccine-related adverse events after day 22. Safety analyses were done on all participants as treated. This trial is registered with ClinicalTrials.gov ([NCT02406729](https://clinicaltrials.gov/ct2/show/study/NCT02406729)) and is ongoing.

Findings: Of 16 363 participants assessed for eligibility, 16 235 were randomly assigned between Feb 22, 2016, and July 5, 2019, and received single-dose Butantan-DV (10 259 participants) or placebo (5976 participants). 16 162 participants (Butantan-DV n=10 215; placebo n=5947) were included in the per-protocol population and 16 235 (Butantan-DV n=10 259; placebo n=5976) in the safety population. At the data cutoff (July 13, 2021), participants had 2-5 years of follow-up (mean 3·7 years [SD 1·0], median 4·0 years [IQR 3·2-4·5]). 356 VCD cases were captured through the follow-up (128 in the vaccine group and 228 in the placebo group). Vaccine efficacy against VCD caused by any DENV serotype was 67·3% (95% CI 59·4-73·9); cases caused by DENV-3 or DENV-4 were not observed. The proportions of participants who had serious adverse events were similar between treatment groups (637 [6·2%] in the vaccine group and 395 [6·6%] in the placebo group) up until the cutoff.

Interpretation: A single dose of Butantan-DV was generally well tolerated and efficacious against symptomatic VCD (caused by DENV-1 and DENV-2) for a mean of 3·7 years. These findings support the continued development of Butantan-DV to prevent dengue disease in children, adolescents, and adults regardless of dengue serostatus.

Am J Trop Med Hyg. 2024 May 28;111(1):102-106.

doi: 10.4269/ajtmh.23-0549. Print 2024 Jul 3.

IgG, IgM, and Nonstructural Protein 1 Response Profiles after Receipt of Tetravalent Dengue Vaccine TAK-003 in a Phase 2 Randomized Controlled Trial

[Jenny G Low^{1,2}](#), [Helen M Oh³](#), [Yee-Sin Leo^{4,5}](#), [Shirin Kalimuddin^{1,2}](#), [Limin Wijaya¹](#), [Junxiong Pang^{4,5,6}](#), [Tau Hong Lee⁷](#), [Kelley J Moss⁸](#), [Manja Brose⁸](#), [Vianney Tricou⁹](#)

Abstract

The profiles of vaccine-induced dengue antibodies may differ from those produced following natural infection and could potentially interfere with the interpretation of diagnostic tests. We assessed anti-dengue IgG and IgM antibodies, and nonstructural protein 1 antigen

profiles in the serum of adults who received a single dose of the tetravalent dengue vaccine TAK-003 as either an initially developed high-dose formulation or the standard approved formulation in a phase 2 study in Singapore ([#NCT02425098](#)). Immunoglobulin G and IgM profiles during the first 30 days postvaccination varied by baseline serostatus (microneutralization assay). Nonstructural protein 1 antigen was not detected in the serum of any participants. Vaccine-induced IgG and IgM antibodies can affect serological confirmation of subsequent dengue infection in vaccinees. These results highlight the limitations of using serological tests for dengue diagnosis, particularly in a postvaccination setting, and emphasize the need for more sensitive antigen- and molecular-based testing for accurate dengue diagnosis.

Travel Med Infect Dis. 2025 May-Jun;65:102840.

doi: 10.1016/j.tmaid.2025.102840. Epub 2025 Mar 20.

[Operational challenges and lessons learned from conducting febrile surveillance in a long-term randomized dengue vaccine trial in Latin America and Asia-Pacific](#)

[Harald Pfaar¹](#), [Eduardo López-Medina²](#), [Ian Escudero³](#), [Yanee Hutagalung⁴](#), [Nicholas Roubinis¹](#), [Seloni Thakrar¹](#), [Charissa Fay Corazon Borja-Tabora⁵](#), [Vianney Tricou¹](#), [Suely Tuboi⁶](#)

Abstract

Background: In trials, dengue vaccine efficacy evaluation relies on participants presenting with febrile illness/clinically suspected dengue contacting the study site for sample collection and clinical assessment within a short timeframe. Here, we present key considerations to maintain high compliance with the febrile surveillance procedures in a trial that assessed TAK-003 efficacy.

Methods: DEN-301 ([NCT02747927](#)) is a randomized phase 3 trial in children/adolescents from eight dengue-endemic countries in Latin America (LATAM) and Asia-Pacific (APAC). Febrile surveillance consisted of weekly contact with the participant to identify cases of fever ($\geq 38^\circ\text{C}$; two of three consecutive days). Blood samples were collected for molecular testing, preferably ≤ 5 days of fever onset, together with thorough clinical assessment by the investigators. The data are presented descriptively.

Results: Of the 20,071 (LATAM, 11,080; APAC, 8991) participants who received TAK-003/placebo, 18,260 (91.0 %) completed 4.5 years of follow-up. The overall incidence of febrile illness was 30 (LATAM, 26.0; APAC, 35.1) cases per 100 person-years. The rate samples collected during the acute phase was 98.1 %. The overall rate of samples collected after 5 days of fever onset (missed/out-of-window) was 6 % (LATAM, 10 %; APAC, 2 %). A trend toward reduced missed/out-of-window samples was observed after implementing measures, such as transportation, engagement, and healthcare aid tailored per study site in 2017, which appeared to increase during the COVID-19 pandemic.

Conclusion: The design of the febrile surveillance protocol ensured high compliance in the trial. Maintaining engagement and access to healthcare beyond the protocol was important in improving febrile case evaluation ≤ 5 days of fever onset.

Ebola vaccine

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doi: 10.1016/j.jinf.2024.106237. Epub 2024 Aug 8.

[Replication, safety and immunogenicity of the vectored Ebola vaccine rVSV-ΔG-ZEBOV-GP in a sub-Saharan African paediatric population: A randomised controlled, open-label trial in children aged 1-12 years living in Lambaréné, Gabon](#)

[Ayodele Alabi](#)¹, [Kossiwa Kokou](#)², [Saidou Mahmoudou](#)², [Ranmali Kavishna](#)³, [Sravya S Nakka](#)³, [Sylvia Rothenberger](#)⁴, [Fungai P Musangomune](#)², [Bisola F Olubiyi](#)², [Juste C Bie-Ondo](#)², [Anita L Kabwende](#)², [Thirumalaisamy P Velavan](#)⁵; [VSV-EBOPPLUS Consortium](#); [Donata Medaglini](#)⁶, [Helder I Nakaya](#)⁷, [Olivier Engler](#)⁸, [Ali M Harandi](#)⁹, [Claire-Anne Siegrist](#)¹⁰, [Peter G Kremsner](#)¹¹, [Selidji T Agnandji](#)¹²

Abstract

Background: Unlike adults, children experienced stronger and longer vector replication in plasma and shedding in saliva following rVSVΔG-ZEBOV-GP vaccination. The resulting risks of immunosuppression or immune hyperactivation leading to increased Adverse Events (AEs) and altered antibody responses are concerns that have been addressed in the present manuscript.

Methods: Children aged 1-12 years living in Gabon received either rVSVΔG-ZEBOV-GP (ERVEBO®) vaccine or the varicella-zoster virus (VZV) vaccine (VZV). The concentration of rVSVΔG vector in blood and saliva, the occurrence of AEs up to day 28; the anti-rVSVΔG-ZEBOV-GP and anti-VZV IgG antibody titres, neutralising and avidity functions of anti-rVSVΔG-ZEBOV-GP by day 365; were assessed in serum. (PACTR202005733552021) **FINDINGS:** In the rVSVΔG-ZEBOV-GP group, 70% and 7% of children had >0 copies/ml of rVSVΔG respectively in plasma by day 3 and in saliva by day 14 after vaccination, with no detection on day 28. Significantly higher but transient AEs occurred in the rVSVΔG-ZEBOV-GP group. Both vaccines induced seroconversion on day 28 and sustainable IgG antibody titres by day 365. Avidity and neutralisation functions of the anti-rVSVΔG-ZEBOV-GP antibodies peaked at day 28 and were maintained by day 365.

Interpretation: The replication and shedding do not affect the favourable risk-benefit balance of the rVSVΔG-ZEBOV-GP in children.

Lancet Microbe. 2024 Oct 4:100923.

doi: 10.1016/S2666-5247(24)00163-0. Online ahead of print.

[Safety and immunogenicity of a delayed booster dose of the rVSVΔG-ZEBOV-GP vaccine for prevention of Ebola virus disease: a multicentre, open-label, phase 2 randomised controlled trial](#)

[Richard T Davey Jr](#)¹, [Gary L Collins](#)², [Nadine Rouphael](#)³, [Guillaume Poliquin](#)⁴, [Rosemary McConnell](#)⁵, [Gabrielle Grubbs](#)⁶, [Susan L Moir](#)⁷, [Joanne M Langley](#)⁸, [Marc Teitelbaum](#)⁹, [Angela L Hewlett](#)¹⁰, [Susan L F McLellan](#)¹¹, [Nahid Bhadelia](#)¹², [Vanessa N Raabe](#)¹³, [Mark J Mulligan](#)¹³, [Irina Maljkovic Berry](#)¹⁴, [Bonnie Dighe](#)¹⁴, [Jonathan R Kurtz](#)¹⁴, [Lisa E Hensley](#)¹⁴, [Nelson C E Dozier](#)¹⁴, [Lindsay C B Marron](#)¹⁴, [Alain DuChene](#)², [Jens H Kuhn](#)¹⁴, [Shawn K Brown](#)¹⁵, [Surender Khurana](#)⁶, [H Clifford Lane](#)⁷, [James D Neaton](#)²

Abstract

Background: rVSVΔG-ZEBOV-GP is the first approved vaccine with clinical efficacy against Ebola virus disease. Although a seroprotective threshold has not been defined for those at occupational risk of exposure, the current vaccine strategy is to attain a sustained high level of antibody titres. The aim of this trial was to explore the effects of delayed boosting upon both the height and duration of antibody titres following primary immunisation.

Methods: In this open-label phase 2 randomised controlled trial, we compared antibody titres at month 36 in participants who had received a homologous booster dose at month 18 following primary immunisation with those who had received no booster. From Oct 25, 2016, to Jan 29, 2020, healthy adults aged 18 years or older deemed at occupational risk of exposure to Ebola virus due to laboratory work, clinical duties, or travel to an active endemic region were recruited from four hospital clinics in the USA and one hospital clinic in Canada and received primary vaccination with 2×10^7 plaque-forming unit per mL of VSVΔG-ZEBOV-GP. 18 months later, individuals who consented and were still eligible were randomly assigned 1:1 to receive either a homologous booster dose or no booster. Study visits for safety and serial blood collections for antibody titres were done on enrolled participants at months 0, 1, 3, 6, 12, 18, 19, 24, 30, and 36. Through July, 2021, a web-based application was used for randomisation, including assignments with schedules for each of the five sites using mixed permuted blocks. The trial was not masked to participants or site staff. The primary endpoint was a comparison of geometric mean titres (GMTs) of anti-Ebola virus glycoprotein IgG antibody at month 36 (ie, 18 months after randomisation) for all randomly assigned participants who completed the 36 months of follow-up (primary analysis cohort). Investigators were aware of antibody titres from baseline (enrolment) through month 18 but were masked to summary data by randomisation group after month 18. This study is registered with ClinicalTrials.gov ([NCT02788227](https://clinicaltrials.gov/ct2/show/study/NCT02788227)).

Findings: Of the 248 participants who enrolled and received their primary immunisation, 114 proceeded to the randomisation step at month 18. The two randomisation groups were balanced: 57 participants (24 [42%] of whom were female; median age was 42 years [IQR 35-50]) were randomly assigned to the booster group and 57 (24 [42%] of whom were female; median age was 42 years [IQR 36-51]) to the no-booster group. Of those randomly assigned, 92 participants (45 in the booster group and 47 in the no-booster group) completed 36 months of follow-up. At 18 months after primary immunisation, GMTs in the no-booster group increased from a baseline of 10 ELISA units (EU)/mL (95% CI 7-14) to 1451 EU/mL (1118-1882); GMTs in the booster group increased from 9 EU/mL (6-16) to 1769 EU/mL (1348-2321). At month 19, GMTs were 31 408 EU/mL (23 181-42 554) for the booster group and 1406 EU/mL (1078-1833) for the no-booster group; at month 36, GMTs were 10 146 EU/mL (7960-12 933) for the booster group and 1240 EU/mL (984-1563) for the no-booster group. Accordingly, the geometric mean ratio (GMR) of antibody titres had increased almost 21-fold more in the booster versus no-booster group at 1 month after booster administration (GMR 20·6; 95% CI 18·2-23·0; $p < 0·0001$) and was still over 7-fold higher at month 36 (GMR 7·8; 95% CI 5·5-10·2; $p < 0·0001$). Consistent with previous reports of this vaccine's side-effects, transient mono-articular or oligo-articular arthritis was diagnosed in 18 (9%) of 207 primary vaccination recipients; after randomisation, arthritis was diagnosed in one (2%) of 57 participants in the no-booster group. No new cases of arthritis developed after booster administration. Four serious adverse events occurred following randomisation: one (epistaxis) in the booster group and three (gastrointestinal haemorrhage, prostate cancer, and tachyarrhythmia) in the no-booster group. None of the serious adverse events was judged attributable to the booster vaccination assignment.

Interpretation: In addition to no new safety concerns and in marked contrast to earlier trials evaluating short-term boosting, delaying a rVSVΔG-ZEBOV-GP booster until month 18 resulted in an increase in GMT that remained several-fold above the no-booster group GMT for at least 18 months. These findings could have implications for defining the optimal timing of booster doses as pre-exposure prophylaxis in populations at ongoing risk for Ebola virus exposure.

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Evaluation of waning of IgG antibody responses after rVSVΔG-ZEBOV-GP and Ad26.ZEBOV, MVA-BN-Filo Ebola virus disease vaccines: a modelling study from the PREVAC randomized trial

[Simon Valayer^{1,2}](#), [Marie Alexandre^{2,3}](#), [Mélanie Prague^{2,3}](#), [Abdoul Habib Beavogui⁴](#), [Seydou Doumbia⁵](#), [Mark Kieh⁶](#), [Brian Greenwood⁷](#), [Bailah Leigh⁸](#), [Marie Poupelin²](#), [Christine Schwimmer⁹](#), [Samba O Sow¹⁰](#), [Irina Maljkovic Berry¹¹](#), [Jens H Kuhn¹¹](#), [Daniela Fusco^{12,13}](#), [Natasha Dubois Cauwelaert¹⁴](#), [Deborah Watson-Jones⁷](#), [Rodolphe Thiébaut^{2,3,9,15}](#), [Yves Lévy^{3,14,16}](#), [Yazdan Yazdanpanah^{1,14,17}](#), [Laura Richert^{2,3,9,15}](#), [Edouard Lhomme^{2,3,9,15}](#); [PREVAC Study Team¹](#)

Abstract

rVSVΔG-ZEBOV-GP and Ad26.ZEBOV, MVA-BN-Filo are WHO-prequalified vaccination regimens against Ebola virus disease (EVD). Challenges associated with measuring long-term clinical protection warrant the evaluation of immune response kinetics after vaccination. Data from a large phase 2 randomized double-blind clinical trial (PREVAC) were used to evaluate waning of anti-Ebola virus (EBOV) glycoprotein (GP_{1,2}) antibody concentrations after rVSVΔG-ZEBOV-GP or Ad26.ZEBOV, MVA-BN-Filo vaccination with linear mixed-effect regression models. After a post-vaccination peak, each vaccination strategy was associated with a decrease of anti-EBOV GP_{1,2} antibody concentrations with distinct kinetics, highlighting a less-rapid decline in antibody levels after vaccination by rVSVΔG-ZEBOV-GP. One year after administration of the vaccine, antibody concentrations were higher in children compared to adults for both vaccines, although with different effect sizes: 1.74-fold higher concentrations (95% confidence interval [CI] [1.48; 2.02]) for children 12-17 years old to 3.10-fold higher concentrations (95% CI [2.58; 3.69]) for those 1-4 years old compared to adults for Ad26.ZEBOV, MVA-BN-Filo versus 1.36-fold (95% CI [1.12; 1.61]) to 1.41-fold (95% CI [1.21; 1.62]) higher at month 12 higher than these values for adults, with relatively small changes from one age category of children to another for rVSVΔG-ZEBOV-GP. Antibody concentrations also differed according to geographical location, pre-vaccination antibody concentration, and sex. In combination with knowledge on memory response, characterization of the major determinants of immune response durability of both vaccinations may guide future EVD control protocols

Enterovirus 71 vaccine

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The efficacy and effectiveness of enterovirus A71 vaccines against hand, foot, and mouth disease: A systematic review and meta-analysis

[Xuemei Yan¹](#), [Yuanhua Liu²](#), [Fengkun Chen²](#), [Zhaorui Chang³](#), [Zhijie Zhang²](#), [Margarita Pons-Salort¹](#), [Nicholas C Grassly¹](#)

Abstract

Enterovirus A71 (EV-A71) is a major cause of severe hand, foot, and mouth disease (HFMD) among children in the Asia-Pacific region. Here we review randomised clinical trial data and post-licensure effectiveness studies of inactivated EV-A71 vaccines following their development and licensure in China since late 2015. We searched PubMed, Web of Science Core Collection, Elsevier ScienceDirect, China National Knowledge Infrastructure (CNKI), and Wanfang Data on 20 May 2024 with no date restriction in English and Mandarin, using key terms including "EV-A71", "enterovirus 71", "hand, foot, and mouth disease", "HFMD", "vaccine", "efficacy", "effectiveness", "protection" and "impact". Phase III randomized controlled trials (RCTs) reporting vaccine efficacy and observational studies on effectiveness were eligible for inclusion. We excluded studies that evaluated non-laboratory confirmed HFMD associated outcomes, abstracts, reviews, comments, animal studies, cross-sectional studies, and modelling studies. Summary measures of vaccine efficacy and effectiveness were based on random-effects models. After screening, 14 articles were eligible for inclusion, including 6 reporting 4 different phase III RCTs. Estimated efficacy of 2 doses of EV-A71 vaccine against EV-A71 associated HFMD 1 year after vaccination ranged from 90.0% to 97.9%, with an overall estimate for all products of 95.6% (95% Confidence Interval: 92.1, 97.5). Efficacy remained high at 26 months post-vaccination, ranging from 94.7% to 94.8%. The estimated overall effectiveness of 2-dose vaccination against any EV-A71-HFMD across five test-negative case-control studies was 84.3% (95% CI: 75.2, 90.0) among children aged 0-12 years. Effectiveness was higher in older children compared to younger children (85.3% (72.9, 92.1) vs. 79.8% (61.2, 89.5)) and higher against severe compared with non-severe EV-A71-HFMD (90.0% (80.0, 95.0) vs. 76.5% (50.0, 89.0)). The effectiveness declined in more recent studies with longer follow-up. Inactivated EV-A71 vaccines offer a high level of protection against EV-A71 HFMD. Longer term studies are needed to evaluate the persistence of protection beyond 2 years post-vaccination.

Haemophilus influenzae type b vaccine

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Disparate kinetics in immune response of two different *Haemophilus influenzae* type b conjugate vaccines: Immunogenicity and safety observations from a randomized controlled phase IV study in healthy infants and toddlers using a 2+1 schedule

[Federico Martínón-Torres^{1,2,3}](#), [Ignacio Salamanca de la Cueva⁴](#), [Michael Horn⁵](#), [Soeren Westerholt⁶](#), [Samantha Bosis⁷](#), [Nadia Meyer⁸](#), [Brigitte Cheuvart⁸](#), [Navpreet Virk⁹](#), [Rupert W Jakes¹⁰](#), [Maurine Duchenne⁸](#), [Peter Van den Steen⁸](#)

Abstract

Since the introduction of *Haemophilus Influenzae* type b (Hib) conjugate vaccines, invasive Hib disease has strongly declined worldwide, yet continued control of Hib disease remains

important. In Europe, currently three different hexavalent combination vaccines containing Hib conjugates are marketed. In this phase IV, single-blind, randomized, controlled, multi-country study ([NCT04535037](#)), we aimed to compare, in a 2 + 1 vaccination schedule, the immunogenicity and safety and show non-inferiority, as well as superiority, of DTPa-HBV-IPV/Hib (Ih group) versus DTaP5-HB-IPV-Hib (Va group) in terms of anti-polyribosylribitol phosphate (PRP) antibody geometric mean concentrations (GMCs) and proportion of participants reaching anti-PRP antibody concentrations greater than or equal to a threshold of 5 µg/mL. One month after the booster vaccination, the anti-PRP antibody GMC ratio (Ih group/Va group) was 0.917 (95% CI: 0.710-1.185), meeting the non-inferiority criteria. The difference in percentage of participants (Ih group - Va group) reaching GMCs ≥5 µg/mL was -6.3% (95% CI: -14.1% to 1.5%), not reaching the predefined non-inferiority threshold. Interestingly, a slightly higher post-booster antibody avidity was observed in the Ih group versus the Va group. Both vaccines were well tolerated, and no safety concerns were raised. This study illustrates the different kinetics of the anti-PRP antibody response post-primary and post-booster using the two vaccines containing different Hib conjugates and indicates a potential differential impact of concomitant vaccinations on the anti-PRP responses. The clinical implications of these differences should be further studied.

Hepatitis A vaccine

Hepatitis B vaccine

J Viral Hepat. 2024 Sep 24.

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Immunogenicity of a Birth Dose of Hepatitis B Vaccine in Kinshasa, Democratic Republic of Congo: A Randomised, Controlled Trial

[Samantha E Tulenko¹](#), [Patrick Ngimbi²](#), [Kashamuka Mwandagaliwa²](#), [Martine Tabala²](#), [Jolie Matondo²](#), [Sarah Ntambua²](#), [Nana Mbonze²](#), [Charles Mbendi³](#), [Christophe Luhata⁴](#), [Ravi Jhaveri⁵](#), [Jessie K Edwards¹](#), [Sylvia Becker-Dreps^{1,6}](#), [Ann M Moormann⁷](#), [Didine Kaba²](#), [Marcel Yotebieng⁸](#), [Jonathan B Parr⁹](#), [Emily W Gower¹](#), [Peyton Thompson¹⁰](#)

Abstract

The WHO recommends hepatitis B birth-dose vaccination (HepB-BD), but it is not routinely given in most sub-Saharan African countries. We aimed to assess the immunogenicity of HepB-BD in addition to the existing hepatitis B vaccine (HepB3) schedule in Kinshasa, Democratic Republic of Congo among HBV-unexposed and HBV-exposed infants. Using an open-label, randomised, controlled design, HBV-unexposed infants were randomised (1:1) to receive the standard HepB3 vaccine series (group U3), or to receive HepB-BD in addition to HepB3 (group U4). A supplemental cohort of HBV-exposed infants (group E4) received HepB-BD and HepB3. We compared the proportion of infants with protective antibodies against HBV (HBV surface antibody ≥ 10 mIU/mL) between groups U3 and U4 and groups U4 and E4 at 12 months of age. Between August 20 and October 9, 2019, we enrolled 281 mother/infant dyads; 88 (31.3%) returned at 12 months. Most infants had protective antibodies against HBV at 12 months: 92.9% (75.7%-98.2%) in group U3, 85.7% (67.5%-94.5%) in group U4 and 96.9% (95% CI: 81.2%-99.6%) in group E4. Trends held in estimates adjusted for loss-to-follow-up (LTFU) and baseline imbalance across groups. In this first randomised trial assessing the

addition of HepB-BD to the hepatitis B vaccine schedule in SSA, we found that HBV-unexposed infants who received the 3-dose and 4-dose vaccine series had similar immunogenicity against HBV at 12 months. A high proportion of infants, and notably HBV-exposed infants, had protective antibodies. Though extrapolation of findings may be limited by LTFU, this study adds real-world evidence regarding HepB-BD implementation in sub-Saharan Africa.

Vaccine. 2024 Oct 18;42(26):126461.

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[A prospective, multicenter study of hepatitis B birth-dose vaccine with or without hepatitis B immunoglobulin in preventing mother-to-child transmission of hepatitis B virus in Ethiopia](#)

[Mebrihit Arefaine](#)¹, [Asgeir Johannessen](#)², [Tilahun Teklehaymanot](#)³, [Adane Mihret](#)⁴, [Dawit Hailu Alemayehu](#)⁴, [Mahlet Osman](#)⁴, [Andargachew Mulu](#)⁴, [Nega Berhe](#)⁵

Abstract

Background: Historically, mother-to-child transmission (MTCT) of hepatitis B virus (HBV) was considered uncommon in Africa, leading to a reluctant attitude to birth-dose HBV vaccination on the continent. As a randomized trial would be unethical, real-life data are needed to assess the effect of HBV birth-dose vaccine in Africa.

Methods: A multicenter, prospective, observational study of hepatitis B surface antigen (HBsAg)-positive pregnant women and their infants was carried out in Ethiopia, from January 2019 to May 2021. Pregnant women were screened for HBsAg and HIV as part of routine antenatal care and/or delivery, and HBsAg-positive HIV-negative pregnant women were included in the study. HBV birth-dose vaccine and hepatitis B immunoglobulin (HBIG) were recommended but not all newborns received it as it was not national policy. All infants, however, received the pentavalent HBV vaccine at 6, 10, and 14 weeks of age. Vaccination status was confirmed from delivery ward charts and infant vaccination certificates. Infants were tested for HBsAg at 9 months of age and a positive result was taken as evidence of MTCT.

Findings: Of 290 HBsAg-positive pregnant women, 168 mother/infant pairs returned for their 9-month follow-up visit and were included in this analysis. Two of 112 (1.8 %) infants who received birth-dose vaccine with HBIG, and 2 of 23 (8.7 %) who received birth-dose vaccine alone were HBsAg positive at nine months of age, compared to 8 of 33 (24.2 %) who received neither vaccine nor HBIG at birth ($p = 0.002$). High maternal viral load ($>200,000$ IU/ml; adjusted odds ratio [AOR] 10.4; 95 % confidence interval [CI] 1.2-92.1) and not receiving HBV birth-dose vaccine nor HBIG (AOR 29.2; 95 % CI 4.0-211.3) were independent predictors of MTCT.

Interpretation: Birth-dose HBV vaccine with or without HBIG significantly reduced the risk of MTCT of HBV in Ethiopia. Improved coverage of birth-dose HBV vaccine should be an urgent priority.

HIV vaccine

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Safety and implementation of phase I randomized GLA-SE-adjuvanted CH505TF gp120 HIV vaccine trial in newborns

[Avy Violari¹](#), [Kennedy Ot wombe¹](#), [William Hahn^{2,3}](#), [Shiyu Chen²](#), [Deirdre Josipovic¹](#), [Vuyelwa Baba⁴](#), [Asimenia Angelidou⁵](#), [Kinga K Smolen^{5,6}](#), [Ofer Levy^{5,6}](#), [Nonhlanhla N Mkhize^{7,8}](#), [Amanda S Woodward Davis²](#), [Troy M Martin²](#), [Barton F Haynes⁹](#), [Wilton B Williams¹⁰](#), [Zachary K Sagawa¹¹](#), [James G Kublin²](#), [Laura Polakowski¹²](#), [Margaret Brewinski Isaacs¹²](#), [Catherine Yen¹²](#), [Georgia Tomaras¹³](#), [Lawrence Corey²](#), [Holly Janes²](#), [Glenda E Gray^{1,14}](#)

Abstract

BACKGROUND. The neonatal immune system is uniquely poised to generate broadly neutralizing antibodies (bnAbs), and thus infants are ideal for evaluating HIV vaccine candidates. We present the design and safety of a new-in-infants glucopyranosyl lipid A-stable emulsion (GLA-SE) adjuvant admixed with a first-in-infant CH505 transmitter-founder (CH505TF) gp120 immunogen designed to induce precursors for bnAbs against HIV.

METHODS. HIV Vaccine Trials Network 135 is a phase I randomized, placebo-controlled trial of CH505TF plus GLA-SE or placebo. Healthy infants aged ≤ 5 days, born to mothers living with HIV but HIV nucleic acid-negative at birth, were randomized to 5 doses of CH505TF plus GLA-SE or placebo at birth and 8, 16, 32, and 54 weeks.

RESULTS. Thirty-eight infants (median age 4 days; interquartile range 4-4.75 days) were enrolled November 2020 to January 2022. Among 28 infants assigned to receive CH505TF plus GLA-SE and 10 assigned to receive placebo, most completed the 5-dose immunization series (32/38) and follow-up (35/38). Solicited local and systemic reactions were more frequent in vaccine (8, 28.6% local; 16, 57.1% systemic) versus placebo recipients (1, 10% local, $P = 0.25$; 4, 40.0% systemic, $P = 0.38$). All events were grade 1 except 2 grade 2 events (pain, lethargy). Serious vaccine-related adverse events were not recorded.

CONCLUSION. This study illustrates the feasibility of conducting trials of new-in-infants adjuvanted HIV vaccines in HIV-exposed infants receiving standard infant vaccinations. The safety profile of the CH505TF plus GLA-SE vaccine was reassuring.

Hepatitis E vaccine

Lancet Glob Health. 2024 Aug;12(8):e1300-e1311.

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Receipt of hepatitis E vaccine and fetal loss in rural Bangladesh: further analysis of a double-blind, cluster-randomised, controlled trial

[Asma Binte Aziz¹](#), [Susanne Dudman²](#), [Cathinka Halle Julin³](#), [Faisal Ahmmed⁴](#), [Kathrine Stene-Johansen³](#), [Synne Sandbu³](#), [Joakim Øverbø³](#), [Jennifer L Dembinski³](#), [Torbjørn Wisløff⁵](#), [Sohel Rana⁴](#), [Ahsan-Ul Habib Basunia⁴](#), [Warda Haque⁴](#), [Firdausi Qadri⁴](#), [Khalequ Zaman⁴](#), [John D Clemens⁶](#)

Abstract

Background: Vaccination constitutes an attractive control measure for hepatitis E virus (HEV), a major cause of maternal and perinatal mortality globally. Analysis of pregnant participants in an effectiveness trial of the HEV vaccine HEV239 showed possible HEV239-associated fetal losses. We aimed to conduct a detailed analysis of this safety signal.

Methods: In a double-blind, cluster-randomised trial, 67 villages in Matlab, Bangladesh, were randomly allocated (1:1) to two vaccine groups, in which non-pregnant women aged 16-39 years received either HEV239 (HEV239 group) or Hepa-B (a hepatitis B vaccine; control group). We implemented weekly surveillance for pregnancy detection, and follow-up of pregnancies once every 2 weeks, using physician-confirmed diagnoses to evaluate fetal loss outcomes (miscarriage [spontaneous abortion], stillbirth, and elective termination). Data from a parallel system of reproductive health surveillance in Matlab were used to clarify study diagnoses when necessary. Miscarriage was assessed only among participants whose first positive pregnancy test and vaccination date (for whichever dose was closest to the date of last menstrual period [LMP]) were before 20 weeks' gestation. We defined the following analysis periods of interest: from 90 days before the LMP until the pregnancy outcome (the proximal period); from the LMP date until the pregnancy outcome (the pregnancy period); from 90 days before the LMP until the LMP date (90 days pre-LMP period); and from enrolment until 90 days before the LMP (the distal period). Both Poisson and Cox regression models were used to assess the associations between receipt of HEV239 and fetal loss outcomes. The trial was registered with ClinicalTrials.gov ([NCT02759991](https://clinicaltrials.gov/ct2/show/study/NCT02759991)).

Findings: Among the 19 460 non-pregnant participants enrolled in the trial, 5011 were identified as having pregnancies within 2 years following vaccination and met the criteria for analysis (2407 in the HEV239 group and 2604 in the control group). Among participants vaccinated in the proximal period and evaluated for miscarriage, miscarriage occurred in 54 (8.9%) of 607 in the HEV239 group and 32 (4.5%) of 719 in the control group (adjusted relative risk [aRR] 2.0 [95% CI 1.3-3.1], $p=0.0009$). Similarly, the risk of miscarriages was increased in the HEV239 group versus the control group among participants inadvertently vaccinated during pregnancy (22 [10.5%] miscarriages among 209 participants in the HEV239 group vs 14 [5.3%] of 266 in the control group; aRR 2.1 [95% CI 1.1-4.1], $p=0.036$) and among those vaccinated within 90 days pre-LMP (32 [8.0%] of 398 vs 18 [4.0%] of 453; 1.9 [1.1-3.2], $p=0.013$). No increased risk of miscarriage was observed in those who received HEV239 in the distal period (93 [5.6%] of 1647 vs 80 [4.5%] of 1773; 1.3 [0.8-1.9], $p=0.295$). Stillbirth and elective termination showed no increased risk among women administered HEV239 versus those administered Hepa-B in any of the analysis periods.

Interpretation: HEV239 given shortly before or during pregnancy was associated with an elevated risk of miscarriage. This association poses a possible safety concern for programmatic use of HEV239 in women of childbearing age.

Hookworm vaccine

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[Safety and immunogenicity of the co-administered Na-APR-1 and Na-GST-1 hookworm vaccines in school-aged children in Gabon: a randomised, controlled, observer-blind, phase 1, dose-escalation trial](#)

[Jeannot F Zinsou¹](#), [David J Diemert²](#), [Jean Claude Dejon-Agobé³](#), [Bayodé R Adégbité⁴](#), [Yabo Josiane Honkpehedji⁵](#), [Kafui G Vodonou³](#), [Rodrigue Bikangui³](#), [Jean Ronald Edoa³](#), [Marguerite Massinga Loembe³](#), [Guangzhao Li⁶](#), [Maria Yazdanbakhsh⁷](#), [Maria Elena](#)

[Bottazzi⁸](#), [Remko van Leeuwen⁹](#), [Peter G Kremsner¹⁰](#), [Peter J Hotez⁸](#), [Jeffrey M Bethony⁶](#), [Martin P Grobusch¹¹](#), [Ayola A Adegnika¹²](#)

Abstract

Background: A human hookworm vaccine is being developed to protect children against iron deficiency and anaemia associated with chronic infection with hookworms. *Necator americanus* aspartic protease-1 (Na-APR-1) and *N americanus* glutathione S-transferase-1 (Na-GST-1) are components of the blood digestion pathway critical to hookworm survival in the host. Recombinant Na-GST-1 and catalytically inactive Na-APR-1 (Na-APR-1[M74]) adsorbed to Alhydrogel were safe and immunogenic when delivered separately or co-administered to adults in phase 1 trials in non-endemic and endemic areas. We aimed to investigate the safety and immunogenicity of these antigens in healthy children in a hookworm-endemic area.

Methods: This was a randomised, controlled, observer-blind, phase 1, dose-escalation trial, conducted in a clinical research centre, in 60 children aged six to ten years in Lambaréné, a hookworm-endemic region of Gabon. Healthy children (determined by clinical examination and safety laboratory testing) were randomised 4:1 to receive co-administered Na-GST-1 on Alhydrogel plus Na-APR-1(M74) on Alhydrogel and glucopyranosyl lipid A in aqueous formulation (GLA-AF), or co-administered ENGERIX-B hepatitis B vaccine (HBV) and saline placebo, injected into the deltoid of each arm. Allocation to vaccine groups was observer-masked. In each vaccine group, children were randomised 1:1 to receive intramuscular injections into each deltoid on two vaccine schedules, one at months 0, 2, and 4 or at months 0, 2, and 6. 10 µg, 30 µg, and 100 µg of each antigen were administered in the first, second, and third cohorts, respectively. The intention-to-treat population was used for safety analyses; while for immunogenicity analyses, the per-protocol population was used (children who received all scheduled vaccinations). The primary outcome was to evaluate the vaccines' safety and reactogenicity in healthy children aged between six and ten years. The secondary outcome was to measure antigen-specific serum IgG antibody levels at pre-vaccination and post-vaccination timepoints by qualified ELISAs. The trial is registered with ClinicalTrials.gov, [NCT02839161](#), and is completed.

Findings: Between Jan 23 and Oct 3, 2017, 137 children were screened, of whom 76 were eligible for this trial. 60 children were recruited, and allocated to either 10 µg of the co-administered antigens (n=8 for each injection schedule), 30 µg (n=8 for each schedule), 100 µg (n=8 for each schedule), or HBV and placebo (n=6 for each schedule) in three sequential cohorts. Co-administration of the vaccines was well tolerated; the most frequent solicited adverse events were mild-to-moderate injection-site pain, observed in up to 12 (75%) of 16 participants per vaccine group, and mild headache (12 [25%] of 48) and fever (11 [23%] of 48). No vaccine-related serious adverse events were observed. Significant anti-Na-APR-1(M74) and anti-Na-GST-1 IgG levels were induced in a dose-dependent manner, with peaks seen 14 days after the third vaccinations, regardless of dose (for Na-APR-1[M74], geometric mean levels [GML]=2295.97 arbitrary units [AU] and 726.89 AU, while for Na-GST-1, GMLs=331.2 AU and 21.4 AU for the month 0, 2, and 6 and month 0, 2, and 4 schedules, respectively). The month 0, 2, and 6 schedule induced significantly higher IgG responses to both antigens (p=0.01 and p=0.04 for Na-APR-1[M74] and Na-GST-1, respectively).

Interpretation: Co-administration of recombinant Na-APR-1(M74) and Na-GST-1 to school-aged Gabonese children was well tolerated and induced significant IgG responses. These results justify further evaluation of this antigen combination in proof-of-concept controlled-infection and efficacy studies in hookworm-endemic areas.

HPV vaccine

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Durability of immunogenicity at 5 years after a single dose of human papillomavirus vaccine compared with two doses in Tanzanian girls aged 9-14 years: results of the long-term extension of the DoRIS randomised trial

[Deborah Watson-Jones¹](#), [John Chagalucha²](#), [Caroline Maxwell¹](#), [Hilary Whitworth¹](#), [Paul Mutani²](#), [Troy J Kemp³](#), [Beatrice Kamala²](#), [Jackton Indangasi¹](#), [George Constantine²](#), [Ramadhan Hashim²](#), [David Mwanzalima²](#), [Rebecca Wiggins⁴](#), [Devis Mmbando²](#), [Nicholas Connor⁵](#), [Miquel A Pavon⁶](#), [Brett Lowe⁵](#), [Saidi Kapiga⁷](#), [Philippe Mayaud⁵](#), [Silvia de Sanjosé⁸](#), [Joakim Dillner⁹](#), [Richard J Hayes¹⁰](#), [Charles J Lacey⁴](#), [Ligia Pinto³](#), [Kathy Baisley¹¹](#)

Abstract

Background: WHO has recommended that one dose of human papillomavirus (HPV) vaccine can be given to individuals aged 9-20 years to prevent HPV infection. Estimating durability of immune responses after a single dose in the target age for vaccination is important. We report immunogenicity results in Tanzanian girls up to 5 years after receiving a dose.

Methods: In this open-label, randomised controlled trial (the Dose Reduction Immunobridging and Safety Study of Two HPV Vaccines in Tanzanian Girls [DoRIS] trial), 930 Tanzanian schoolgirls aged 9-14 years were enrolled and randomly allocated to receive one, two, or three doses of either the two-valent vaccine (Cervarix; GSK, Wavre, Belgium) or nine-valent vaccine (Gardasil-9; Merck Sharp & Dohme, Haarlem, Netherlands). Seropositivity specific to HPV16 or HPV18, antibody geometric mean concentrations (GMCs), and antibody avidity were measured annually up to month 36. Participants in the one-dose and two-dose groups were followed annually in a long-term extension of the DoRIS trial to month 60; the primary outcome was seropositivity specific to HPV16 or HPV18 comparing one dose with two doses.

Findings: Single-dose seropositivity for HPV16 IgG antibodies at month 60 with either vaccine was more than 99% and non-inferior to two doses. 98% of girls in the one-dose two-valent vaccine group and 93% in the one-dose nine-valent group were seropositive for HPV18 at month 60; however, the non-inferiority criteria for HPV18 seropositivity comparing one dose with two doses were not met. Although HPV16 and HPV18 antibody GMCs after one dose were lower than those observed after two doses, antibody GMCs in the one-dose groups remained stable from month 12 to month 60. There was no evidence of a difference between the one-dose and two-dose groups in HPV16 or HPV18 antibody avidity at month 36 for either vaccine.

Interpretation: A single dose of HPV vaccine in girls aged 9-14 years continues to provide stable immune responses 5 years after vaccination, although ongoing surveillance for potential waning immunity after a single dose is needed. Participants are being followed up to 9 years after vaccination.

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[A theory-based educational intervention to increase mothers' intention to vaccinate their daughters against human papillomavirus: A randomised controlled trial](#)

[Areej Alqethami](#)¹, [Eman Alhalal](#)²

Abstract

Objective: The current study aimed to examine the effectiveness of a web-based educational intervention based on the theory of planned behaviour (TPB) in enhancing mothers' knowledge of human papillomavirus (HPV) and its vaccine, attitudes towards the HPV vaccine, subjective norms, perceived behavioural control, and intention to vaccinate their daughters against HPV.

Method: A randomised controlled trial was conducted. The sample comprised 214 mothers of adolescents from 10 intermediate schools in Saudi Arabia. After collecting baseline data, the participants were randomly assigned to control and intervention groups. The TPB-based intervention was delivered online to the intervention group, and post-test data were collected from both groups. A mixed-effects model of covariance was used to test the effect of the intervention.

Results: There were no significant differences between the two groups at baseline. One month after delivery, the intervention was found to have a significant effect on mothers' knowledge ($F(1, 211.15) = 72.40, p < .001$), attitudes ($F(1, 211.11) = 110.57, p < .001$), subjective norms ($F(1, 211) = 34.55, p < .001$), perceived control behaviour ($F(1, 211.12) = 144.01, p < .001$), and intention to vaccinate their daughters against HPV ($F(1, 211.05) = 113.64, p < .001$).

Conclusion: The study showed that the web-based intervention based on the TPB was effective in increasing mothers' knowledge, attitude, subjective norms, perceived control behaviour, and intention to vaccinate their daughters after 1 month.

Practice implications: The findings underscore the significance of popularising and implementing such interventions to boost HPV vaccine coverage among adolescents.

Influenza vaccine

Vaccine. 2024 Aug 30;42(21):126182.

doi: 10.1016/j.vaccine.2024.126182. Epub 2024 Aug 6.

[Lot-to-lot consistency, immunogenicity and safety of a quadrivalent split virion inactivated influenza vaccine in healthy population aged 9-59 years: A randomized, double-blind, controlled, phase IV clinical trial](#)

[Yuanxue Gao](#)¹, [Xinyi Yang](#)², [Xiaoyu Li](#)³, [Hu Chen](#)¹, [Yuwei Li](#)⁴, [Xue Tan](#)¹, [Dan Yu](#)⁴, [Tian Feng](#)¹, [Siliang Zhou](#)², [Shiguang Lei](#)¹, [Chenyan Zhao](#)⁵, [Jieru Wang](#)⁶, [Qinghu Guan](#)⁷

Abstract

Objectives: This study was to assess the lot-to-lot consistency, immunogenicity and safety of three manufacturing lots of a quadrivalent inactivated influenza vaccine (IIV4).

Methods: A randomized, double-blind, phase IV clinical trial was conducted in healthy children, adolescents and adults aged 9-59 years in Guizhou Province, China. Eligible

participants were enrolled and randomized into three groups in a ratio of 1:1:1 to receive a single dose of one of three manufacturing lots of IIV4. Serum samples were collected before and 28 days after vaccination for hemagglutination inhibition (HI) antibody testing. Safety data were collected for up to 28 days after vaccination. The primary objective was to evaluate the lot-to-lot consistency of immune response as assessed by the geometric mean titer (GMT) of HI antibody at 28 days after vaccination.

Results: Between November 27, 2022 and December 18, 2022, 1260 eligible participants were enrolled, with similar participant demographics among groups. Immune responses after vaccination were comparable across groups, with the 95% confidence intervals (CIs) of GMT ratios for all 4 strains falling into the equivalence criterion of (0.67, 1.5). The seroconversion rates (SCRs) and seroprotection rates (SPRs) met the US Center for Biologics Evaluation and Research (CBER) criteria for all strains for each lot (lower limit of 95% CI of $SCR \geq 40\%$ and $SPR \geq 70\%$). The incidences of solicited and unsolicited adverse reactions were similar among three groups, most of which (91.9%) were mild or moderate in severity. A total of 11 serious adverse events were reported during the study, and all were considered unrelated to vaccination.

Conclusion: The three manufacturing lots of IIV4 demonstrated consistent immunogenicity. IIV4 can elicit satisfactory immune responses for all four strains and no safety concerns were identified.

Hum Vaccin Immunother. 2024 Dec 31;20(1):2416329.

doi: 10.1080/21645515.2024.2416329. Epub 2024 Oct 24.

[A prospective, randomized, parallel, active controlled, phase III Indian study of immunogenicity and safety of two inactivated influenza vaccines - Vaxiflu-4 and Fluarix tetra in children aged 6 months to 35 months](#)

[Kairav Kothari](#)¹, [Shreyansh Shah](#)², [Vinay Kumar Gill](#)³, [Rajib Kumar Ray](#)⁴, [N Ravi Kumar](#)⁵, [Jayesh Sanmukhani](#)⁶, [Pavankumar Daultani](#)⁶, [Ravindra Mittal](#)⁶, [Trayambak Dutta](#)⁷, [Manish Mahajan](#)⁸, [Samir Desai](#)⁹

Abstract

Influenza is highly prevalent in children under five years, particularly those under two, accounting for 5-10% of acute respiratory infections (ARIs) in India. This study was conducted to compare the immunogenicity and safety of two tetravalent inactivated influenza vaccines in healthy children aged 6-35 months. The dose recommendation for this group increased from 0.25 mL to 0.5 mL to ensure adequate immune response, as per the Advisory Committee on Immunization Practices. This Phase III, randomized, single-blind, active-controlled, multicentre study was conducted from May to October 2022 across five centers in India. A total of 346 subjects were randomized to receive two doses of either the test vaccine (Vaxiflu-4, Zydus Lifesciences Limited; $n = 174$) or the reference vaccine (Fluarix Tetra, GlaxoSmithKline; $n = 172$). The primary objective was to compare immunogenicity using seroprotection rate, seroconversion rate, and geometric mean titers (GMTs) against four vaccine strains. Safety profiles were also compared. Both vaccines demonstrated non-inferiority, with seroprotection rates over 95%, seroconversion rates above 90%, and significant GMT increases. Adverse events (AEs) were similar for both vaccines, including pain at the injection site, erythema, swelling, and pyrexia. The test vaccine, Vaxiflu-4, showed non-inferiority in terms of immunogenicity and safety when compared with reference vaccine, Fluarix Tetra

Lancet Microbe. 2025 Jan 17:100971.

doi: 10.1016/j.lanmic.2024.100971. Online ahead of print.

Interactions between live attenuated influenza vaccine and nasopharyngeal microbiota among children aged 24-59 months in The Gambia: a phase 4, open-label, randomised controlled trial

[Chikondi Peno¹](#), [Ya Jankey Jagne²](#), [Melanie Clerc³](#), [Carlos Balcazar Lopez³](#), [Edwin P Armitage²](#), [Hadijatou Sallah²](#), [Sainabou Drammeh²](#), [Elina Senghore²](#), [Gabriel Goderski⁴](#), [Sophie van Tol⁴](#), [Adam Meijer⁴](#), [Alicia Ruiz-Rodriguez³](#), [Wouter de Steenhuijsen Pijters⁵](#), [Emma de Koff⁵](#), [Sheikh Jarju²](#), [Benjamin B Lindsey⁶](#), [Janko Camara²](#), [Sulayman Bah²](#), [Nuredin I Mohammed²](#), [Beate Kampmann⁷](#), [Ed Clarke²](#), [David H Dockrell³](#), [Thushan I de Silva⁸](#), [Debby Bogaert⁹](#)

Abstract

Background: Live attenuated influenza vaccines (LAIVs) alter nasopharyngeal microbiota in adults. It is poorly understood why LAIV immunogenicity varies across populations, but it could be linked to the microbiome. We aimed to investigate the interactions between intranasal immunisation with LAIV and nasopharyngeal microbiota composition in children from The Gambia.

Methods: We conducted a phase 4, open-label, randomised controlled trial in Sukuta, The Gambia. Children aged 24-59 months with no underlying illness or history of respiratory illness for at least 14 days before recruitment were eligible. Participants were randomly assigned (2:1) by use of a computer-generated sequence in permuted blocks of 15, stratified by sex, to receive trivalent LAIV either on day 0 (intervention group) or after active follow-up at day 21 (control group). The investigator team was initially masked to block size and randomisation sequence; however, group allocation was later revealed to the team. Microbiome profiles were characterised from nasopharyngeal samples collected from all participants on days 0, 7, and 21 by use of 16S rRNA sequencing. The primary outcomes were the effect of LAIV on nasopharyngeal microbiome profiles on day 7 and day 21, and the association between the nasopharyngeal microbiome at baseline and LAIV-induced mucosal IgA responses at day 21, assessed with permutational ANOVA tests. Asymptomatic respiratory viral co-infection at baseline and year of recruitment (2017 or 2018) were included as covariates. This trial is registered with ClinicalTrials.gov ([NCT02972957](#)) and is closed.

Findings: Between Feb 8 and April 12, 2017, and Jan 15 and March 28, 2018, 343 children were screened for eligibility, of whom 220 (64%) children were randomly assigned to the intervention group and 110 (32%) to the control group. 213 (97%) children in the intervention group and 108 (98%) in the control group completed the study and were included in the final analysis. Although we did not observe an independent effect of LAIV on microbial community composition at days 7 or 21, we found that LAIV had an effect dependent on the year of recruitment. LAIV affected microbial community composition in 2018 (R^2 1·97% [95% CI 0·85-5·94]; $p=0·037$), but not in 2017 (1·23% [0·49-4·46]; $p=0·091$). We also found that viral co-infection at baseline had an effect on microbial composition at day 7, regardless of recruitment year (R^2 1·01% [95% CI 0·28-3·01]; $p=0·026$). Nasopharyngeal microbial community composition at baseline had no effect on mucosal IgA responses to LAIV administration (R^2 0·51% [95% CI 0·23-2·49]; $p=0·46$).

Interpretation: Our findings suggest that the effect of LAIVs on nasopharyngeal microbiota composition in children is modest and temporary; therefore, LAIVs could be used as an intervention to curb influenza in children from low-income and middle-income countries, without causing long-lasting perturbations in nasopharyngeal microbiota. However, nasopharyngeal microbiota at the time of vaccination might not explain the variability observed between individuals in LAIV-induced IgA responses.

Hum Vaccin Immunother. 2024 Dec 31;20(1):2425149.

doi: 10.1080/21645515.2024.2425149. Epub 2024 Nov 14.

[Safety and immunogenicity of full-dose quadrivalent influenza vaccine in children 6-35 months of age in China: A randomized, double-blind, clinical trial](#)

[Shilei Wang¹](#), [Yanxia Wang²](#), [Dandan Chen¹](#), [Wenting Xu¹](#), [Peng Duan¹](#), [Wei Ji³](#), [Weijun Liu³](#), [Weijin Huang⁴](#), [Bing Wu¹](#), [Wenqing Chai¹](#), [Chenyan Zhao⁴](#), [Yongli Yang⁵](#), [Jian Luo¹](#), [Dongyang Zhao²](#), [Xiuling Li^{1,6}](#)

Abstract

A half-dose influenza vaccine (7.5 µg hemagglutinin per strain) has been used for children under 3 years of age for a long time. However, several studies indicate that a full-dose influenza vaccine (15 µg hemagglutinin per strain) may bring more benefit to this population without increasing the risk of adverse reactions. We conducted a clinical study in children aged 6-35 months in China. Participants were randomized to receive two doses of full-dose quadrivalent influenza vaccine (F-QIV), half-dose quadrivalent vaccine (H-QIV), and two half-dose trivalent vaccines (H-TIV) in a 2:2:1:1 ratio. The safety and tolerability profile of the vaccine was evaluated for 6 months postvaccination. Hemagglutination inhibition (HI) antibody titers were measured for immunogenicity assessment. The primary objective was to assess whether the results of all vaccines met the criteria. A total of 1,980 participants were enrolled in the study. Both H-QIV and F-QIV were well tolerated after vaccination. Although the geometric mean increase (GMI), seroconversion rate (SCR), and seroprotection rate (SPR) for both H-QIV and F-QIV were achieved by the criteria, superior immunogenicity in terms of geometric mean titer (GMT) ratio was observed in F-QIV to H-QIV for A/H3N2 (GMT ratio (95% CI) of 1.37 (1.11 ~ 1.68)) and B/Yamagata (1.21 (1.05 ~ 1.39)). Antibody responses to the QIV were non-inferior to the response to the TIV for the matched strains. In conclusion, F-QIV and H-QIV were both safe and immunogenic for children. F-QIV induced a stronger immune response to influenza viruses and may provide more protection and benefit by promoting the use of F-QIV in children aged 6-35 months.

Japanese encephalitis virus vaccine

Malaria vaccine

J Infect Dis. 2024 Aug 16;230(2):e486-e495.

doi: 10.1093/infdis/jiae075.

[Could Less Be More? Accounting for Fractional-Dose Regimens and Different Number of Vaccine Doses When Measuring the Impact of the RTS,S/AS01E Malaria Vaccine](#)

[Nelli Westercamp¹](#), [Lawrence Osei-Tutu²](#), [Lode Schuerman³](#), [Simon K Kariuki⁴](#), [Anne Bollaerts³](#), [Cynthia K Lee⁵](#), [Aaron M Samuels^{1,6}](#), [Christian Ockenhouse⁵](#), [Dennis K Bii⁴](#), [Samuel Adjei²](#), [Martina Oneko⁴](#), [Marc Lievens³](#), [Maame Anima Attobrah Sarfo²](#), [Cecilia Atieno⁴](#), [Ashura Bakari²](#), [Tony Sang⁴](#), [Maame Fremah Kotoh-Mortty²](#), [Kephass Otieno⁴](#), [François Roman³](#), [Patrick Boakye Yiadom Buabeng²](#), [Yaw Ntiamaoh²](#), [Daniel Ansong²](#), [Tsiri Agbenyega²](#), [Opokua Ofori-Anyinam³](#)

Abstract

Background: The RTS,S/AS01E (RTS,S) malaria vaccine is recommended for children in malaria endemic areas. This phase 2b trial evaluates RTS,S fractional- and full-dose regimens in Ghana and Kenya.

Methods: In total, 1500 children aged 5-17 months were randomized (1:1:1:1) to receive RTS,S or rabies control vaccine. RTS,S groups received 2 full RTS,S doses at months 0 and 1 and either full (groups R012-20, R012-14-26) or fractional doses (one-fifth; groups Fx012-14-26, Fx017-20-32).

Results: At month 32 post-dose 1, vaccine efficacy against clinical malaria (all episodes) ranged from 38% (R012-20; 95% confidence interval [CI]: 24%-49%) to 53% (R012-14-26; 95% CI: 42%-62%). Vaccine impact (cumulative number of cases averted/1000 children vaccinated) was 1344 (R012-20), 2450 (R012-14-26), 2273 (Fx012-14-26), and 2112 (Fx017-20-32). To account for differences in vaccine volume (fractional vs full dose; post hoc analysis), we estimated cases averted/1000 RTS,S full-dose equivalents: 336 (R012-20), 490 (R012-14-26), 874 (Fx012-14-26), and 880 (Fx017-20-32).

Conclusions: Vaccine efficacy was similar across RTS,S groups. Vaccine impact accounting for full-dose equivalence suggests that using fractional-dose regimens could be a viable dose-sparing strategy. If maintained through trial end, these observations underscore the means to reduce cost per regimen thus maximizing impact and optimizing supply.

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doi: 10.1016/S1473-3099(24)00527-9. Epub 2024 Oct 23.

[The effect of Plasmodium falciparum exposure and maternal anti-circumsporozoite protein antibodies on responses to RTS,S/AS01E vaccination in infants and children: an ancillary observational immunological study to a phase 3, randomised clinical trial](#)

[Dídac Macià¹](#), [Joseph J Campo²](#), [Chenjerai Jairoce³](#), [Maximilian Mpina⁴](#), [Hermann Sorgho⁵](#), [David Dosoo⁶](#), [Selidji Todagbe Agnandji⁷](#), [Kwadwo Asamoah Kusi⁸](#), [Luis M Molinos-Albert⁹](#), [Simon Kariuki¹⁰](#), [Claudia Daubenberger¹¹](#), [Benjamin Mordmüller¹²](#), [Gemma Moncunill¹](#), [Carlota Dobaño¹³](#)

Abstract

Background: The RTS,S/AS01E malaria vaccine showed lower antibody response and protective efficacy in infants aged 6-12 weeks compared with children aged 5-17 months (for whom this vaccine is recommended). We aimed to study the effect of previous Plasmodium falciparum exposure on the antibody responses to RTS,S/AS01E vaccination in infants and children, and the mediating effect of baseline (including maternal) anti-circumsporozoite protein (CSP) antibodies.

Methods: In this observational study, we included children and infants from six African countries (Burkina Faso, Gabon, Ghana, Kenya, Mozambique, and Tanzania) enrolled in the MAL067 immunology ancillary study of the RTS,S/AS01E phase 3 clinical trial from March 27,

2009, to Jan 21, 2011. We used comparator-vaccinated infants and children to identify antibody-based signatures of previous *P falciparum* exposure, which were later applied to RTS,S/AS01_E-vaccinated infants and children. In these participants, we explored the relationship between vaccine antibody immunoglobulin G (IgG) responses measured by ELISA and pre-vaccination serological markers of malaria exposure by assessing the IgG levels against 1000 *P falciparum* antigens using partial proteome microarrays.

Findings: We included 718 comparator-vaccinated infants (348 [48%]) and children (370 [52%]) and 606 RTS,S/AS01_E-vaccinated infants (329 [54%]) and children (277 [46%]). Anti-CSP IgG responses to primary vaccination did not correlate with a baseline signature of previous exposure in children, suggesting that prior *P falciparum* exposure does not significantly affect antibody immunogenicity in children (Pearson's $r=-0.02$ [95% CI -0.13 to 0.10]). By contrast, high *P falciparum* exposure signature levels at the time of vaccination in infants, presumably driven by maternally transferred antibodies and declining within the initial 6-12 months of life, correlated with reduced RTS,S/AS01_E responses ($r=-0.17$ [-0.27 to -0.06]). This negative correlation was stronger for anti-CSP IgG than for the exposure signature or any other more immunogenic blood stage *P falciparum* antigens ($r=-0.42$ [-0.50 to -0.33]), persisted after adjustment by baseline levels of the exposure signature (semi-partial correlation $r=-0.44$ [-0.55 to -0.33]), and involved antibodies to the central NANP region ($r=-0.39$ [-0.49 to -0.28]) but not the C-terminal region ($r=0.02$ [-0.10 to 0.15]) of CSP. The negative effect of maternal anti-CSP IgG in infants did not appear to be confounded by other malaria transmission-dependent variables.

Interpretation: Interference between passive immunity and vaccine response is clinically significant and might affect the implementation of next-generation CSP-based vaccines for young infants and mothers as well as passive immunisation with human monoclonal antibodies.

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Antibody mechanisms of protection against malaria in RTS,S-vaccinated children: a post-hoc serological analysis of phase 2 trial

[Liriye Kurtovic¹](#), [Gaoqian Feng²](#), [Alessia Hysa²](#), [Ali Haghiri³](#), [Katherine O'Flaherty⁴](#), [Bruce D Wines⁵](#), [Rebeca Santano⁶](#), [Laura D'Andrea⁴](#), [Heidi E Drummer⁷](#), [P Mark Hogarth⁵](#), [Jahit Sacarlal⁸](#), [Freya J I Fowkes⁹](#), [Julie A Simpson¹⁰](#), [Carlota Dobaño¹¹](#), [James G Beeson¹²](#)

Abstract

Background: The RTS,S malaria vaccine is currently recommended for children aged 5-6 months in regions with moderate-to-high *Plasmodium falciparum* transmission. However, vaccination only confers 55% efficacy over 12 months and wanes within 18 months. The immunological mechanisms of RTS,S-mediated immunity are poorly understood; therefore, we aimed to identify antibody response types associated with protection against malaria in children vaccinated with RTS,S.

Methods: In this post-hoc analysis, we evaluated antibody responses in 737 children aged 1-4 years vaccinated with RTS,S in a phase 2b clinical trial conducted in Mozambique in 2003.

We evaluated all available samples collected from children 30 days after the three-dose vaccination schedule at study month 3 (M3; n=737 available of 803 children allocated to receive RTS,S). For comparison, we tested a subset of samples collected before vaccination at study month 0 (M0; n=50) and from children in the control vaccine group (M0 n=25; M3 n=99). We quantified the induction of antibodies to different regions of the vaccine antigen that function by fixing serum complement proteins and binding to Fcγ receptors (FcγRs; FcγRI, FcγRIIa, and FcγRIII) expressed on immune cells as potential mechanisms of immunity.

Findings: Functional antibody responses to the C-terminal region of the vaccine antigen, circumsporozoite protein (CSP), were associated with a reduced risk of malaria (C1q p=0.0060, FcγRIIa p=0.014, and FcγRIII p=0.019). These associations remained significant in male participants when the analyses were stratified by sex (C1q p=0.012, FcγRI p=0.023, FcγRIIa p=0.0070, and FcγRIII p=0.0080). IgA to the central repeat (p=0.0010) and C-terminal (p=0.0040) regions of CSP were also associated with protection. We show that IgA can bind FcαRI and mediate opsonic phagocytosis using a serum pool and monoclonal antibodies. Multiparameter analysis using machine-learning methods suggest that IgA, complement fixation, and FcγRI binding were most predictive of protection against malaria (hazard ratio <1) and suggested that associations differed between male and female participants.

Interpretation: We provide evidence that functional antibody responses mediated by IgG and IgA are associated with protection against malaria in young children vaccinated with RTS,S, and suggest potential differences in the correlates of immunity between males and females. These findings reveal new avenues that could be used to achieve malaria vaccines with higher efficacy.

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doi: 10.1016/S1473-3099(24)00179-8. Epub 2024 May 6.

Genotypic analysis of RTS,S/AS01_E malaria vaccine efficacy against parasite infection as a function of dosage regimen and baseline malaria infection status in children aged 5-17 months in Ghana and Kenya: a longitudinal phase 2b randomised controlled trial

[Michal Juraska¹](#), [Angela M Early²](#), [Li Li³](#), [Stephen F Schaffner²](#), [Marc Lievens⁴](#), [Akanksha Khorgade²](#), [Brian Simpkins³](#), [Nima S Hejazi⁵](#), [David Benkeser⁶](#), [Qi Wang⁷](#), [Laina D Mercer⁸](#), [Samuel Adjei⁹](#), [Tsiri Agbenyega⁹](#), [Scott Anderson²](#), [Daniel Ansong⁹](#), [Dennis K Bii¹⁰](#), [Patrick B Y Buabeng⁹](#), [Sean English²](#), [Nicholas Fitzgerald²](#), [Jonna Grimsby²](#), [Simon K Kariuki¹⁰](#), [Kephass Otieno¹⁰](#), [François Roman⁴](#), [Aaron M Samuels¹¹](#), [Nelli Westercamp¹²](#), [Christian F Ockenhouse⁸](#), [Opokua Ofori-Anyinam⁴](#), [Cynthia K Lee⁸](#), [Bronwyn L MacInnis²](#), [Dyann F Wirth¹³](#), [Peter B Gilbert¹⁴](#), [Daniel E Neafsey¹⁵](#)

Abstract

Background: The first licensed malaria vaccine, RTS,S/AS01_E, confers moderate protection against symptomatic disease. Because many malaria infections are asymptomatic, we conducted a large-scale longitudinal parasite genotyping study of samples from a clinical trial exploring how vaccine dosing regimen affects vaccine efficacy.

Methods: Between Sept 28, 2017, and Sept 25, 2018, 1500 children aged 5-17 months were randomly assigned (1:1:1:1:1) to receive four different RTS,S/AS01_E regimens or a rabies control vaccine in a phase 2b open-label clinical trial in Ghana and Kenya. Participants in the

four RTS,S groups received two full doses at month 0 and month 1 and either full doses at month 2 and month 20 (group R012-20); full doses at month 2, month 14, month 26, and month 38 (group R012-14); fractional doses at month 2, month 14, month 26, and month 38 (group Fx012-14; early fourth dose); or fractional doses at month 7, month 20, and month 32 (group Fx017-20; delayed third dose). We evaluated the time to the first new genotypically detected infection and the total number of new infections during two follow-up periods (12 months and 20 months) in more than 36 000 dried blood spot specimens from 1500 participants. To study vaccine effects on time to the first new infection, we defined vaccine efficacy as one minus the hazard ratio (HR; RTS,S vs control) of the first new infection. We performed a post-hoc analysis of vaccine efficacy based on malaria infection status at first vaccination and force of infection by month 2. This trial (MAL-095) is registered with ClinicalTrials.gov, [NCT03281291](https://clinicaltrials.gov/ct2/show/study/NCT03281291).

Findings: We observed significant and similar vaccine efficacy (25-43%; 95% CI union 9-53) against first new infection for all four RTS,S/AS01_E regimens across both follow-up periods (12 months and 20 months). Each RTS,S/AS01_E regimen significantly reduced the mean number of new infections in the 20-month follow-up period by 1.1-1.6 infections (95% CI union 0.6-2.1). Vaccine efficacy against first new infection was significantly higher in participants who were infected with malaria (68%; 95% CI 50-80) than in those who were uninfected (37%; 23-48) at the first vaccination ($p=0.0053$).

Interpretation: All tested dosing regimens blocked some infections to a similar degree. Improved vaccine efficacy in participants infected during vaccination could suggest new strategies for highly efficacious malaria vaccine development and implementation.

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Safety and efficacy of the blood-stage malaria vaccine RH5.1/Matrix-M in Burkina Faso: interim results of a double-blind, randomised, controlled, phase 2b trial in children

[Hamtandi M Natama¹](#), [Jo Salkeld²](#), [Athanase Somé¹](#), [Seyi Soremekun³](#), [Salou Diallo¹](#), [Ousmane Traoré¹](#), [Toussaint Rouamba¹](#), [Florence Ouédraogo¹](#), [Edouard Ouédraogo¹](#), [K Carine Sonia Daboné¹](#), [Nadine A Koné¹](#), [Z Michael John Compaoré¹](#), [Miguel Kafando¹](#), [Massa Dit Achille Bonko¹](#), [Fabé Konaté¹](#), [Hermann Sorgho¹](#), [Carolyn M Nielsen²](#), [Dimitra Pipini²](#), [Ababacar Diouf⁴](#), [Lloyd D W King²](#), [Umesh Shaligram⁵](#), [Carole A Long⁴](#), [Jee-Sun Cho²](#), [Alison M Lawrie⁶](#), [Katherine Skinner²](#), [Rachel Roberts²](#), [Kazutoyo Miura⁴](#), [John Bradley³](#), [Sarah E Silk²](#), [Simon J Draper²](#), [Halidou Tinto¹](#), [Angela M Minassian⁷](#)

Free article

Abstract

Background: Two pre-erythrocytic vaccines (R21/Matrix-M and RTS,S/AS01) are now approved for *Plasmodium falciparum* malaria. However, neither induces blood-stage immunity against parasites that break through from the liver. RH5.1/Matrix-M, a blood-stage *P falciparum* malaria vaccine candidate, was highly immunogenic in Tanzanian adults and children. We therefore assessed the safety and efficacy of RH5.1/Matrix-M in Burkinabe children.

Methods: In this double-blind, randomised, controlled, phase 2b trial, RH5.1/Matrix-M was given to children aged 5-17 months in Nanoro, Burkina Faso, a seasonal malaria transmission setting. Children received either three intramuscular vaccinations with 10 µg RH5.1 protein

with 50 µg Matrix-M adjuvant or three doses of rabies control vaccine, Rabivax-S, given either in a delayed third-dose (0, 1, and 5 month) regimen (first cohort) or a 0, 1, and 2 month regimen (second cohort). Vaccinations were completed part way through the malaria season. Children were randomly assigned 2:1 within each cohort to receive RH5.1/Matrix-M or Rabivax-S. Participants were assigned according to a random allocation list generated by an independent statistician using block randomisation with variable block sizes. Participants, their families, and the study teams were masked to group allocation; only pharmacists who prepared the vaccines were unmasked. Vaccine safety, immunogenicity, and efficacy were evaluated. The coprimary outcomes assessed were: first, the safety and reactogenicity of RH5.1/Matrix-M; and second, the protective efficacy of RH5.1/Matrix-M against clinical malaria (measured as time to first episode of clinical malaria, using a Cox regression model) from 14 days to 6 months after the third vaccination in the per-protocol sample. This ongoing trial is registered with ClinicalTrials.gov ([NCT05790889](https://clinicaltrials.gov/ct2/show/study/NCT05790889)).

Findings: From April 6 to 13 and July 3 to 7, 2023, 412 children aged 5-17 months were screened, and 51 were excluded. A total of 361 children were enrolled in this study. In the first cohort, 119 were assigned to the RH5.1/Matrix-M delayed third-dose group, and 62 to the equivalent rabies control group. The second cohort included 120 children in the monthly RH5.1/Matrix-M group and 60 in the equivalent rabies control group. The final vaccination was administered to all groups from Sept 4 to 21, 2023. RH5.1/Matrix-M in both cohorts had a favourable safety profile and was well tolerated. Most adverse events were mild, with the most common being local swelling and fever. No serious adverse events were reported. Comparing the RH5.1/Matrix-M delayed third-dose regimen with the pooled control groups resulted in a vaccine efficacy of 55% (95% CI 20 to 75%; $p=0.0071$). The same analysis showed a vaccine efficacy of 40% (-3 to 65%; $p=0.066$) when comparing the monthly regimen with the pooled control groups. Participants vaccinated with RH5.1/Matrix-M in both cohorts showed high concentrations of anti-RH5.1 serum IgG antibodies 14 days after the third vaccination, and the purified IgG showed high levels of in vitro growth inhibition activity against *P falciparum*; these responses were higher in patients who received the RH5.1/Matrix-M vaccine delayed third-dose regimen, as opposed to monthly regimen (growth inhibition activity 79.0% [SD 14.3] vs 74.2% [SD 15.9]; $p=0.016$).

Interpretation: RH5.1/Matrix-M appears safe and highly immunogenic in African children and shows promising efficacy against clinical malaria when given in a delayed third-dose regimen. This trial is ongoing to further monitor efficacy over time.

Maternal immunization

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doi: 10.1016/S2214-109X(24)00409-1.

[Safety and immunogenicity of an acellular pertussis vaccine containing genetically detoxified pertussis toxin administered to pregnant women living with and without HIV and their newborns \(WoMANPOWER\): a randomised controlled trial in Uganda](#)

[Eve Nakabembe](#)¹, [Melanie Greenland](#)², [Kyle Amaral](#)³, [Bahaa Abu-Raya](#)⁴, [Alexander Amone](#)⁵, [Nick Andrews](#)⁶, [Liberty Cantrell](#)², [Elodie Lesne](#)⁷, [Andrew Gorringer](#)⁷, [Rachel Halkerston](#)⁷, [Nikki Mcstraw](#)⁷, [Louisa Dixon](#)⁷, [Olivia F Hunter](#)⁸, [Paul T Heath](#)⁹, [Esther](#)

[Imede¹⁰](#), [Mary Kyohere¹¹](#), [Philippa Musoke⁵](#), [Annetee Nakimuli¹²](#), [Musa Sekikubo¹²](#), [Stephen Taylor⁷](#), [Valerie Tusubira⁵](#), [Manish Sadarangani³](#), [Kirsty Le Doare¹³](#)

Abstract

Background: Immunisation in pregnancy against pertussis can reduce severe disease in infancy. There are few data on the safety and immunogenicity of vaccines given to pregnant women living with HIV and their infants. We aimed to describe the safety and immunogenicity of a tetanus-diphtheria-acellular pertussis (Tdap) vaccine containing genetically detoxified pertussis toxin given to pregnant women living with HIV and the effect of the vaccine on infant whole-cell pertussis vaccine responses.

Methods: We conducted an observer-blind, randomised, phase 2, multicentre, non-inferiority trial evaluating safety and immunogenicity of a vaccine containing genetically detoxified acellular pertussis in pregnant women living with HIV in Uganda. Women aged at least 18 years between 16 weeks and 26 weeks of gestation were randomly assigned to receive the tetanus-diphtheria (Td) vaccine or Tdap vaccine. Stratified block randomisation using blocks of four with a 1:1:1:1 ratio stratified by participant HIV status was used to distribute participants into equal groups (50 participants per group for a total of 200 participants). The intervention was a 0.5 mL single intramuscular dose of Tdap vaccine. Td or Tdap vaccination was randomly assigned to different clinic days using randomisation software. Primary immunogenicity endpoints were anti-pertussis toxin and anti-filamentous haemagglutinin IgG concentrations in infants at delivery and 18 weeks following three doses of a whole-cell pertussis containing vaccine. This study is registered at ClinicalTrials.gov, [NCT04589312](#).

Findings: Between Oct 28, 2020, and May 21, 2021, 438 pregnant women were screened and 181 were randomly assigned: 90 to Tdap vaccine (40 HIV-positive participants and 50 HIV-negative participants) and 91 to Td vaccine (41 HIV-positive participants and 50 HIV-negative participants). All participants received Td, and 4 weeks later, 177 received either Td or Tdap. 32 serious adverse events occurred, none related to the study vaccine. At delivery, anti-pertussis toxin IgG concentrations for Tdap versus Td were superior in infants who were HIV-exposed but uninfected (geometric mean ratio 9.61, 95% CI 5.21-17.74) and HIV-unexposed infants (21.6, 11.2-41.7). In infants at 18 weeks, anti-pertussis toxin IgG concentrations for Tdap versus Td-vaccinated mothers were significantly lower for both infants who were HIV-exposed but uninfected (0.19, 0.09-0.43) and infants who were not HIV-exposed (0.17, 0.08-0.33). Serum bactericidal antibody generation following whole-cell pertussis vaccination in infants was not affected.

Interpretation: Tdap was safe and immunogenic in pregnant women living with HIV and their infants. Tdap provided superior anti-pertussis toxin IgG concentrations at delivery. Following routine vaccination with whole-cell pertussis vaccine, infants born to women receiving the Tdap vaccine had lower anti-pertussis toxin IgG concentrations than infants born to women receiving Td. In the absence of a correlate of protection against pertussis disease, the clinical significance of this finding is unclear.

Obstet Gynecol. 2025 Feb 1;145(2):147-156.

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Preterm Birth Frequency and Associated Outcomes From the MATISSE (Maternal Immunization Study for Safety and Efficacy) Maternal Trial of the Bivalent Respiratory Syncytial Virus Prefusion F Protein Vaccine

[Shabir A Madhi¹](#), [Beate Kampmann](#), [Eric A F Simões](#), [Philip Zachariah](#), [Barbara A Pahud](#), [David Radley](#), [Uzma N Sarwar](#), [Emma Shittu](#), [Conrado Llapur](#), [Gonzalo Pérez Marc](#), [Yvonne Maldonado](#), [Alisa Kachikis](#), [Heather J Zar](#), [Kena A Swanson](#), [Maria Maddalena Lino](#), [Annaliesa S Anderson](#), [Alejandra Gurtman](#), [Iona Munjal](#)

Abstract

Objective: To describe preterm birth frequency and newborn and infant outcomes overall and among preterm children in the MATISSE (Maternal Immunization Study for Safety and Efficacy) trial of maternal vaccination with bivalent respiratory syncytial virus (RSV) prefusion F protein-based vaccine (RSVpreF) to protect infants against severe RSV-associated illness.

Methods: MATISSE was a global, phase 3, randomized, double-blind trial. Pregnant individuals received single injections of RSVpreF or placebo. Adverse events of special interest, including preterm birth (gestational age less than 37 weeks) and low birth weight (2,500 g or less), were collected through 6 months after delivery (pregnant participants) and from birth through age 12 or 24 months (pediatric participants).

Results: Overall, 7,386 pregnant participants received RSVpreF (n=3,698) or placebo (n=3,688); 7,305 newborns and infants were included in the analysis. Most children in both groups were born full term (more than 93%) with normal birth weight (95% or higher). Newborn and infant outcomes, including rates of low birth weight and neonatal hospitalization, were favorable and comparable between groups. Preterm birth rates were 5.7% in the RSVpreF arm and 4.7% in the placebo arm (relative risk [RR] 1.20, 95% CI, 0.98-1.46); most were late preterm. Newborn and infant outcomes, including rates of low birth weight and neonatal hospitalization, were comparable between groups. Twenty-two newborn or infant deaths occurred during the study (RSVpreF n=8, placebo n=14). When stratified by income region, preterm birth rates in RSVpreF and placebo recipients were both 5.0% in high-income countries. Rates in non-high-income countries were 7.0% and 4.0% in the RSVpreF and placebo groups, respectively, and 8.3% and 4.0% in South Africa (RR 2.06, 95% CI, 1.21-3.51).

Conclusion: In this study of maternal RSVpreF vaccination, no clinically significant increase in adverse events of special interest, including preterm birth, low birth weight, or neonatal hospitalization, was observed among pregnant people in the overall analysis. In subgroup analysis of non-high-income countries, an elevated risk of preterm birth was observed. More research is needed to better ascertain preterm delivery risk factors, particularly aimed at minimizing disparities among geographic regions.

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Efficacy, Safety, and Immunogenicity of the MATISSE (Maternal Immunization Study for Safety and Efficacy) Maternal Respiratory Syncytial Virus Prefusion F Protein Vaccine Trial

[Eric A F Simões¹](#), [Barbara A Pahud](#), [Shabir A Madhi](#), [Beate Kampmann](#), [Emma Shittu](#), [David Radley](#), [Conrado Llapur](#), [Jeffrey Baker](#), [Gonzalo Pérez Marc](#), [Shaun L Barnabas](#), [Merlin Fausett](#), [Tyler Adam](#), [Nicole Perreras](#), [Marlies A Van Houten](#), [Anu Kantele](#), [Li-Min Huang](#), [Louis](#)

[J Bont](#), [Takeo Otsuki](#), [Sergio L Vargas](#), [Joanna Gullam](#), [Bruce Tapiero](#), [Renato T Stein](#), [Fernando P Polack](#), [Heather J Zar](#), [Nina B Staerke](#), [María Duron Padilla](#), [Peter C Richmond](#), [Uzma N Sarwar](#), [James Baber](#), [Kenneth Koury](#), [Maria Maddalena Lino](#), [Elena V Kalinina](#), [Weiqiang Li](#), [David Cooper](#), [Annaliesa S Anderson](#), [Kena A Swanson](#), [Alejandra Gurtman](#), [Iona Munjal](#); [MATISSE \(Maternal Immunization Study for Safety and Efficacy\) Clinical Trial Group](#)

Abstract

Objective: To evaluate descriptive efficacy data, exploratory immunogenicity data, and safety follow-up through study completion from the global, phase 3 MATISSE (Maternal Immunization Study for Safety and Efficacy) maternal vaccination trial of bivalent respiratory syncytial virus (RSV) prefusion F protein vaccine (RSVpreF).

Methods: MATISSE was a phase 3, randomized, double-blinded, placebo-controlled trial. Healthy pregnant participants aged 19 years or younger at 24-36 weeks of gestation were randomized (1:1) to receive a single RSVpreF 120 micrograms or placebo dose. Primary efficacy endpoints included newborn and infant severe RSV-associated medically attended lower respiratory tract illness within 180 days after birth. The RSV-A and RSV-B serum neutralizing antibody titers were determined in a subset of pregnant participants and their newborns.

Results: In this final analysis, 7,420 pregnant participants were randomized, and 7,307 children were born (RSVpreF n=3,660, placebo n=3,647). Vaccine efficacy, defined as protection against newborn and infant severe RSV-associated medically attended lower respiratory tract illness, was 82.4% (95% CI, 57.5-93.9) and 70.0% (95% CI, 50.6-82.5) within 90 and 180 days of birth, respectively. The RSVpreF induced robust immune responses in pregnant participants and resulted in highly efficient transfer of maternal antibodies to their newborns across subgroups (by gestational age at delivery and at vaccination, number of days from vaccination to delivery, country, maternal age). Final RSVpreF safety results in pregnant and newborn and infant participants were consistent with the primary analysis with no new safety concerns identified.

Conclusion: This final analysis of MATISSE trial data confirms the primary analysis conclusions: Maternal vaccination with RSVpreF has a favorable safety profile in both pregnant and newborn and infant participants and demonstrates efficacy against RSV-associated lower respiratory tract illness in infants through age 6 months. The RSVpreF induces robust immune responses in pregnant individuals, with corresponding high RSV-neutralizing titers in their newborns.

Measles vaccine

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[Contradictory mortality results in early 2-dose measles vaccine trials: interactions with oral polio vaccine may explain differences](#)

[Sebastian Nielsen](#)¹, [Ane B Fisker](#)², [Ali Sie](#)³, [Olaf Müller](#)⁴, [Eric Nebie](#)³, [Heiko Becher](#)⁵, [Fiona van der Klis](#)⁶, [Sofie Biering-Sørensen](#)⁷, [Stine Byberg](#)⁷, [Sanne M Thyssen](#)⁷, [Isaquel da](#)

[Silva⁷](#), [Amabelia Rodrigues⁷](#), [Cesario Martins⁷](#), [Hilton C Whittle⁸](#), [Peter Aaby²](#), [Christine S Benn⁹](#)

Abstract

Objectives: Between 2003 and 2019, three trials (randomised controlled trials [RCTs]) in Guinea-Bissau randomised infants to an early 2-dose measles vaccine (MV) schedule at 4 and 9 months vs standard MV at 9 months. The RCTs produced contradictory mortality results; the effect being beneficial in the 2-dose group in the first but tending to have higher mortality in the last two RCTs. We hypothesised that increased frequency of campaigns with oral polio vaccine (C-OPV) explained the pattern.

Methods: We performed per-protocol analysis of individual-level survival data from the three RCTs in Cox proportional hazards models yielding hazard ratios (HR) for the 2-dose vs the 1-dose MV group. We examined whether timing of C-OPVs and early administration of OPV0 (birth to day 14) affected the HRs for 2-dose/1-dose MV.

Results: The combined HR(2-dose/1-dose) was 0.79 (95% confidence interval: 0.62-1.00) for children receiving no C-OPV-before-enrolment, but 1.39 (0.97-1.99) for those receiving C-OPV-before-enrolment (homogeneity, $P = 0.01$). C-OPV-before-enrolment had a beneficial effect in the 1-dose group but tended to have a negative effect in the 2-dose group, especially in females. These effects were amplified further by early administration of OPV0.

Conclusion: In the absence of C-OPVs, an early 2-dose MV strategy had beneficial effects on mortality, but frequent C-OPVs may have benefitted the 1-dose group more than the 2-dose MV group, leading to varying results depending on the intensity of C-OPVs.

Measles, mumps, rubella (MMR) vaccine

*** Lancet Child Adolesc Health. 2025 May;9(5):306-314.

doi: 10.1016/S2352-4642(25)00090-2. Epub 2025 Mar 31.

[Immunogenicity and safety of a measles and rubella-containing vaccine at age 6 and 9 months in Bangladesh: an open-label, randomised trial](#)

[Takudzwa S Sayi¹](#), [Umid M Sharapov²](#), [Zachary Matson³](#), [Melissa M Coughlin³](#), [Stephen N Crooke³](#), [Qian An³](#), [Jennifer K Knapp³](#), [Asma Binte Aziz⁴](#), [Mohammad Yunus⁵](#), [Warda Haque⁵](#), [Sohel Rana⁵](#), [Md Al Fazal Khan⁵](#), [James P Alexander³](#), [Katrina Kretsinger²](#), [Paul A Rota³](#), [Khalequ Zaman⁵](#), [Abhijeet Anand³](#)

Abstract

Background: The first dose of measles-rubella (MR) vaccine is routinely administered to infants aged 9 months as part of a standard two-dose schedule. However, during large measles outbreaks and in other settings of increased circulation or increased risk, WHO recommends administering a supplementary dose at age 6 months to protect young infants. We aimed to assess the immunogenicity and safety of a first dose of MR vaccine administered to infants aged 6 months and its effect on the immune response to the routine MR vaccine at age 9 months.

Methods: This open-label, randomised trial enrolled healthy infants aged 6 months in Matlab, Bangladesh, who had never received an MR vaccine dose and had no history of measles or rubella. Using a computer-generated block randomisation scheme, infants were randomly assigned (1:1) to receive either two doses of the MR vaccine, one at age 6 months

and the second at age 9 months (two-dose group), or one dose at age 9 months (one-dose group). Baseline characteristics were recorded for all enrolled participants at age 6 months. Blood samples were drawn for antibody assays before each vaccination and at final follow up when infants were aged 11 months. The primary outcome was immunogenicity of a first MR vaccine in infants aged 6 months or 9 months and the immunogenicity of a second MR vaccine in infants aged 9 months who received their first MR vaccine at 6 months. Immunogenicity was measured as the proportion of infants who seroconverted in the 12 weeks after vaccination at age 6 months or the 8 weeks after vaccination at age 9 months. Seroconversion was defined as a 4-times increase in IgG concentrations relative to the pre-vaccination concentrations or achieving seroprotective antibody concentrations between study timepoints. The modified intention-to-treat analysis included all infants who received MR vaccines per group assignment and had antibody results at baseline, 9 months, and 11 months. All enrolled infants were included in the safety analysis of the immediate reactions (observed by study staff at the fixed-site clinic in the first 30 min after vaccination), adverse events within 48 h of vaccination among infants in the two-dose group receiving their first MR vaccine at age 6 months, and adverse events observed by study staff or parents at any time during the study. The trial is registered on ClinicalTrials.gov, [NCT03071575](https://clinicaltrials.gov/ct2/show/study/NCT03071575), and is closed to enrolment.

Findings: Between March 9, 2017, and March 18, 2018, 620 infants were enrolled and randomly assigned to the two study groups (312 in the two-dose group and 308 in the one-dose group). Of the 301 infants vaccinated at 6 months, 282 seroconverted for measles (94%, 95% CI 90-96), and 283 seroconverted for rubella (94%, 91-96). By 11 months, after receiving a second dose at age 9 months, 297 (cumulative 99%, 95% CI 97-100) infants seroconverted for measles and 297 infants seroconverted for rubella (cumulative 99%, 96-100). Of the 292 infants vaccinated at 9 months only, 291 seroconverted for both antigens by age 11 months (100%, 95% CI 98-100). 123 adverse events were observed; 72 in the two-dose group and 51 in the one-dose group, with no differences in severity ($p=0.78$) or outcomes ($p=0.71$) by study group. 12 (17%) events in the two-dose group and seven (14%) in the one-dose group were severe; most events were mild, resolved without sequelae, and were unrelated to the MR vaccine. One death occurred in the one-dose group before the infant received the 9-month dose of the vaccine, and therefore was deemed to be unrelated to the MR vaccine.

Interpretation: The data presented support use of MR vaccine at 6 months to protect young infants during measles outbreaks and in settings with increased risk or high transmission. We recommend additional studies to evaluate longer-term immunity based on age at vaccination.

Meningococcal vaccine

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doi: 10.1016/S0140-6736(25)00046-7. Epub 2025 Mar 11.

[Safety and immunogenicity of a pentavalent meningococcal conjugate vaccine targeting serogroups A, C, W, Y, and X when co-administered with routine childhood vaccines at ages 9 months and 15 months in Mali: a single-centre, double-blind, randomised, controlled, phase 3, non-inferiority trial](#)

[Fatoumata Diallo¹](#), [Fadima C Haidara¹](#), [Milagritos D Tapia²](#), [Clara P Dominguez Islas³](#), [Mark R Alderson⁴](#), [William P Hausdorff⁵](#), [Lionel Martellet⁴](#), [Nancy Hosken⁴](#), [Dhananjay Kapse⁶](#), [Prasad S Kulkarni⁶](#), [Kelly Townsend-Payne⁷](#), [Francesca Vanni⁸](#), [Christine M Posavad⁹](#), [Samba O Sow¹](#), [Karen L Kotloff²](#), [Wilbur H Chen¹⁰](#); [NmCV-5 EPI study team](#)

Abstract

Background: Invasive meningococcal disease is a devastating public health problem for the African meningitis belt. We assessed the safety and immunogenicity of a pentavalent meningococcal conjugate vaccine targeting serogroups A, C, Y, W, and X (NmCV-5) relative to a licensed, quadrivalent meningococcal conjugate vaccine (MenACWY-TT) when co-administered with routine childhood vaccines at ages 9 months and 15 months.

Methods: In this single-centre, double-blind, randomised, controlled, phase 3, non-inferiority trial, children aged 9-11 months who had completed their local infant Expanded Program on Immunization (EPI) vaccines were recruited at the Centre pour le Développement des Vaccins in Bamako, Mali. Participants were randomly assigned (1:1·2) at their 9-month EPI visits to receive a meningococcal vaccine at either their 9-month or 15-month EPI vaccination visits. At each participant's designated EPI visit, they were randomly assigned a second time (2:1) to receive either NmCV-5 or MenACWY-TT. Study vaccines and designated EPI vaccines were prepared and administered by assigned unmasked study personnel. Parents or guardians, investigators, and all other trial staff were masked to meningococcal vaccine assignments. The meningococcal vaccines were co-administered with a measles and rubella vaccine (first dose) and a yellow fever vaccine at age 9 months or with a measles and rubella vaccine (second dose) at age 15 months. The primary endpoint, seroprotective response, was defined as a rabbit complement serum bactericidal antibody titre of 8 or higher, with the estimand, given as the difference in the proportions of participants for each of the five meningococcal serogroups who showed this response 28 days after vaccination, assessed in the per-protocol population. The prespecified non-inferiority margin was -10% for all five serogroups in both age groups. The non-inferiority of the NmCV-5 seroprotective response to serogroup X was evaluated in comparison with the lowest seroprotective response for MenACWY-TT among serogroups A, C, W, or Y. Safety was a secondary endpoint, assessed over 6 months in a modified intention-to-treat population that included all participants who received a randomly assigned meningococcal vaccine. This trial is registered with ClinicalTrials.gov, [NCT05093829](#).

Findings: Between March 24 and Aug 15, 2022, 1325 participants were enrolled and randomly assigned to receive a meningococcal vaccine at either age 9 months (n=602) or age 15 months (n=723). Meningococcal vaccines were administered to 600 of the 602 participants assigned to the 9-month vaccination group during that same period. Between Sept 27, 2022, and Feb 6, 2023, 600 participants received meningococcal vaccines at their 15-month visits. In both groups, 400 participants received NmCV-5 and 200 participants received MenACWY-TT. The per-protocol population assessed in the non-inferiority analysis included 564 participants vaccinated at age 9 months (373 who received NmCV-5 and 191 who received MenACWY-TT) and 549 participants vaccinated at age 15 months (367 who received NmCV-5 and 182 who received MenACWY-TT). Among the participants in the per-protocol population who received NmCV-5 at age 9 months, the difference in seroprotection prevalence for NmCV-5 relative to MenACWY-TT was 0·0% (95% CI -1·0 to 2·0) for serogroup A, -0·5% (-2·3 to 1·9) for serogroup C, -3·0% (-6·3 to 0·8) for serogroup W, and -3·0% (-5·4 to -0·4) for serogroup Y. For serogroup X, non-inferiority was assessed relative to seroprotection for serogroup W in participants who received MenACWY-TT, with a difference of 2·3% (95% CI 0·3 to 4·7). The

difference in the prevalence of seroprotection among the participants who received NmCV-5 at age 15 months relative to participants who received MenACWY-TT at age 15 months was 0·8% (95% CI -0·6 to 3·7) for serogroup A, -0·8% (-3·3 to 2·5) for serogroup C, 0·3% (-1·8 to 3·5) for serogroup W, and 1·4% (-0·6 to 4·8) for serogroup Y. For serogroup X, non-inferiority was assessed in relation to seroprotection for serogroup Y in participants who received MenACWY-TT, with a difference of 1·9% (95% CI 0·0 to 4·4). NmCV-5 responses in both age groups were non-inferior to MenACWY-TT responses for all five serogroups. Six serious adverse events were recorded but none were deemed related to vaccination.

Interpretation: When compared with a licensed, quadrivalent meningococcal conjugate vaccine, and given alongside other routine vaccines, a single dose of NmCV-5 was safe and elicited a non-inferior immune response in infants aged 9 months and young children aged 15 months.

Norovirus vaccine

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Safety and immunogenicity of a bivalent norovirus vaccine candidate in infants from 6 weeks to 5 months of age: A phase 2, randomized, double-blind trial

[Xavier Sáez-Llorens^{1,2,3}](#), [Rodrigo deAntonio¹](#), [Eduardo López-Medina⁴](#), [Pío López⁴](#), [Taisei Masuda⁵](#), [Paul M Mendelman⁶](#), [Jim Sherwood^{5,7}](#), [Frank Baehner⁵](#), [Astrid Borkowski^{5,7}](#)

Abstract

As infants suffer significant morbidity and mortality due to norovirus-related acute gastroenteritis (AGE), we assessed four formulations of the bivalent virus-like particle (VLP) vaccine candidate (HIL-214) in Panamanian and Colombian infants. 360 infants aged 6 weeks to 5 months were randomly allocated to 8 groups to receive three doses of HIL-214 or two doses of HIL-214 and one dose of placebo (Days 1, 56 and 112), where HIL-214 doses contained 15/15, 15/50, 50/50 or 50/150 µg of GI.1/GII.4c genotype VLPs and 0.5 mg Al(OH)₃. Solicited injection-site and systemic adverse events (AE) were collected within 7 days after each dose, unsolicited AEs were collected within 28 days after each, and serious AEs throughout the study. Pan-Ig and histoblood group antigen-blocking antibodies (HBGA) were measured on Days 1, 56, 84, and 140. All formulations were well-tolerated causing mainly mild-to-moderate transient solicited AEs, most frequently local pain and irritability/fussiness, but no vaccine-related serious AEs. Two doses of each formulation induced high titers of high avidity Pan-Ig and also HBGA antibodies; a third dose increased titers against both antigens and the avidity of Pan-Ig antibodies against GII.4c but not against GI.1. Two and three doses of HIL-214 were well-tolerated and induced potent immune responses at 4-6 months of age supporting further clinical assessment to protect against norovirus-related AGE.

Pertussis vaccine

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doi: 10.1016/S2352-4642(24)00173-1.

[A reduced-dose recombinant pertussis vaccine booster in Thai adolescents: a phase 2/3, observer-blinded, randomised controlled, non-inferiority trial](#)

[Thanyawee Puthanakit¹](#), [Auchara Tangsathapornpong²](#), [Suvaporn Anugulruengkitt¹](#), [Rapisa Nantanee¹](#), [Pornumpa Bunjoungmanee³](#), [Souad Mansouri⁴](#), [Librada Fortuna⁴](#), [Wassana Wijagkanalan⁴](#), [Terapong Tantawichien⁵](#); [TDA205 study team](#)

Abstract

Background: A resurgence of pertussis has increased the demand for low-cost vaccines. The aim of this study was to test the immunogenicity of a booster acellular monovalent pertussis vaccine containing reduced-dose (2 µg) recombinant pertussis toxin (PT) and 5 µg filamentous haemagglutinin (FHA; ap_{gen}) against a version of ap_{gen} containing tetanus and reduced-dose diphtheria toxoids (Tdap_{gen}) and a licensed vaccine containing chemically detoxified PT and FHA combined with tetanus toxoid and reduced-dose diphtheria toxoid (Tdap_{chem}).

Methods: This phase 2/3, observer-blinded, randomised, controlled, non-inferiority trial was done in adolescents aged 9-17 years at two clinical research centres in Bangkok and Pathum Thani, Thailand. Eligible participants were screened and randomly assigned (1:1:1) to receive one booster dose of ap_{gen}, Tdap_{gen}, or Tdap_{chem} vaccine. Participants were followed up until day 336 post-immunisation. The primary endpoint was non-inferior seroconversion rates in Tdap_{gen} and Tdap_{chem} vaccine groups, with seroconversion rate defined as the proportion of participants with at least a four-fold increase on day 28 post-immunisation relative to baseline of anti-PT and anti-FHA IgG. The non-inferiority for seroconversion rates of anti-PT and anti-FHA IgG was defined as the lower bound of the two-sided 95% CI of the seroconversion rate for Tdap_{gen} compared with Tdap_{chem} exceeding -10%. Immunogenicity was analysed in the per-protocol population. All safety data were collected, and the prevalence of adverse events was analysed in the intention-to-treat population. This trial was registered on the Thai Clinical Trial Registry (TCTR20181031001).

Findings: Between June 18, and Aug 3, 2019, 450 adolescents (mean age 12·1 years, SD 2·5) were enrolled and randomly assigned (150 participants in each group). Day 28 anti-PT IgG seroconversion rates were 141 (94%) of 150 participants who received Tdap_{gen} (95% CI 88·8-97·0) and 105 (71%) of 149 participants who received Tdap_{chem} (62·7-77·2; p<0·0001). Day 28 anti-FHA IgG seroconversion rates were 144 (96%) of 150 participants who received Tdap_{gen} (91·4-98·3) and 124 (83%) of 149 participants who received Tdap_{chem} (76·4-88·4; p<0·0001). The difference in seroconversion rates was 23·5% (95% CI 15·3-31·8) for anti-PT IgG and 12·8% (6·0-19·6) for anti-FHA IgG, when comparing the Tdap_{gen} versus the Tdap_{chem} vaccine group. No vaccine-related serious adverse events were reported.

Interpretation: Recombinant Tdap_{gen} vaccine showed non-inferior immunogenicity compared with Tdap_{chem} at day 28 in terms of seroconversion rate of anti-PT IgG and anti-FHA IgG relative to baseline. The reduced-dose approach for Tdap_{gen} vaccines thus presents as a potentially cost-saving booster strategy to protect adolescents against pertussis.

Prentavalent vaccine (DTP-HepB-Hib)

Pneumococcal vaccine

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Memory B cell responses induced by pneumococcal conjugate vaccine schedules with fewer doses: analysis of a randomised-controlled trial in Viet Nam

[Darren Suryawijaya Ong^{#1,2}](#), [Thanh V Phan^{#3}](#), [Beth Temple^{#1,4,5}](#), [Zheng Quan Toh^{1,2}](#), [Cattram Duong Nguyen^{1,2}](#), [Kien Vientrung³](#), [Hoang Van Anh Nguyen³](#), [Vo Thi Trang Dai³](#), [Kathryn Bright¹](#), [Hau Phuc Tran³](#), [Rachel Ann Higgins¹](#), [Yin Bun Cheung^{6,7}](#), [Thuong Vu Nguyen³](#), [Kim Mulholland^{1,2,5}](#), [Paul Vincent Licciardi^{8,9}](#)

Abstract

The use of pneumococcal conjugate vaccine (PCV) schedules with fewer doses are being considered to reduce costs and improve access, particularly in low- and middle-income countries. While several studies have assessed their immunogenicity, there are limited data on their potential for long-term immune protection, as assessed by pneumococcal serotype-specific memory B cell (B_{mem}) responses. This current study reports secondary outcome data that aims to compare B_{mem} responses following reduced-dose (0 + 1 and 1 + 1) schedules of PCV10 and PCV13 in Vietnamese infants from our randomised-controlled trial (trial registration number [NCT03098628](#)). Following vaccination at 12 months of age, B_{mem} levels for most serotypes peaked seven days post-vaccination and were higher in magnitude for the 1 + 1 than 0 + 1 schedules and for PCV13 than PCV10. Furthermore, B_{mem} did not wane as rapidly as IgG levels by 24 months of age. Further studies are needed to assess the use of B_{mem} as markers of long-term protection against pneumococcal carriage and disease, which is crucial to generate data for immunisation program decision-making.

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doi: 10.3310/YWHA3079.

Immunogenicity and seroefficacy of pneumococcal conjugate vaccines: a systematic review and network meta-analysis

[Shuo Feng¹](#), [Julie McLellan²](#), [Nicola Pidduck²](#), [Nia Roberts³](#), [Julian Pt Higgins⁴](#), [Yoon Choi⁵](#), [Alane Izu⁶](#), [Mark Jit⁷](#), [Shabir A Madhi^{6,8}](#), [Kim Mulholland^{7,9,10}](#), [Andrew J Pollard^{1,11}](#), [Simon Procter⁷](#), [Beth Temple^{7,9,10}](#), [Merryn Voysey^{1,11}](#)

Abstract

Background: Vaccination of infants with pneumococcal conjugate vaccines is recommended by the World Health Organization. Evidence is mixed regarding the differences in immunogenicity and efficacy of the different pneumococcal vaccines.

Objectives: The primary objective was to compare the immunogenicity of pneumococcal conjugate vaccine-10 versus pneumococcal conjugate vaccine-13. The main secondary objective was to compare the seroefficacy of pneumococcal conjugate vaccine-10 versus pneumococcal conjugate vaccine-13.

Methods: We searched the Cochrane Library, EMBASE, Global Health, MEDLINE, ClinicalTrials.gov and trialsearch.who.int up to July 2022. Studies were eligible if they directly compared either pneumococcal conjugate vaccine-7, pneumococcal conjugate

vaccine-10 or pneumococcal conjugate vaccine-13 in randomised trials of children under 2 years of age, and provided immunogenicity data for at least one time point. Individual participant data were requested and aggregate data used otherwise. Outcomes included the geometric mean ratio of serotype-specific immunoglobulin G and the relative risk of seroinfection. Seroinfection was defined for each individual as a rise in antibody between the post-primary vaccination series time point and the booster dose, evidence of presumed subclinical infection. Each trial was analysed to obtain the log of the ratio of geometric means and its standard error. The relative risk of seroinfection ('seroefficacy') was estimated by comparing the proportion of participants with seroinfection between vaccine groups. The log-geometric mean ratios, log-relative risks and their standard errors constituted the input data for evidence synthesis. For serotypes contained in all three vaccines, evidence could be synthesised using a network meta-analysis. For other serotypes, meta-analysis was used. Results from seroefficacy analyses were incorporated into a mathematical model of pneumococcal transmission dynamics to compare the differential impact of pneumococcal conjugate vaccine-10 and pneumococcal conjugate vaccine-13 introduction on invasive pneumococcal disease cases. The model estimated the impact of vaccine introduction over a 25-year time period and an economic evaluation was conducted.

Results: In total, 47 studies were eligible from 38 countries. Twenty-eight and 12 studies with data available were included in immunogenicity and seroefficacy analyses, respectively. Geometric mean ratios comparing pneumococcal conjugate vaccine-13 versus pneumococcal conjugate vaccine-10 favoured pneumococcal conjugate vaccine-13 for serotypes 4, 9V and 23F at 1 month after primary vaccination series, with 1.14- to 1.54-fold significantly higher immunoglobulin G responses with pneumococcal conjugate vaccine-13. Risk of seroinfection prior to the time of booster dose was lower for pneumococcal conjugate vaccine-13 for serotype 4, 6B, 9V, 18C and 23F than for pneumococcal conjugate vaccine-10. Significant heterogeneity and inconsistency were present for most serotypes and for both outcomes. Twofold higher antibody after primary vaccination was associated with a 54% decrease in risk of seroinfection (relative risk 0.46, 95% confidence interval 0.23 to 0.96). In modelled scenarios, pneumococcal conjugate vaccine-13 or pneumococcal conjugate vaccine-10 introduction in 2006 resulted in a reduction in cases that was less rapid for pneumococcal conjugate vaccine-10 than for pneumococcal conjugate vaccine-13. The pneumococcal conjugate vaccine-13 programme was predicted to avoid an additional 2808 (95% confidence interval 2690 to 2925) cases of invasive pneumococcal disease compared with pneumococcal conjugate vaccine-10 introduction between 2006 and 2030.

Limitations: Analyses used data from infant vaccine studies with blood samples taken prior to a booster dose. The impact of extrapolating pre-booster efficacy to post-booster time points is unknown. Network meta-analysis models contained significant heterogeneity which may lead to bias.

Conclusions: Serotype-specific differences were found in immunogenicity and seroefficacy between pneumococcal conjugate vaccine-13 and pneumococcal conjugate vaccine-10. Higher antibody response after vaccination was associated with a lower risk of subsequent infection. These methods can be used to compare the pneumococcal conjugate vaccines and optimise vaccination strategies. For future work, seroefficacy estimates can be determined for other pneumococcal vaccines, which could contribute to licensing or policy decisions for new pneumococcal vaccines.

Expert Rev Vaccines. 2025 Dec;24(1):121-127.

doi: 10.1080/14760584.2025.2458179. Epub 2025 Jan 27.

Serotype-specific serum immunoglobulin G at 18 months of age following one or two doses of a primary series of 10-valent or 13-valent pneumococcal conjugate vaccine and a booster dose at nine months of age: a randomized controlled study

[Alane Izu^{1,2}](#), [Eleanora Aml Mutsaerts^{1,2,3}](#), [Courtney Olwagen^{1,2}](#), [Lisa Jose^{1,2}](#), [Anthonet Koen^{1,2}](#), [Amit J Nana^{1,2}](#), [Clare L Cutland⁴](#), [Shabir A Madhi^{1,2}](#)

Abstract

Background: Due to high costs of pneumococcal conjugate vaccines (PCV), transitioning from a two (2 + 1) to a single dose (1 + 1) primary series with a booster should be considered. This study evaluated the immune response at 18 months of age following a 1 + 1 compared to a 2 + 1 schedule of 10-valent (PCV10) and 13-valent (PCV13) vaccines.

Research design and methods: A single-center, open-label, randomized trial conducted in Soweto, South Africa, evaluated the immunogenicity of differing dosing schedule for PCV10 and PCV13. Six hundred children were randomly assigned to six study arms (1:1:1:1:1:1). Non-inferiority was concluded when the lower limit of the 96% confidence interval of the ratio of geometric mean concentrations (GMCs) of the 1 + 1 and 2 + 1 schedules was >0.5 for at least 10 and eight of the PCV13 and PCV10 serotypes, respectively.

Results: GMCs in children who received the PCV13_6w + 1 and PCV13_14w + 1 schedule were non-inferior for 11 and 10 of the PCV13 serotypes, respectively, compared with the PCV13_2 + 1 arm. For PCV10, GMCs for both 1 + 1 schedules were non-inferior to a 2 + 1 schedule for nine of the PCV10 serotypes.

Conclusion: Transitioning to a 1 + 1 schedule should be considered for early immunization programs.

Lancet Infect Dis. 2025 Jan 8:S1473-3099(24)00719-9.

doi: 10.1016/S1473-3099(24)00719-9. Online ahead of print.

Effect of mass campaigns with full and fractional doses of pneumococcal conjugate vaccine (Pneumasil) on the reduction of nasopharyngeal pneumococcal carriage in Niger: a three-arm, open-label, cluster-randomised trial

[Matthew E Coldiron¹](#), [Issaka Soumana²](#), [Elisabeth Baudin³](#), [Céline Langendorf³](#), [Corinne Mamiafo Tchoula²](#), [Souleymane Brah⁴](#), [Angela Karani⁵](#), [Katherine E Gallagher⁶](#), [E Wangeci Kagucia⁵](#), [J Anthony G Scott⁶](#), [Rebecca F Grais³](#)

Abstract

Background: In settings with low pneumococcal conjugate vaccine (PCV) coverage, multi-age cohort mass campaigns could increase population immunity, and fractional dosing could increase affordability. We aimed to evaluate the effect of mass campaigns on nasopharyngeal pneumococcal carriage of Pneumasil (PCV10) in children aged 1-9 years in Niger.

Methods: In this three-arm, open-label, cluster-randomised trial, 63 clusters of one to four villages in Niger were randomly assigned (3:3:1) using block randomisation to receive campaigns consisting of a single full dose of a 10-valent PCV (Pneumasil), a single one-fifth dose of Pneumasil, or no campaign. Independently sampled carriage surveys were done among 2268 households 6 months before and after vaccination, collecting nasopharyngeal

swabs from healthy children for culture and serotyping; those with contraindication to nasopharyngeal swabbing were excluded. The primary outcome was nasopharyngeal carriage of vaccine-serotype pneumococcus. We tested whether vaccine-type carriage was reduced in full-dose versus control clusters; and whether fractional doses were non-inferior to full-doses (lower bound 95% CI more than -7.5%), using generalised estimating equations to analyse cluster summaries at baseline and follow-up, controlling for covariates to estimate risk differences and their 95% CIs. The study is registered with ClinicalTrials.gov ([NCT05175014](https://clinicaltrials.gov/ct2/show/study/NCT05175014)) and the Pan-African Clinical Trials Registry (PACTR20211257448484).

Findings: Surveys were done between Dec 22, 2021, and March 18, 2022, and between Dec 12, 2022, and March 9, 2023. The vaccination campaign ran from June 15 to Aug 2, 2022. Participants' characteristics were consistent across surveys and groups. Pre-vaccination, vaccine-type carriage was 15.6% (149 of 955 participants) in the full-dose group, 17.9% (170 of 948) in the fractional-dose group, and 18.8% (60 of 320) in the control group. Post-vaccination, vaccine-type carriage was 4.6% (44 of 967) in the full-dose group, 8.0% (77 of 962) in the fractional-dose group, and 16.5% (53 of 321) in the control group. The primary analysis showed a risk difference of -16.2% (95% CI -28.6 to -3.0) between the full-dose group and control group ($p=0.002$ for superiority), and -3.8% (-6.1 to -1.6) between the full-dose group and fractional-dose group, meeting the non-inferiority criteria. No adverse events were judged to be related to vaccination.

Interpretation: Multi-age cohort campaigns had a marked effect on vaccine-type carriage and fractional-dose campaigns met non-inferiority criteria. Such campaigns should be considered in low-coverage settings, including humanitarian emergencies, to accelerate population protection.

Polio vaccine

Vaccine. 2024 Aug 30;42(21):126183.

doi: 10.1016/j.vaccine.2024.126183. Epub 2024 Jul 31.

[Safety and 6-month immune persistence of inactivated poliovirus vaccine \(Sabin strains\) simultaneously administered with other vaccines for primary and booster immunization in Jiangxi Province, China](#)

[Shicheng Guo](#)¹, [Zhen Li](#)², [Min Zheng](#)¹, [Fengyun Wu](#)¹, [Jianwen Sun](#)², [Ling Tuo](#)², [Su Li](#)³, [Xiang Li](#)⁴, [Lijuan Wei](#)⁴, [Zhiyong Xia](#)⁵, [Pinxing Xie](#)⁵, [Xiaomei Chen](#)⁵, [Yanwei Zhao](#)², [Yongjun Gao](#)², [Dan Yu](#)⁶

Abstract

Objectives: This study aims to evaluate the safety of a new inactivated poliomyelitis vaccine (Sabin strains) (sIPV) for large-scale use in primary and booster immunizations, whether simultaneously administered with other vaccines or not and to explore the persistence of all vaccines at approximately six months after vaccination.

Method: A total of 3200 infants were recruited into this study, including 2000 infants aged 2-3 months randomly assigned (1:1) into the "sIPV basic" or the "sIPV+DTaP" group for primary immunization of sIPV. Another 1200 children aged 18 months old and above were randomly assigned (2:2:1:1) into the "sIPV booster," "sIPV+HepA-I," "sIPV+MMR", or "sIPV+HepA-L"

group for booster immunization of sIPV. Adverse events within 30 days of each vaccination dose in all participants were self-reported by guardians using a WeChat mini-program. Approximately 200 blood samples were collected at 5-7 months after the final vaccination to test for antibodies against poliovirus and other viruses.

Results: 3198 participants in total were included in the safety study, including 1999 infants aged 2-3 months old and 1199 children aged 18-26 months old. For primary immunization, the incidence of adverse reactions in the "sIPV basic" and the "sIPV+DTaP" group were 3.19 and 6.21% ($P = 0.001$), respectively. For booster immunization, the incidences of adverse reaction for the "sIPV booster" group were 2.25%, while the incidence for the "sIPV +others" group in total was 2.50% ($P = 0.788$). Most adverse reactions were mild. Fever was the most common symptom in all groups. No vaccine-related serious adverse events (SAEs) were observed in this study. The seropositivity rates of antibodies in the "sIPV basic" and the "sIPV+DTaP" group were 92.31 and 100% against type 1 poliovirus ($P = 0.031$); 96.15% and 98.57% against type 2 poliovirus ($P = 0.575$); 98.08% and 91.43% against type 3 poliovirus ($P = 0.237$), respectively. Regarding booster vaccination with sIPV, whether co-administered with other vaccines or not, the seropositivity rates of antibodies against the three types of polioviruses were all 100%. Seropositivity rates of antibodies against hepatitis A, measles, mumps, and rubella were all no <77%, except for pertussis, which was <30%.

Conclusion: sIPV demonstrated good safety and immune persistence for primary and booster vaccinations, whether administered singly or simultaneously. Antibodies against hepatitis A, measles, mumps and rubella were not disrupted by the co-vaccination. However, the seropositivity rates and geometric mean concentrations (GMCs) of antibodies against pertussis indicate the necessity for a booster dose.

Vaccine. 2024 Sep 17;42(22):126216.

doi: 10.1016/j.vaccine.2024.126216. Epub 2024 Aug 14.

Assessing the mucosal intestinal and systemic humoral immunity of sequential schedules of inactivated poliovirus vaccine and bivalent oral poliovirus vaccine for essential immunization in Bangladesh: An open-label, randomized controlled trial

Cynthia J Snider¹, Khalequ Zaman², Concepcion F Estivariz³, Asma Binte Aziz², Mohammad Yunus², Warda Haque², William S Hendley¹, William C Weldon¹, M Steven Oberste¹, Mark A Pallansch¹, Steven G F Wassilak¹, Abhijeet Anand¹

Abstract

In 2012, the Strategic Advisory Group of Experts on Immunization (SAGE) recommended introduction of at least one inactivated poliovirus vaccine (IPV) dose in essential immunization programs. We evaluated systemic humoral and intestinal mucosal immunity of a sequential IPV-bivalent oral poliovirus vaccine (bOPV) schedule compared with a co-administration IPV + bOPV schedule in an open-label, randomized, controlled, non-inferiority, inequality trial in Dhaka, Bangladesh. Healthy infants aged 6 weeks were randomized to either: (A) IPV and bOPV at 6 and bOPV at 10 and 14 weeks (IPV + bOPV-bOPV-bOPV); or (B) IPV at 6 and bOPV at 10 and 14 weeks (IPV-bOPV-bOPV). Of 456 participants enrolled and randomly assigned during May-August 2015, 428 (94%) were included in the modified intention-to-treat analysis (arm A: 211, arm B: 217). Humoral immune responses did not differ at 18 weeks between study arms: type 1 (98% versus 96%; $p = 0.42$), type 2 (37% versus 39%; $p = 0.77$), and type 3 (97% versus 93%; $p = 0.07$). Virus shedding one week after the bOPV challenge dose in arm B was non-inferior to arm A (type 1 difference = -3% [90%

confidence interval: -6 - 0.4%]; type 3 difference: -3% [-6 to -0.2%]). Twenty-six adverse events including seven serious adverse events were reported among 25 participants including one death; none were attributed to study vaccines. An IPV-bOPV-bOPV sequential schedule induced comparable systemic humoral immunity to all poliovirus types and types 1 and 3 intestinal mucosal immunity as an IPV + bOPV-bOPV-bOPV co-administration schedule.

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Effect of a campaign with oral polio vaccine on general health: A cluster-randomised trial in rural Guinea-Bissau

[Line M Nanque¹](#), [Anshu Varma²](#), [Sanne M Thyssen³](#), [Christine S Benn⁴](#), [Justiniano Sd Martins²](#), [Aksel Kg Jensen⁵](#), [Claudino Correia²](#), [Sören Möller⁶](#), [Anita Van den Biggelaar⁷](#), [Peter Aaby⁸](#), [Ane B Fisker⁹](#)

Abstract

Objectives: To investigate in a cluster-randomised trial whether a campaign with oral polio vaccine (C-OPV) reduced mortality and morbidity.

Methods: We randomised 222 village clusters under demographic surveillance to an intervention (health check and C-OPV) or control group (health check only). Children aged 0-8 months were eligible. In Cox proportional hazards models with age as the underlying timescale, we compared rates of non-accidental mortality/hospital admission (composite primary outcome) during 12 months of follow-up. Secondary analyses considered non-accidental admission and mortality as separate outcomes. Potential effect modifiers identified in prior studies including sex, season, and timing of the first routine OPV dose (OPV0, scheduled at birth) were assessed.

Results: Among 10,175 children (5288 in 111 intervention clusters/4887 in 111 control clusters), we observed 265 deaths/admissions during 7616 person-years at risk (intervention: 129; control: 136). C-OPV did not reduce the composite endpoint, hazard ratio (HR): 0.87, 95%CI: 0.68-1.12 or its separate components. C-OPV reduced the risk in children receiving OPV0<15 days of birth (HR=0.66, 95%CI: 0.46-0.95), but not in other children (p for interaction: 0.03). Interactions for other potential effect modifiers were not statistically significant.

Conclusions: C-OPV had no overall effect on mortality/admissions, but the effect differed by early priming with OPV0.

Rabies vaccine

Front Immunol. 2024 Nov 7;15:1444686.

doi: 10.3389/fimmu.2024.1444686. eCollection 2024.

Safety, immunogenicity and immune-persistence of a lyophilized human rabies vaccine (Vero cells) under Zagreb and Essen regimens: a randomized, open-label, controlled phase III clinical trial in healthy participants aged 10-60 years in China

[Zhenzhen Liang^{#1}](#), [Xu Chen^{#2}](#), [Bo Xing¹](#), [Xiaosong Hu¹](#), [Miaomiao Liu³](#), [Xinpei Zhang⁴](#), [Yugang Shen⁵](#), [Yan Wang³](#), [Yingping Chen¹](#), [Huakun Lv¹](#), [Yu Mao³](#)

Abstract

Background: Rabies continues to be a significant global public health concern, particularly in the Asia region where it is associated with high mortality rate. The administration of effective vaccination is essential in preventing this potentially fatal viral infection. The objective of this study was to evaluate the immunogenicity and safety of two rabies vaccination schedules: the Zagreb (2-1-1) and Essen (1-1-1-1-1) regimens, in a cohort of healthy Chinese individuals aged 10-60 years.

Methods: We conducted a randomized, open-label, controlled, non-inferiority phase 3 trial from July 2021 to November 2022, enrolling a total of 1200 participants. Participants were randomly assigned to receive either the Zagreb or Essen vaccination regimen. The primary outcomes were safety, immunogenicity, and immune persistence. Safety was monitored through adverse event reporting, while immunogenicity was determined by measuring rabies-virus-neutralizing antibody (RVNA) concentrations using the rapid fluorescent focus inhibition test (RFFIT). Immune persistence was evaluated at 3, 6, and 12 months post-vaccination.

Results: The two vaccination regimens exhibited comparable safety records, with mild and transient adverse events predominantly occurring within 0-3 days post-vaccination. The Zagreb regimen demonstrated non-inferiority in terms of seroconversion rates and geometric mean concentrations (GMCs) of antibodies compared to the Essen regimen at both 14 days post-first vaccination and 14 days post-full vaccination. Additionally, both groups displayed nearly 100% seropositivity rate at 3, 6, and 12 months. No serious adverse events associated with vaccination were reported.

Conclusion: The findings of this Phase 3 clinical trial provide compelling evidence that the Zagreb regimen is a feasible alternative when compared to the Essen regimen for rabies vaccination, offering a more pragmatic and cost-efficient approach to rabies prevention and control.

Hum Vaccin Immunother. 2024 Dec 31;20(1):2426289.

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[Safety and immunogenicity of freeze-dried human rabies vaccines: A phase 3 clinical trial of Zagreb and Essen regimes](#)

[Jia Li¹](#), [Zhiang Wu²](#), [Xiaohong Wu¹](#), [Yunpeng Wang¹](#), [Leitai Shi¹](#), [Danhua Zhao¹](#), [Haiyan Liang²](#), [Zhaojun Mo³](#), [Shouchun Cao¹](#)

Abstract

Recently optimized freeze-dried rabies vaccines (Vero cell) are promising for rabies prevention; however, comparisons of Essen 5-dose and Zagreb 4-dose regimens are needed for clinical applications. This phase III clinical trial aimed to assess the safety and immunogenicity of candidate freeze-dried rabies vaccines developed for human use by Shandong Yeedo Biotechnology (Registration No.: CTR20182016, <http://www.chinadrugtrials.org.cn/index.html>). In total, 40 participants in stage I and 1797 subjects in stage II with an age range of 10-60 years were recruited. Both 4-dose and 5-dose experimental vaccines were well-tolerated in stage 1, with similar overall adverse event (AE) rates. In stage 2, systemic fever (35.39%) and local pain (48.91%) were common, and the rate of Grade 3 AEs was approximately 2.5%. Rates of local reactions and unsolicited AEs differed

among groups ($p = .045$ and 0.011). Immunogenicity analyses showed higher antibody levels, seroconversion rates, and pre-immune seroconversion rates in the 4-dose experimental group versus the 5-dose group ($p < .001$) on day 7 post-first dose, with similar GMCs (geometric mean concentrations) by day 14. Pre-immune negative subjects had comparable antibody levels in the 4-dose and 5-dose experimental groups, outperforming the 5-dose control group ($p = .039$). The rate difference (95% CI) for first-dose seroconversion at 14 days post-vaccination among pre-immune antibody-negative subjects indicated non-inferiority between the 5-dose experimental and control groups. Overall, the Shandong Yeedo rabies vaccine demonstrated satisfactory safety and efficacy, offering a new option for rabies prevention.

Hum Vaccin Immunother. 2024 Dec 31;20(1):2403177.

doi: 10.1080/21645515.2024.2403177. Epub 2024 Oct 2.

Immunogenicity and immune persistence of Zagreb 2-1-1 regimen of rabies vaccine in Chinese healthy individuals: A randomized, parallel-controlled of homologous vaccine with different immune procedure study

[Li Li¹](#), [Jingyi Xu¹](#), [Jiao Zhang¹](#), [Fang Wang¹](#), [Jianlin Cai¹](#), [Liqing Yang¹](#), [Zhenggang Zhu²](#), [Yunhua Bai¹](#), [Bin Jia¹](#), [Jianxin Ma¹](#), [Nianming Shi¹](#), [Shuping Li¹](#)

Abstract

This study was a randomized, parallel-controlled of homologous vaccines with different immune procedure research to evaluate the immunogenicity and immune persistence of Zagreb 2-1-1 regimen of rabies vaccine in Chinese healthy individuals. 240 subjects aged ≤ 20 、21-50、 ≥ 51 y were randomly divided into 2 groups (1:1), Zagreb 2-1-1 regimen receivers as experimental group and Essen 5 regimen receivers as controlled group. Researchers collected venous blood of each subject before vaccine injection and on the day 7, 14, 42, 180, 365 after first dose. The immunogenicity and immune persistence was assessed by neutralizing antibody. The positive rate of neutralizing antibody in experimental group was 14.53% on the 7th day, and raised to 100% on the 14th day. It showed no significant difference between experimental and controlled group ($P > 0.05$). Either in experimental or controlled group, GMC of neutralizing antibody was up to the peak on the 14th day, and it showed no significant difference between two groups ($P > 0.05$). On the 42nd day, the antibody positive rate remained 100% with both Zagreb 2-1-1 and Essen 5 regimens, and the GMC of antibodies also remained high level. Then, on the 180th and 365th day with both regimens, the GMC of antibodies dropped dramatically, although it remained above the protective level of 0.5 IU/ml, the positive rates dropped to 84.40% and 84.11% (on the 180th day), and 61.29% and 58.62% (on the 365th day). Rabies vaccine injected by Zagreb 2-1-1 regimen can produce neutralizing antibody fastly and perdurably

Rotavirus vaccine

Viruses. 2024 Sep 19;16(9):1488.

doi: 10.3390/v16091488.

Rotavirus-Specific Maternal Serum Antibodies and Vaccine Responses to RV3-BB Rotavirus Vaccine Administered in a Neonatal or Infant Schedule in Malawi

[Benjamin Morgan¹](#), [Eleanor A Lyons¹](#), [Amanda Handley^{1,2}](#), [Nada Bogdanovic-Sakran¹](#), [Daniel Pavlic¹](#), [Desiree Witte^{3,4}](#), [Jonathan Mandolo^{3,5}](#), [Ann Turner⁴](#), [Khuzwayo C Jere^{3,4}](#), [Frances Justice¹](#), [Darren Suryawijaya Ong¹](#), [Rhian Bonnici¹](#), [Karen Boniface¹](#), [Celeste M Donato¹](#), [Ashley Mpakiza³](#), [Anell Meyer^{1,6}](#), [Naor Bar-Zeev⁴](#), [Miren Iturriza-Gomara^{4,7}](#), [Nigel A Cunliffe⁴](#), [Margaret Danchin^{1,7,8}](#), [Julie E Bines^{1,6,9}](#)

Abstract

High titres of rotavirus-specific maternal antibodies may contribute to lower rotavirus vaccine efficacy in low- and middle-income countries (LMICs). RV3-BB vaccine (G3P[6]) is based on a neonatal rotavirus strain that replicates well in the newborn gut in the presence of breast milk. This study investigated the association between maternal serum antibodies and vaccine response in infants administered the RV3-BB vaccine. Serum was collected antenatally from mothers of 561 infants enrolled in the RV3-BB Phase II study conducted in Blantyre, Malawi, and analysed for rotavirus-specific serum IgA and IgG antibodies using enzyme-linked immunosorbent assay. Infant vaccine take was defined as cumulative IgA seroconversion (≥ 3 fold increase) and/or stool vaccine shedding. Maternal IgA or IgG antibody titres did not have a negative impact on vaccine-like stool shedding at any timepoint. Maternal IgG (but not IgA) titres were associated with reduced take post dose 1 ($p < 0.005$) and 3 ($p < 0.05$) in the neonatal vaccine schedule group but not at study completion (week 18). In LMICs where high maternal antibodies are associated with low rotavirus vaccine efficacy, RV3-BB in a neonatal or infant vaccine schedule has the potential to provide protection against severe rotavirus disease.

Nat Commun. 2025 Apr 11;16(1):3432.

doi: 10.1038/s41467-025-58632-6.

Early-life gut microbiome associates with positive vaccine take and shedding in neonatal schedule of the human neonatal rotavirus vaccine RV3-BB

[Josef Wagner^{1,2,3}](#), [Amanda Handley^{4,5}](#), [Celeste M Donato^{4,6}](#), [Eleanor A Lyons⁴](#), [Daniel Pavlic⁴](#), [Darren Suryawijaya Ong⁴](#), [Rhian Bonnici⁴](#), [Nada Bogdanovic-Sakran⁴](#), [Edward P K Parker⁷](#), [Christina Bronowski⁸](#), [Jarir At Thobari^{9,10}](#), [Cahya Dewi Satria¹⁰](#), [Hera Nirwati¹¹](#), [Desiree Witte^{8,12}](#), [Khuzwayo C Jere^{8,12}](#), [Ashley Mpakiza¹²](#), [Emma Watts⁴](#), [Ann Turner¹²](#), [Karen Boniface⁴](#), [Jonathan Mandolo^{12,13}](#), [Frances Justice⁴](#), [Naor Bar-Zeev⁸](#), [Miren Iturriza-Gomara^{8,14}](#), [Jim P Buttery^{4,6,15}](#), [Nigel A Cunliffe⁸](#), [Yati Soenarto¹⁰](#), [Julie E Bines^{16,17,18}](#)

Abstract

Rotavirus vaccines are less effective in high mortality regions. A rotavirus vaccine administered at birth may overcome challenges to vaccine uptake posed by a complex gut microbiome. We investigated the association between the microbiome and vaccine responses following RV3-BB vaccine (G3P[6]) administered in a neonatal schedule (dose 1: 0-5 days), or infant schedule (dose 1: 6-8 weeks) in Indonesia (Phase 2b efficacy study) (n = 478 samples/193 infants) (ACTRN12612001282875) and in Malawi (Immunogenicity study) (n = 355 samples/186 infants) ([NCT03483116](#)). Vaccine responses assessed using anti-rotavirus IgA seroconversion (IgA), stool shedding of vaccine virus and vaccine take (IgA seroconversion and/or shedding). Here we report, high alpha diversity, beta diversity differences and high

abundance of *Bacteroides* is associated with positive vaccine take and shedding following RV3-BB administered in the neonatal schedule, but not with IgA seroconversion, or in the infant schedule. Higher alpha diversity was associated with shedding after three doses of RV3-BB in the neonatal schedule compared to non-shedders, or the placebo group. High abundance of *Streptococcus* and *Staphylococcus* is associated with no shedding in the neonatal schedule group. RV3-BB vaccine administered in a neonatal schedule modulates the early microbiome environment and presents a window of opportunity to optimise protection from rotavirus disease.

Hum Vaccin Immunother. 2024 Dec 31;20(1):2324538.

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A phase 3 randomized, open-label study evaluating the immunogenicity and safety of concomitant and staggered administration of a live, pentavalent rotavirus vaccine and an inactivated poliomyelitis vaccine in healthy infants in China

[Shaomin Chen¹](#), [Zhifang Ying²](#), [Yan Liu³](#), [Yuan Li¹](#), [Yebin Yu⁴](#), [Meilian Huang⁴](#), [Zhuhan Huang¹](#), [Zhiqiang Ou¹](#), [Yuyi Liao¹](#), [Yong Zhang³](#), [Guixiu Liu⁵](#), [Weiwei Zhao⁶](#), [Rong Fu⁶](#), [Qiong Shou⁶](#), [Minghuan Zheng⁵](#), [Xueyan Liao⁵](#), [Yingmei Tu⁷](#), [Jon Stek⁷](#), [Jonathan Hartzel⁸](#), [Changgui Li⁹](#), [Jikai Zhang¹⁰](#)

Abstract

This open-label, randomized, phase 3 study in China (V260-074; [NCT04481191](#)) evaluated the immunogenicity and safety of concomitant and staggered administration of three doses of an oral, live, pentavalent rotavirus vaccine (RV5) and three doses of an intramuscular, inactivated poliomyelitis vaccine (IPV) in 400 healthy infants. The primary objective was the non-inferiority of neutralizing antibody (nAb) responses in the concomitant- versus the staggered-use groups. Antibody responses were measured at baseline and 1-month post-dose 3 (PD3). Parents/legal guardians recorded adverse events for 30 or 15 d after study vaccinations in the concomitant-use or staggered-use groups, respectively. At PD3, >98% of participants seroconverted to all three poliovirus types, and the primary objective was met as lower bounds of the two-sided 95% CI for between-group difference in nAb seroconversion percentages ranged from - 4.3% to - 1.6%, for all poliovirus types, $p < .001$. At PD3, geometric mean titers (GMTs) of nAb responses to poliovirus types 1, 2, and 3 in the concomitant-use group and the staggered-use group were comparable; 100% of participants had nAb titers $\geq 1:8$ and $\geq 1:64$ for all poliovirus types. Anti-rotavirus serotype-specific IgA GMTs and participants with ≥ 3 -fold rise in postvaccination titers from baseline were comparable between groups. Administration of RV5 and IPV was well tolerated with comparable safety profiles in both groups. The immunogenicity of IPV in the concomitant-use group was non-inferior to the staggered-use group and RV5 was immunogenic in both groups. No safety concerns were identified. These data support the concomitant use of RV5 and IPV in healthy Chinese infants.

RSV vaccine

Obstet Gynecol. 2025 Feb 1;145(2):147-156.

doi: 10.1097/AOG.0000000000005817. Epub 2025 Jan 2.

[Preterm Birth Frequency and Associated Outcomes From the MATISSE \(Maternal Immunization Study for Safety and Efficacy\) Maternal Trial of the Bivalent Respiratory Syncytial Virus Prefusion F Protein Vaccine](#)

[Shabir A Madhi¹](#), [Beate Kampmann](#), [Eric A F Simões](#), [Philip Zachariah](#), [Barbara A Pahud](#), [David Radley](#), [Uzma N Sarwar](#), [Emma Shittu](#), [Conrado Llapur](#), [Gonzalo Pérez Marc](#), [Yvonne Maldonado](#), [Alisa Kachikis](#), [Heather J Zar](#), [Kena A Swanson](#), [Maria Maddalena Lino](#), [Annaliesa S Anderson](#), [Alejandra Gurtman](#), [Iona Munjal](#)

Abstract

Objective: To describe preterm birth frequency and newborn and infant outcomes overall and among preterm children in the MATISSE (Maternal Immunization Study for Safety and Efficacy) trial of maternal vaccination with bivalent respiratory syncytial virus (RSV) prefusion F protein-based vaccine (RSVpreF) to protect infants against severe RSV-associated illness.

Methods: MATISSE was a global, phase 3, randomized, double-blind trial. Pregnant individuals received single injections of RSVpreF or placebo. Adverse events of special interest, including preterm birth (gestational age less than 37 weeks) and low birth weight (2,500 g or less), were collected through 6 months after delivery (pregnant participants) and from birth through age 12 or 24 months (pediatric participants).

Results: Overall, 7,386 pregnant participants received RSVpreF (n=3,698) or placebo (n=3,688); 7,305 newborns and infants were included in the analysis. Most children in both groups were born full term (more than 93%) with normal birth weight (95% or higher). Newborn and infant outcomes, including rates of low birth weight and neonatal hospitalization, were favorable and comparable between groups. Preterm birth rates were 5.7% in the RSVpreF arm and 4.7% in the placebo arm (relative risk [RR] 1.20, 95% CI, 0.98-1.46); most were late preterm. Newborn and infant outcomes, including rates of low birth weight and neonatal hospitalization, were comparable between groups. Twenty-two newborn or infant deaths occurred during the study (RSVpreF n=8, placebo n=14). When stratified by income region, preterm birth rates in RSVpreF and placebo recipients were both 5.0% in high-income countries. Rates in non-high-income countries were 7.0% and 4.0% in the RSVpreF and placebo groups, respectively, and 8.3% and 4.0% in South Africa (RR 2.06, 95% CI, 1.21-3.51).

Conclusion: In this study of maternal RSVpreF vaccination, no clinically significant increase in adverse events of special interest, including preterm birth, low birth weight, or neonatal hospitalization, was observed among pregnant people in the overall analysis. In subgroup analysis of non-high-income countries, an elevated risk of preterm birth was observed. More research is needed to better ascertain preterm delivery risk factors, particularly aimed at minimizing disparities among geographic regions.

Obstet Gynecol. 2025 Feb 1;145(2):157-167.

doi: 10.1097/AOG.0000000000005816. Epub 2025 Jan 2.

Efficacy, Safety, and Immunogenicity of the MATISSE (Maternal Immunization Study for Safety and Efficacy) Maternal Respiratory Syncytial Virus Prefusion F Protein Vaccine Trial

[Eric A F Simões¹](#), [Barbara A Pahud](#), [Shabir A Madhi](#), [Beate Kampmann](#), [Emma Shittu](#), [David Radley](#), [Conrado Llapur](#), [Jeffrey Baker](#), [Gonzalo Pérez Marc](#), [Shaun L Barnabas](#), [Merlin Fausett](#), [Tyler Adam](#), [Nicole Perreras](#), [Marlies A Van Houten](#), [Anu Kantele](#), [Li-Min Huang](#), [Louis J Bont](#), [Takeo Otsuki](#), [Sergio L Vargas](#), [Joanna Gullam](#), [Bruce Tapiero](#), [Renato T Stein](#), [Fernando P Polack](#), [Heather J Zar](#), [Nina B Staerke](#), [María Duron Padilla](#), [Peter C Richmond](#), [Uzma N Sarwar](#), [James Baber](#), [Kenneth Koury](#), [Maria Maddalena Lino](#), [Elena V Kalinina](#), [Weiqiang Li](#), [David Cooper](#), [Annaliesa S Anderson](#), [Kena A Swanson](#), [Alejandra Gurtman](#), [Iona Munjal](#); [MATISSE \(Maternal Immunization Study for Safety and Efficacy\) Clinical Trial Group](#)

Abstract

Objective: To evaluate descriptive efficacy data, exploratory immunogenicity data, and safety follow-up through study completion from the global, phase 3 MATISSE (Maternal Immunization Study for Safety and Efficacy) maternal vaccination trial of bivalent respiratory syncytial virus (RSV) prefusion F protein vaccine (RSVpreF).

Methods: MATISSE was a phase 3, randomized, double-blinded, placebo-controlled trial. Healthy pregnant participants aged 49 years or younger at 24-36 weeks of gestation were randomized (1:1) to receive a single RSVpreF 120 micrograms or placebo dose. Primary efficacy endpoints included newborn and infant severe RSV-associated medically attended lower respiratory tract illness within 180 days after birth. The RSV-A and RSV-B serum neutralizing antibody titers were determined in a subset of pregnant participants and their newborns.

Results: In this final analysis, 7,420 pregnant participants were randomized, and 7,307 children were born (RSVpreF n=3,660, placebo n=3,647). Vaccine efficacy, defined as protection against newborn and infant severe RSV-associated medically attended lower respiratory tract illness, was 82.4% (95% CI, 57.5-93.9) and 70.0% (95% CI, 50.6-82.5) within 90 and 180 days of birth, respectively. The RSVpreF induced robust immune responses in pregnant participants and resulted in highly efficient transfer of maternal antibodies to their newborns across subgroups (by gestational age at delivery and at vaccination, number of days from vaccination to delivery, country, maternal age). Final RSVpreF safety results in pregnant and newborn and infant participants were consistent with the primary analysis with no new safety concerns identified.

Conclusion: This final analysis of MATISSE trial data confirms the primary analysis conclusions: Maternal vaccination with RSVpreF has a favorable safety profile in both pregnant and newborn and infant participants and demonstrates efficacy against RSV-associated lower respiratory tract illness in infants through age 6 months. The RSVpreF induces robust immune responses in pregnant individuals, with corresponding high RSV-neutralizing titers in their newborns.

Salmonella typhi vaccine

Schistosomiasis vaccine

Typhoid vaccine

Lancet. 2024 Oct 12;404(10461):1419-1429.

doi: 10.1016/S0140-6736(24)01494-6.

[5-year vaccine protection following a single dose of Vi-tetanus toxoid conjugate vaccine in Bangladeshi children \(TyVOID\): a cluster randomised trial](#)

[Firdausi Qadri¹](#), [Farhana Khanam²](#), [Yiyuan Zhang³](#), [Prasanta Kumar Biswas²](#), [Merryn Voysey³](#), [Yama F Mujadidi³](#), [Sarah Kelly³](#), [Amirul Islam Bhuiyan²](#), [Nazmul Hasan Rajib²](#), [Ismail Hossen²](#), [Nazia Rahman²](#), [Sadia Islam²](#), [Virginia E Pitzer⁴](#), [Young Chan Kim³](#), [John D Clemens⁵](#), [Andrew J Pollard³](#), [Xinxue Liu⁶](#)

Abstract

Background: WHO currently recommends a single dose of typhoid conjugate vaccine (TCV) in high-burden countries based on 2-year vaccine efficacy data from large randomised controlled trials. Given the decay of immunogenicity, the protection beyond 2 years is unknown. We therefore extended the follow-up of the TyVAC trial in Bangladesh to assess waning of vaccine protection to 5 years after vaccination.

Methods: We conducted a cluster randomised controlled trial (TyVAC; ISRCTN11643110) in Dhaka, Bangladesh, between 2018 and 2021. Children aged 9 months to 15 years were invited to receive a single dose of TCV or Japanese encephalitis vaccine between April 15, 2018, and November 16, 2019, based on the randomisation of their clusters of residence. Children who received the Japanese encephalitis vaccine were invited to receive TCV at the final visit between Jan 6, and Aug 31, 2021, according to the protocol. This follow-on study extended the follow-up of the original trial until Aug 14, 2023. The primary endpoint of this study was to compare the incidence of blood culture-confirmed typhoid between children who received TCV in 2018-19 (the previous-TCV group) and those who received the vaccine in 2021 (the recent-TCV group), to evaluate the relative decline in vaccine protection. We also did a nested study using the test-negative design comparing the recent-TCV and previous-TCV groups with unvaccinated individuals, as well as an immunogenicity study in a subset of 1500 children.

Findings: Compared with the recent-TCV group, the previous-TCV group had an increased risk of typhoid fever between 2021-23, with an adjusted incidence rate ratio of 3.10 (95% CI 1.53 to 6.29; $p < 0.0001$), indicating a decline in the protection of a single-dose of TCV 3-5 years after vaccination. The extrapolated vaccine effectiveness in years 3-5 was 50% (95% CI -13 to 78), and was validated using the test-negative design analysis, with a vaccine effectiveness of 84% (74 to 90) in the recent-TCV group and 55% (36 to 68) in the previous-TCV group, compared with unvaccinated individuals. Anti-Vi-IgG responses declined over the study period. The highest rate of decay was seen in children vaccinated at younger than 2 years in

the original trial. The inverse correlation between age and the decay of antibodies was also seen in the subgroup analysis of vaccine effectiveness, where the youngest age group (<7 years at fever visits) exhibited the fastest waning, with vaccine effectiveness dropping to 24% (95% CI -29 to 55) at 3-5 years after vaccination.

Interpretation: A decline in the protection conferred by a single-dose TCV was observed 3-5 years after vaccination, with the greatest decline in protection and immune responses observed in children vaccinated at younger ages. A booster dose of TCV around school entry age might be needed for children vaccinated while younger than 2 years to sustain protection against typhoid fever during the school years when the risk is the highest.

Am J Trop Med Hyg. 2024 Aug 13;111(4):848-852.

doi: 10.4269/ajtmh.24-0181. Print 2024 Oct 2.

Field Effectiveness of a Typhoid Conjugate Vaccine: The 2018 Navi Mumbai Pediatric TCV Campaign

[Kashmira Date¹](#), [Christopher LeBoa²](#), [Seth A Hoffman²](#), [Pradeep Haldar³](#), [Pauline Harvey⁴](#), [Qian An¹](#), [Chenhua Zhang¹](#), [Vijay N Yewale⁵](#), [Savita Daruwalla⁶](#), [Dhanya Dharmapalan⁵](#), [Jeetendra Gavhane⁷](#), [Shrikrishna Joshi⁸](#), [Rajesh Rai⁹](#), [Varsha Rathod¹⁰](#), [Keertana Shetty¹¹](#), [Divyalatha S Warriar¹²](#), [Shalini Yadav¹³](#), [Rahul Shimpi⁴](#), [Niniya Jayaprasad⁴](#), [Lily Horng²](#), [Kirsten Fagerli¹](#), [Priyanka Borhade⁴](#), [Debjit Chakraborty¹⁴](#), [Arun Katkar⁴](#), [Abhishek Kunwar⁴](#), [Jason R Andrews²](#), [Sunil Bahl¹⁵](#), [Pankaj Bhatnagar⁴](#), [Shanta Dutta¹⁴](#), [Stephen P Luby²](#)

Abstract

Typbar-TCV®, a typhoid conjugate vaccine (TCV), was prequalified by the World Health Organization in 2017. We evaluated its effectiveness in a mass vaccination program targeting children 9 months to 14 years in Navi Mumbai, India, from September 2018 to July 2020. We compared laboratory-confirmed typhoid cases from six clinical sites with age-matched community controls. Of 38 cases, three (8.6%) received TCV through the campaign, compared with 53 (37%) of 140 controls. The adjusted odds ratio of typhoid fever among vaccinated children was 0.16 (95% CI: 0.05-0.55), equivalent to a vaccine effectiveness of 83.7% (95% CI: 45.0-95.3). Vaccine effectiveness of Typbar-TCV in this large public sector vaccine introduction was similar to prior randomized controlled trials, providing reassurance to policymakers that TCV effectiveness is robust in a large-scale implementation.

* Editor note: not a randomised trial, but a phase IV trial

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Comparative immune response of Typbar TCV® (typhoid conjugate vaccine) in extremes of age: An Indian experience

[Krishna Mohan Vadrevu¹](#), [Siddharth Reddy Chiteti¹](#), [Raju Dugyala¹](#), [Vinay Kumar Aileni¹](#), [Akhila Kunta¹](#), [Badri Narayan Patnaik¹](#), [Raches Ella¹](#)

Abstract

Typhoid fever is a significant health concern in low- and middle-income countries, with millions of cases and thousands of deaths each year. Typhoid Conjugate Vaccines, such as

Typbar TCV[®], have been developed to provide longer-lasting protection for young children. This publication includes the readouts from two different studies in Children and elderly: a Comparator Study and Age Extension Study. In the first study, children are included, whereas the latter study also includes elderly subjects. A total of 340 children were enrolled, and a subset received a booster dose of Typbar TCV[®], 180 days later. Results established that Typbar TCV[®] induced significantly higher antibody titer compared to Typhim Vi on days 28 and 90 ($p < .001$). No significant differences in adverse events were found between the two vaccine arms. Overall, Typbar TCV[®] was well tolerated, inducing higher anti-Vi-IgG titers than Typhim Vi[®], with sustained response over the study period. The booster dose post-6 months in the Typbar TCV[®] group was significantly less immunogenic compared to a booster at 2 years ($p < .001$), suggesting a delayed booster might enhance the anamnestic response, a fact confirmed in our previous clinical studies of Typbar TCV[®]. In the Age Extension study, 300 healthy volunteers, including younger (18-65) and elderly adults (65 and older), received a single dose of Typbar TCV[®]. The vaccine is reported to be safe and induced similar anti Vi-Ab geometric mean titers (GMTs) in young and elderly adults. Thus, Typbar TCV[®] was studied effectively from 6 months to above 85 years, which is the upper age limit.

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Single and two-dose typhoid conjugate vaccine safety and immunogenicity in HIV-exposed uninfected and HIV-unexposed uninfected Malawian children

[Nginache Nampota-Nkomba^{1,2}](#), [Oswald M Nyirenda¹](#), [Victoria Mapemba¹](#), [Rhoda Masonga¹](#), [Priyanka D Patel³](#), [Theresa Misiri³](#), [Felistas Mwakiseghile³](#), [Richard Wachepa³](#), [John M Ndaferankhande³](#), [Bright Lipenga³](#), [Pratiksha Patel³](#), [Happy Banda³](#), [Jennifer Oshinsky⁴](#), [Marcela F Pasetti⁴](#), [Robert S Heyderman^{3,5}](#), [Leslie P Jamka⁴](#), [Divya Hosangadi²](#), [Shrimati Datta⁴](#), [Melita A Gordon^{3,6}](#), [Kathleen M Neuzil^{4,7}](#), [Matthew B Laurens⁴](#)

Abstract

Vaccine safety and immunogenicity data in human immunodeficiency virus (HIV)-exposed uninfected (HEU) children are important for decision-making in HIV and typhoid co-endemic countries. In an open-label study, we recruited Malawian HEU and HIV unexposed uninfected (HUU) infants aged 9 - 11 months. HEU participants were randomized to receive Vi-tetanus toxoid conjugate vaccine (Vi-TT) at 9 months, Vi-TT at 15 months, or Vi-TT at 9 and 15 months. HUU participants received Vi-TT at 9 and 15 months. Safety outcomes included solicited and unsolicited adverse events (AE) and serious AEs (SAEs) within 7 days, 28 days, and 6 months of vaccination, respectively. Serum was collected before and at day 28 after each vaccination to measure anti-Vi IgG antibodies by enzyme-linked immunosorbent assay (ELISA). Cohort 1 (66 participants) enrollment began 02 December 2019, and follow-up was terminated before completion due to the COVID-19 pandemic. Cohort 2 (100 participants) enrollment began 25 March 2020. Solicited AEs were mostly mild, with no significant differences between HEU and HUU participants or one- and two-dose groups. All six SAEs were unrelated to vaccination. Anti-Vi geometric mean titers (GMT) increased significantly from 4.1 to 4.6 ELISA units (EU)/mL at baseline to 2572.0 - 4117.6 EU/mL on day 28 post-vaccination, and similarly between HEU and HUU participants for both one- and two-dose schedules. All participants seroconverted (>4-fold increase in GMT) by the final study visit.

Our findings of comparable safety and immunogenicity of Vi-TT in HUU and HEU children support country introductions with single-dose Vi-TT in HIV-endemic countries.

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The validity of test-negative design for assessment of typhoid conjugate vaccine protection: comparison of estimates by different study designs using data from a cluster-randomised controlled trial

[Shuo Feng¹](#), [Yiyuan Zhang²](#), [Farhana Khanam³](#), [Merryn Voysey²](#), [Virginia E Pitzer⁴](#), [Firdausi Qadri³](#), [John D Clemens⁵](#), [Andrew J Pollard²](#), [Xinxue Liu⁶](#)

Abstract

Background: Typhoid fever remains a substantial public health challenge in low-income and middle-income countries. By 2023, typhoid conjugate vaccines (TCVs) had been introduced in six countries globally, with more than 50 million doses distributed. Now that TCVs are being deployed, there is a need for observational studies to assess vaccine effectiveness in the field. We aimed to evaluate the validity of different observational study designs in estimating vaccine protection.

Methods: We compared different observational and experimental study designs for assessing vaccine effectiveness by re-analysing data from the TyVAC Bangladesh trial, a participant-blinded and observer-blinded cluster-randomised controlled trial done in Mirpur, Dhaka, Bangladesh. 150 geographical clusters were randomly assigned (1:1) to receive either TCV or Japanese encephalitis vaccine. Eligible children aged 9 months to 15 years were offered a single dose of the vaccine randomly assigned to their cluster of residence, and baseline vaccination was done between April 15 and May 15, 2018. We compared estimates of vaccine effectiveness from the cluster-randomised controlled trial analysis-which assessed the risk of blood-culture-confirmed typhoid fever among recipients of TCV versus recipients of Japanese encephalitis vaccine-with estimates from cohort study and test-negative case-control study design (TND) analyses, which compared recipients of TCV with non-vaccinees in the 75 geographical clusters where TCV was administered. We further conducted negative-control exposure (NCE) and negative-control outcome (NCO) analyses as bias indicators.

Findings: 41 344 (67%) of 62 025 age-eligible children in the study area received the TCV or Japanese encephalitis vaccine during the baseline vaccination campaign. Among the 62 025 age-eligible children, 5582 blood-culture specimens were collected by passive surveillance, including 2546 (46%) specimens from the 75 TCV clusters. The estimated vaccine efficacy was 89% (95% CI 81-93) in the cluster-randomised controlled trial analysis, 79% (70-86) by the cohort design, 88% (79-93) by the TND when pan-negatives were used as test-negative controls, and 90% (75-96) by the TND when specimens positive for pathogens other than *Salmonella enterica* serotype Typhi were used as test-negative controls. Using NCE analysis, Japanese encephalitis vaccination was associated with an increased risk of typhoid fever compared with non-vaccinees in the 75 Japanese encephalitis clusters in the cohort design (incidence rate ratio 1.98 [95% CI 1.56-2.52]), but no significant association between Japanese encephalitis vaccination and typhoid fever was found with the TND. Similarly, an increased risk of non-typhoid infections was observed in the cohort NCO analyses when

comparing vaccinees with non-vaccinees in both Japanese encephalitis vaccine clusters and TCV clusters, but not in the TND NCO analyses.

Interpretation: Our findings suggests that the TND provides reliable estimates of TCV effectiveness, whereas the cohort design can bias vaccine effectiveness estimates, possibly due to unmeasured confounding effects, such as health-care-seeking behaviours. NCE and NCO approaches are useful tools for identifying such biases.

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Typhoid conjugate vaccines for preventing typhoid fever (enteric fever)

[Natasha R Gloeck¹](#), [Trudy D Leong¹](#), [Mashudu Mthethwa¹](#), [Chinwe Juliana Iwu-Jaja²](#), [Patrick Dmc Katoto³⁴⁵](#), [Charles S Wiysonge²⁶](#), [Tamara Kredo¹⁷⁸](#)

Abstract

Rationale: Typhoid fever is a major cause of enteric disease-related morbidity and mortality. Vaccination reduces disease burden and prevents outbreaks, but policies and programmes should be informed by the most recent evidence as newer vaccines become available.

Objectives: To assess the benefits and harms of typhoid conjugate vaccines (TCVs) compared to no vaccine, placebo, typhoid-inactive agents (vaccines for another disease) or other typhoid vaccines for preventing morbidity and mortality associated with typhoid fever in adults and children.

Search methods: In April 2024, we searched the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, CINAHL, Global Index Medicus, United States Advisory Committee on Immunization Practices and the World Health Organization vaccine repository for randomised controlled trials (RCTs), with no restrictions. We also searched clinical trial registries for ongoing trials (www.

Clinicaltrials: gov and the WHO International Clinical Trials Registry Platform), grey literature, bibliographic citations of reviews and key articles for additional studies. We contacted study authors for information about ongoing studies.

Eligibility criteria: We included RCTs and cluster-RCTs of children and adults living in typhoid-endemic areas or travelling to typhoid-endemic areas. We included studies comparing TCVs to controls (i.e. no vaccine, placebo or vaccines for another disease), non-conjugated typhoid vaccines or other TCVs.

Outcomes: Outcomes included acute typhoid fever, defined by laboratory-confirmed isolation of *Salmonella typhi*, all-cause mortality, adverse events (AEs) and serious adverse events (SAEs).

Risk of bias: Review authors independently assessed risk of bias for all outcomes, using the Cochrane RoB 2 tools. We resolved disagreements through discussion or adjudication. We assessed the intention-to-treat effect and used the overall RoB judgement to assess the certainty of evidence for each outcome.

Synthesis methods: Three review authors independently screened titles and abstracts for eligible studies, followed by full-text assessment. Disagreements were resolved through discussion or adjudication by a fourth author. Four authors independently extracted characteristics of included studies and outcome data using a piloted, standardised data extraction form. We synthesised results for each outcome where possible, using the Mantel-Haenszel statistical method and random-effects analysis model. Where meta-analysis was

not possible due to the nature of the data, we planned to synthesise results based on direction of effect. We used GRADE to assess the certainty of evidence for each outcome, assessing risk of bias, inconsistency, indirectness, imprecision and other bias.

Included studies: We included 19 trials (17 RCTs and two cluster-RCTs). The 19 trials enrolled 395,650 participants, with ages ranging from six weeks to 60 years. Vaccines were delivered as a single dose in 14 studies; two doses, ranging from four to 24 weeks apart, in six studies; and three doses, four weeks apart, in one study. Comparators included: no vaccine, placebo and other vaccines. Seven studies compared TCV with non-conjugated typhoid vaccines. Six studies compared one TCV to another TCV.

Synthesis of results: TCV compared to control may result in a large reduction in acute typhoid fever (risk ratio (RR) 0.20, 95% confidence interval (CI) 0.12 to 0.32; $I^2 = 70\%$; 6 studies, 101,896 participants; low-certainty evidence) and probably results in little to no difference in all-cause mortality (RR 0.80, 95% CI 0.35 to 1.85; $I^2 = 52\%$; 4 studies, 100,337 participants; moderate-certainty evidence). TCV results in little to no difference in AEs when compared to control (RR 0.91, 95% CI 0.76 to 1.09; $I^2 = 0\%$; 3 studies, 29,465 participants; high-certainty evidence) and a slight reduction in SAEs compared to control (RR 0.82, 95% CI 0.71 to 0.95; $I^2 = 0\%$; 6 studies, 89,625 participants; high-certainty evidence). TCV compared to non-conjugated typhoid vaccines may result in little to no difference in acute typhoid fever (RR 0.90, 95% CI 0.48 to 1.69; 1 study, 78 participants; low-certainty evidence). There were no deaths in the included studies. When compared to non-conjugated typhoid vaccines, TCV likely results in little to no difference in AEs (RR 1.00, 95% CI 0.77 to 1.31; $I^2 = 0\%$; 3 studies, 244 participants; moderate-certainty evidence) and likely results in a slight reduction in SAEs (RR 0.30, 95% CI 0.05 to 1.88; $I^2 = 0\%$; 2 studies, 732 participants; moderate-certainty evidence). For TCV compared to another TCV, none of the studies reported on acute typhoid fever. Vi tetanus toxoid vaccine (Vi-TT) may result in little to no difference in all-cause mortality compared to a different TCV (RR 5.19, 95% CI 0.54 to 49.80; $I^2 = 0\%$; 2 studies, 2422 participants; low-certainty evidence). Vi-TT likely results in little to no difference in AEs compared to another TCV (RR 1.18, 95% CI 0.92 to 1.51; $I^2 = 39\%$; 4 studies, 2916 participants; moderate-certainty evidence) and may result in little to no difference in SAEs (RR 2.48, 95% CI 0.74 to 8.36; $I^2 = 0\%$; 3 studies, 2866 participants; low-certainty evidence). The certainty of evidence was consistently reduced due to imprecision, indirectness and bias.

Authors' conclusions: This review highlights that TCVs, compared to controls, are effective in preventing typhoid fever, and may confer protection for up to four years. TCVs compared to non-conjugated typhoid vaccines may result in little to no difference in acute typhoid fever and AEs, and likely result in a slight reduction in SAEs. Vi-TT compared to another TCV may result in little to no difference in all-cause mortality or SAEs, and likely results in little to no difference in AEs.

Varicella vaccine

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[Immunogenicity and safety of an ORF7-deficient skin-attenuated and neuro-attenuated live vaccine for varicella: a randomised, double-blind, controlled, phase 2a trial](#)

[Hong-Xing Pan¹](#), [Ling-Xian Qiu²](#), [Qi Liang¹](#), [Zhen Chen³](#), [Ming-Lei Zhang⁴](#), [Sheng Liu⁴](#), [Guo-Hua Zhong²](#), [Kong-Xin Zhu²](#), [Meng-Jun Liao²](#), [Jia-Lei Hu¹](#), [Jia-Xue Li⁴](#), [Jin-Bo Xu⁴](#), [Yong Fan⁴](#), [Yue Huang²](#), [Ying-Ying Su²](#), [Shou-Jie Huang²](#), [Wei Wang²](#), [Jin-Le Han⁵](#), [Ji-Zong Jia⁵](#), [Hua Zhu⁶](#), [Tong Cheng²](#), [Xiang-Zhong Ye⁵](#), [Chang-Gui Li³](#), [Ting Wu⁷](#), [Feng-Cai Zhu¹](#), [Jun Zhang⁸](#), [Ning-Shao Xia⁹](#)

Abstract

Background: The Oka varicella vaccine strain remains neurovirulent and can establish lifelong latent infection, raising safety concerns about vaccine-related herpes zoster. In this study, we aimed to evaluate the immunogenicity and safety of a skin-attenuated and neuro-attenuated varicella vaccine candidate (v7D vaccine).

Methods: We did this randomised, double-blind, controlled, phase 2a clinical trial in Jiangsu, China. Healthy children aged 3-12 years with no history of varicella infection or vaccination were enrolled and randomly assigned (1:1:1:1) to receive a single subcutaneous injection of the v7D vaccine at 3.3 log₁₀ plaque forming units (PFU; low-dose v7D group), 3.9 log₁₀ PFU (medium-dose v7D group), and 4.2 log₁₀ PFU (high-dose v7D group), or the positive control varicella vaccine (vOka vaccine group). All the participants, laboratory personnel, and investigators other than the vaccine preparation and management staff were masked to the vaccine allocation. The primary outcome was assessment of the geometric mean titres (GMTs) and seroconversion rates of anti-varicella zoster virus immunoglobulin G (IgG) induced by different dose groups of v7D vaccine at 0, 42, 60, and 90 days after vaccination in the per-protocol set for humoral immune response analysis. Safety was a secondary outcome, focusing on adverse events within 42 days post-vaccination, and serious adverse events within 6 months after vaccination. This study was registered on Chinese Clinical Trial Registry, ChiCTR2000034434.

Findings: On Aug 18-21, 2020, 842 eligible volunteers were enrolled and randomly assigned treatment. After three participants withdrew, 839 received a low dose (n=211), middle dose (n=210), or high dose (n=210) of v7D vaccine, or the vOka vaccine (n=208). In the per-protocol set for humoral immune response analysis, the anti-varicella zoster virus IgG antibody response was highest at day 90. At day 90, the seroconversion rates of the low-dose, medium-dose, and high-dose groups of v7D vaccine and the positive control vOka vaccine group were 100.0% (95% CI 95.8-100.0; 87 of 87 participants), 98.9% (93.8-100.0; 87 of 88 participants), 97.8% (92.4-99.7; 91 of 93 participants), and 96.4% (89.8-99.2; 80 of 83 participants), respectively; the GMTs corresponded to values of 30.8 (95% CI 26.2-36.0), 31.3 (26.7-36.6), 28.2 (23.9-33.2), and 38.5 (31.7-46.7). The v7D vaccine, at low dose and medium dose, elicited a humoral immune response similar to that of the vOka vaccine. However, the high-dose v7D vaccine induced a marginally lower GMT compared with the vOka vaccine at day 90 (p=0.027). In the per-protocol set, the three dose groups of the v7D vaccine induced a similar humoral immune response at each timepoint, with no statistically significant differences. The incidence of adverse reactions in the low-dose, medium-dose, and high-dose groups of v7D vaccine was significantly lower than that in the vOka vaccine group (17% [35 of 211 participants], 20% [41 of 210 participants], and 13% [27 of 210 participants] vs 24% [50 of 208 participants], respectively; p=0.025), especially local adverse reactions (10% [22 of 211 participants], 14% [30 of 210 participants] and 9% [18 of 210 participants] vs 18% [38 of 208 participants], respectively; p=0.016). None of the serious adverse events were vaccine related.

Interpretation: The three dose groups of the candidate v7D vaccine exhibit similar humoral immunogenicity to the vOka vaccine and are well tolerated. These findings encourage

further investigations on two-dose vaccination schedules, efficacy, and the potential safety benefit of v7D vaccine in the future.

Hum Vaccin Immunother. 2025 Dec;21(1):2452681.

doi: 10.1080/21645515.2025.2452681. Epub 2025 Feb 2.

[Immunogenicity and safety of a live attenuated varicella vaccine in children aged 1 to 12 years: A double-blind, randomized, parallel-controlled phase III clinical trial in China](#)
[Shiyuan Wang](#)^{1,2}, [Yang Zhang](#)^{1,3}, [Guifan Li](#)⁴, [Jinhui Shi](#)⁴, [Xianyun Chang](#)⁴, [Hao Zhang](#)⁴, [Fengcai Zhu](#)⁵, [Jingxin Li](#)⁵, [Kai Chu](#)⁵, [Jinfang Sun](#)^{1,2}

Abstract

Chickenpox outbreaks frequently occur in collective settings such as kindergartens and schools, posing a significant threat to children's physical and mental health. This study aimed to evaluate the immunogenicity and safety of the freeze-dried live attenuated varicella vaccine (VarV) developed by Beijing Minhai Biotechnology Co. LTD. in healthy participants aged 1-12 years. In this phase III, single-center, randomized, double-blind, active-controlled trial, 1,200 healthy participants randomly assigned in a 1:1 ratio to receive one dose of either the test vaccine or the active control vaccine. Venous blood samples were collected before vaccination and 42 days after vaccination, and the fluorescent antibody to membrane antigen (FAMA) assay was used to detect VZV antibody. Adverse events (AEs) observed within 42 days after vaccination and serious adverse events (SAEs) within six months after vaccination were recorded. The seroconversion rates in the test and control groups were 96.79% and 96.43%, respectively, with a difference of 0.36% (95% CI, -1.76%-2.48%). The geometric mean titers (GMTs) were 61.74 and 58.04, respectively, with a difference of 1.06 (95% CI, 0.92-1.23). The lower limits of the 95% CI for the differences in seroconversion rates and GMT ratios between the two groups were greater than their respective pre-set non-inferiority margins. The overall incidence of AEs ($p = .0112$) in the test group was significantly lower than that in the control group. The freeze-dried live attenuated VarV developed by Beijing Minhai Biotechnology Co. LTD. demonstrated good immunogenicity and higher safety compared to the active control vaccine in healthy participants aged 1-12 years.

Yellow fever vaccine

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[Immunogenicity of yellow fever vaccine co-administered with 13-valent pneumococcal conjugate vaccine in rural Gambia: A cluster-randomised trial](#)

[Isaac Osei](#)¹, [Jonas Schmidt-Chanasit](#)², [Paul V Licciardi](#)³, [Ousman Secka](#)⁴, [Umberto D'Alessandro](#)⁴, [Rasheed Salaudeen](#)⁴, [Golam Sarwar](#)⁴, [Ed Clarke](#)⁴, [Nuredin I Mohammed](#)⁴, [Cattram Nguyen](#)³, [Brian Greenwood](#)⁵, [Stephanie Jansen](#)⁶, [Grant A Mackenzie](#)⁷

Abstract

Introduction: Because booster doses of pneumococcal conjugate vaccine (PCV) may be given at a similar time to yellow fever vaccine (YF), it is important to assess the immune response to YF when co-administered with PCV. This has been investigated during a reduced-dose PCV trial in The Gambia.

Methods: In this phase 4, parallel-group, cluster-randomized trial, healthy infants aged 0-10 weeks were randomly allocated to receive either a two-dose schedule of PCV13 with a booster dose co-administered with YF vaccine at age 9 months (1 + 1 co-administration) or YF vaccine administered separately at age 10 months (1 + 1 separate) or the standard three early doses of PCV13 with YF vaccine at age 9 months (3 + 0 separate). Blood samples were collected 28-35 days post-vaccination and YF neutralizing antibody (NA) titres were measured. Proportions with seroprotective YF NA titres $\geq 1:8$ were calculated with 95 % confidence intervals (CI). Non-inferiority was demonstrated if the lower limit of the CI for the difference in proportions between the co-administration and separate groups was greater than - 10 %.

Results: Forty-eight, 66, and 98 participants enrolled in 3 + 0 separate, 1 + 1 co-administration, and 1 + 1 separate groups respectively had NA results. Per protocol analysis of the 3 + 0 separate, 1 + 1 co-administration, 1 + 1 separate, and the combined 1 + 1 separate and 3 + 0 separate groups found that 81 %, 85 %, 92 %, and 88 % of participants respectively had YF NA titres $\geq 1:8$. Results were similar with analysis by intention-to-treat. The difference in proportions comparing 1 + 1 co-administration and 1 + 1 separate groups was -7 % (95 % CI, -18 % to 3 %). The difference between 1 + 1 co-administration and 3 + 0 separate groups was 4 % (95 % CI, -10 % to 15 %). There was no statistical difference in the YF seroresponse when the YF vaccine was co-administered with PCV or administered separately.

Conclusions: No evidence was found of the non-inferiority of the seroresponse to YF vaccine when co-administered with PCV13. The levels of YF NA attaining seroprotection (NT $\geq 1:8$) were high in all groups. PCV13 co-administered with YF vaccine at 9 months does not affect seroresponse to YF vaccine

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Adverse events following immunization (AEFI) with fractional one-fifth and one-half doses of yellow fever vaccine compared to full dose in children 9-23 months old in Uganda, 2019-2020 - Preliminary report

[Rebecca M Casey¹](#), [Marjorie Sserunga Najjengo²](#), [Irene Lubega²](#), [Arthur B Sekiziyivu²](#), [Ellon Twinomuhwezi-Oyet²](#), [Winfred Nansozzi Nakato²](#), [Courtney N Sciarratta³](#), [Susan Y Chu³](#), [Reena H Doshi³](#), [Andrew Kambugu²](#), [Jane F Gidudu³](#)

Abstract

Background: In 2016, the World Health Organization recommended that a fractional dose of yellow fever (YF) vaccine could be used in persons 2 years of age or older in response to an emergency that resulted in a global shortage of available YF vaccine. However, this recommendation did not extend to the youngest age group licensed for YF vaccine because there were no published data on the use or safety of fractional dose YF vaccination in children aged 9-23 months. We conducted a single-blind randomized controlled trial, comparing the immunogenicity and safety of fractional one-fifth and one-half doses of Bio-

Manguinhos 17DD YF vaccine with full dose in children aged 9-23 months old in Uganda. In this paper, we present the interim analysis on safety.

Methods: Children aged 9-23 months presenting for routine well-child services were recruited for inclusion at one of three study sites. We collected data during March 26, 2019-August 31, 2020, on all adverse events following immunization (AEFI) during active surveillance for 28 days post-vaccination using multiple collection tools including a diary card with an objective measurement of fever. An independent team from the Uganda national AEFI Committee investigated and classified serious AEFI (SAE) according to Brighton Collaboration Criteria.

Results: Among 1053 enrolled children, 672 (64%) were reported to have a non-serious AEFI (NSAE) and 17 (2%) were reported to have a SAE. The most common AEFI were diarrhoea, fever, and rash, each reported by 355 (34%), 338 (33%), and 188 (18%) participants, respectively. Among 17 participants with SAE, eight were reported to have had seizures and five were hospitalised for seizures or other causes (respiratory symptoms, gastrointestinal illness, malaria). Four SAEs (deaths) occurred >28 days after vaccination. There were no reported cases of pre-specified or vaccine-related SAEs. We observed no significant difference in frequency or severity of adverse events among the study groups.

Conclusions: Using comprehensive active surveillance monitoring, we did not identify any unexpected safety concerns among children aged <2 years receiving YF vaccination, including with the fractional doses. Although we identified a high number of both serious and non-serious AEFI, none were determined to be causally related to YF vaccination. These results provide evidence for the safety of fractional dose YF vaccination among children aged 9-23 months.

Vitamin A

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doi: 10.1038/s41430-025-01620-2. Online ahead of print.

[Red palm olein supplementation as a potential preventive solution for xerophthalmia among vitamin A-deficient primary schoolchildren: a cluster randomized controlled trial](#)

[Pei Yee Tan](#)^{1,2}, [Chuan Chun Lim](#)³, [Katherine Boon Hwei Seng](#)³, [Radhika Loganathan](#)⁴, [Yvonne Ai-Lian Lim](#)², [Kim-Tiu Teng](#)¹, [Syahirah Nadiyah Mohd Johari](#)², [Kanga Rani Selvaduray](#)¹, [Norlina Ramli](#)⁵

Abstract

Objective: This study aimed to investigate the effectiveness of carotenoid-rich red palm olein (RPO) in treating or preventing xerophthalmia among Malaysian rural primary schoolchildren with confirmed vitamin A deficiency (VAD) (plasma retinol <0.70 µmol/L) and marginal vitamin A status (plasma retinol 0.70 to <1.05 µmol/L).

Methods: A double-blinded, cluster randomized controlled trial was conducted on 504 schoolchildren aged 8-12 years from ten rural primary schools in Malaysia. The selected schools were randomly assigned into two groups: the experimental group (n = 249) received RPO-enriched biscuits (326.3 µg retinol equivalents/day), while the control group (n = 255) received palm olein (PO)-enriched biscuits for 6 months (4 days/week). Chi-square test and

mixed effects logistic regression model were applied to examine the effects of supplementation on the resolution or prevention of xerophthalmia.

Results: After 6-month supplementation, a higher resolution rate of xerophthalmia (31.2%) was observed in the experimental group compared to the control group (24.1%), but this difference lacked statistical significance ($p = 0.11$). Nevertheless, the experimental group showed a significantly higher prevention rate of xerophthalmia (81.8%) or conjunctival xerosis (82.5%) than the control group (56.5% or 57.6%, respectively) after 6-month supplementation ($p < 0.001$). Moreover, schoolchildren in the experimental group were 4.8 times less likely to develop xerophthalmia compared to the control group.

Conclusion: A 6-month supplementation of RPO-enriched biscuits demonstrated potential benefits in preventing xerophthalmia or conjunctival xerosis among vitamin A-deficient primary schoolchildren in rural areas of Malaysia. Therefore, RPO may offer a promising preventive solution to xerophthalmia for populations at a high risk of developing VAD.

Vitamin D

(See also Neonates – preterm and low birth weight)

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[Oral Versus Injectable Vitamin D Therapy for Treating Nutritional Rickets in Indian Children: A Comparative Study](#)

[Harshith Patel¹](#), [Vikas Gupta¹](#), [Kamal Jain^{2,3}](#), [Purusharth Yagnik¹](#), [Nandu M S Nair⁴](#), [G R Aditya Reddy⁵](#)

Abstract

Background: Rickets is a common metabolic bone disease in children, primarily caused by vitamin D deficiency. This study aimed to compare the efficacy of oral weekly vitamin D supplementation and injectable stoss therapy in treating nutritional rickets in Indian children.

Methods: This prospective, randomized, controlled trial was conducted over 18 months at a tertiary care center. Forty children aged 6 months to 16 years with clinical, biochemical, and radiological evidence of nutritional rickets were enrolled and randomly assigned to receive either oral vitamin D3 (60,000 IU weekly for 10 weeks) or a single intramuscular injection of vitamin D3 (600,000 IU). Clinical, biochemical, and radiological assessments were conducted at baseline and at 3 weeks, 6 weeks, 3 months, and 6 months post-treatment.

Results: Both treatment regimens significantly improved vitamin D, calcium, phosphorus, alkaline phosphatase, and parathyroid hormone (PTH) levels, with no significant differences between the groups. Radiological healing, assessed by Thacher's score, was achieved in both groups by 6 months. While both treatments were effective, injectable stoss therapy resulted in a more sustained increase in vitamin D levels and may offer better compliance due to its single-dose administration. No cases of local skin complications or vitamin D toxicity or symptomatic hypercalcemia were observed.

Conclusion: Oral weekly and injectable stoss therapies are both effective and safe for treating nutritional rickets. Injectable stoss therapy may be more suitable for the Indian population due to its cost-effectiveness and lower compliance demands. Serum parathyroid

hormone (PTH) levels emerged as a useful early marker of rickets severity as well as treatment response. Early diagnosis and treatment are crucial to prevent long-term skeletal deformities.

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High-dose vitamin D₃ to improve outcomes in the convalescent phase of complicated severe acute malnutrition in Pakistan: a double-blind randomised controlled trial (ViDiSAM)

[Javeria Saleem¹](#), [Rubeena Zakar²](#), [Muhammad Salman Butt^{2,3}](#), [Rameeza Kaleem⁴](#), [Asif Chaudhary⁵](#), [Jaya Chandna⁶](#), [David A Jolliffe⁷](#), [Joseph Piper⁷](#), [Zaigham Abbas⁸](#), [Jonathan C Y Tang^{9,10}](#), [William D Fraser^{9,10}](#), [Nick Freemantle¹¹](#), [Andrew J Prendergast⁷](#), [Adrian R Martineau¹²](#)

Abstract

We have previously shown that high-dose vitamin D₃ improved weight gain and neurodevelopmental indices in children receiving standard therapy for uncomplicated severe acute malnutrition (SAM). Here we present results of a randomised placebo-controlled trial in Lahore, Pakistan, to determine whether two oral doses of 200,000 international units (IU) vitamin D₃ (the first administered on or before the day of hospital discharge and the second administered 14 days later) would benefit children aged 6-59 months during the convalescent phase of complicated SAM. Eligible participants were individually randomised to intervention vs. control arms with a one-to-one allocation ratio and stratification by hospital of recruitment using computer-generated random sequences. Double-blinding to treatment allocation was maintained by concealing allocation from participants' parents or guardians, their medical care providers, and all trial staff. The primary outcome was mean weight-for-height or -length z-score (WHZ) at 2-month follow-up. Secondary efficacy outcomes included mean WHZ at 6-month follow-up and mean lean mass index, Malawi Development Assessment Tool (MDAT) scores and serum 25-hydroxyvitamin D (25[OH]D) concentrations at 2- and 6-month follow-up. The trial has now completed. 259 children were randomised (128 to vitamin D, 131 to placebo), of whom 251 (96.9%) contributed data to analysis of the primary outcome (123 allocated to vitamin D, 128 to placebo). At 2-month follow-up, participants allocated to vitamin D had significantly higher mean serum 25(OH)D concentrations than those allocated to placebo (adjusted mean difference [aMD] 100.0 nmol/L, 95% confidence interval [CI] 72.2-127.8 nmol/L). This was not associated with an inter-arm difference in mean WHZ at 2-month follow-up (aMD 0.02, 95% CI -0.20 to 0.23), or in any anthropometric or neurodevelopmental secondary outcome assessed at 2- or 6-month follow-up. The intervention was safe. In conclusion, high-dose vitamin D₃ elevated mean serum 25(OH)D concentrations in children receiving standard therapy for complicated SAM in Pakistan, but did not influence any anthropometric or neurodevelopmental outcome studied

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Influence of vitamin D supplementation on muscle strength and exercise capacity in South African schoolchildren: secondary outcomes from a randomised controlled trial (ViDiKids)

[Keren Middelkoop^{1,2}](#), [Lisa Micklesfield^{3,4}](#), [Stephanie Hemmings⁵](#), [Neil Walker⁶](#), [Justine Stewart^{1,2}](#), [David A Jolliffe⁷](#), [Amy E Mendham^{4,8}](#), [Jonathan C Y Tang^{9,10}](#), [Cyrus Cooper^{11,12}](#), [Nicholas C Harvey^{11,12}](#), [Robert J Wilkinson^{13,14,15}](#), [Adrian R Martineau⁵](#)

Abstract

Objective: To determine whether vitamin D supplementation influences grip strength, explosive leg power, cardiorespiratory fitness and risk of exercise-induced bronchoconstriction (EIB) in South African schoolchildren.

Methods: Substudy (n=450) in Cape Town schoolchildren aged 8-11 years nested within a phase 3 randomised placebo-controlled trial (ViDiKids). The intervention was weekly oral doses of 10 000 IU vitamin D₃ (n=228) or placebo (n=222) for 3 years. Outcome measures were serum 25-hydroxyvitamin D₃ (25(OH)D₃) concentrations, grip strength, standing long jump distance, peak oxygen uptake (VO_{2peak}, determined using 20 m multistage shuttle run tests) and the proportion of children with EIB, measured at end-study.

Results: 64.7% of participants had serum 25(OH)D₃ concentrations <75 nmol/L at baseline. At 3-year follow-up, children randomised to vitamin D versus placebo had higher mean serum 25(OH)D₃ concentrations (97.6 vs 58.8 nmol/L, respectively; adjusted mean difference 39.9 nmol/L, 95% CI 36.1 to 43.6). However, this was not associated with end-study differences in grip strength, standing long jump distance, VO_{2peak} or risk of EIB.

Conclusion: A 3-year course of weekly oral supplementation with 10 000 IU vitamin D₃ elevated serum 25(OH)D₃ concentrations in South African schoolchildren but did not influence muscle strength, exercise capacity or risk of EIB.

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Influence of vitamin D supplementation on muscle strength and exercise capacity in Mongolian schoolchildren: secondary outcomes from a randomised controlled trial

[Davaasambuu Ganmaa^{1,2}](#), [Stephanie Hemmings³](#), [David A Jolliffe⁴](#), [Uyanga Buyanjargal⁵](#), [Gantsetseg Garmaa⁵](#), [Unaganshagai Adiya⁵](#), [Tumenulzii Tumurbaatar⁵](#), [Khulan Dorjnamjil⁵](#), [Enkhtsetseg Tserenkhuu⁶](#), [Sumiya Erdenenbaatar⁵](#), [Enkhjargal Tsendjav⁵](#), [Nomin Enkhamgalan⁵](#), [Chuluun-Erdene Aghtai⁵](#), [Yagaantsetseg Talhaasuren⁷](#), [Tuya Byambasuren⁷](#), [Erdenetuya Ganbaatar⁸](#), [Erkhembulgan Purevdorj⁵](#), [Adrian R Martineau⁴](#)

Abstract

Objective: To determine whether weekly oral vitamin D supplementation influences grip strength, explosive leg power, cardiorespiratory fitness or spirometric lung volumes in Mongolian schoolchildren.

Methods: Multicentre, randomised, placebo-controlled clinical trial conducted in children aged 6-13 years at baseline attending 18 schools in Ulaanbaatar. The intervention was weekly oral doses of 14 000 IU vitamin D₃ (n=4418) or placebo (n=4433) for 3 years. Outcome measures were grip strength, standing long jump distance and serum 25-hydroxyvitamin D (25(OH)D) concentrations (determined in all participants), peak oxygen uptake (VO_{2peak},

determined in a subset of 632 participants using 20 m multistage shuttle run tests) and spirometric outcomes (determined in a subset of 1343 participants).

Results: 99.8% of participants had serum 25(OH)D concentrations <75 nmol/L at baseline, and mean end-study 25(OH)D concentrations in children randomised to vitamin D versus placebo were 77.4 vs 26.7 nmol/L (mean difference 50.7 nmol/L, 95% CI 49.7 to 51.4). However, vitamin D supplementation did not influence mean grip strength, standing long jump distance, VO_{2peak} , spirometric lung volumes or peak expiratory flow rate, either overall or within subgroups defined by sex, baseline 25(OH)D concentration <25 vs ≥25 nmol/L or calcium intake <500 vs ≥500 mg/day.

Conclusion: A 3-year course of weekly oral supplementation with 14 000 IU vitamin D₃ elevated serum 25(OH)D concentrations in Mongolian schoolchildren with a high baseline prevalence of vitamin D deficiency. However, this intervention did not influence grip strength, explosive leg power, peak oxygen uptake or spirometric lung volumes, either overall or in subgroup analyses.

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Daily versus fortnightly oral vitamin D₃ in treatment of symptomatic vitamin D deficiency in children aged 1-10 years: An open labelled randomized controlled trial

Kumar Arghya Prasanna Mondal¹, Preeti Singh¹, Ritu Singh², Rajeev Kumar Malhotra³, Anju Seth¹

Abstract

Objective: Compare the efficacy and safety of daily versus fortnightly oral vitamin D₃ in treating symptomatic vitamin D deficiency in children aged 1-10 years.

Design: Open labelled randomized controlled trial.

Patients: Eighty children with symptomatic vitamin D deficiency were randomized into group daily (D) and group bolus (B) [40 in each group] to receive oral vitamin D₃, 4000 IU daily or 60,000 IU fortnightly for 12 weeks respectively. Both groups received daily oral calcium of 500 mg/day.

Measurements: Serum calcium (Ca), phosphate (P), alkaline phosphatase (ALP), 25-hydroxy cholecalciferol (25(OH)D), parathyroid hormone (PTH) levels, urine calcium: creatinine ratio and radiological score were assessed at baseline, 4 weeks and 12 weeks. At the end of 12 weeks, 74 children were available for evaluation of the efficacy and safety of both regimens.

Results: Both regimens led to a significant increase in Ca and P levels and a fall in ALP and PTH levels from baseline to 4 and 12 weeks of therapy, with no intergroup difference. At 4- and 12-week assessments, all children in both treatment arms achieved 25(OH)D level in sufficiency range, with no significant difference in their geometric mean. Both regimens were associated with asymptomatic transient hypercalcemia [group D-51.4% vs. group B-34.3%; p -0.14] and hypercalciuria (5.7%) in group D that resolved spontaneously on follow-up.

Conclusions: Daily and fortnightly oral vitamin D₃ in similar cumulative doses are efficacious for treating symptomatic vitamin D deficiency in children (1-10 years). Treated children should be monitored for serum 25(OH)D, Ca and urinary calcium creatinine ratio.

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Weekly Vitamin D Supplementation to Prevent Acute Respiratory Infections in Young Children at Different Latitudes: A Randomized Controlled Trial

[María Loreto Reyes¹](#), [Cecilia Vizcaya²](#), [Catalina Le Roy³](#), [Carolina Loureiro¹](#), [Karin Brinkmann⁴](#), [Mónica Arancibia⁵](#), [Laura Campos⁵](#), [Carolina Iturriaga²](#), [Guillermo Pérez-Mateluna²](#), [Maite Rojas-McKenzie²](#), [Gonzalo Domínguez¹](#), [Carlos A Camargo Jr⁶](#), [Arturo Borzutzky¹](#)

Abstract

Objective: To evaluate the effectiveness of weekly vitamin D supplementation in reducing the number of acute respiratory infections (ARI) in preschool children.

Study design: Randomized, double-blind, placebo-controlled trial in 303 children aged 1.5-3.5 years from 2014 to 2105 in 3 Chilean cities at different latitudes: Santiago (33°S, n = 101), Talcahuano (37°S, n = 103), and Punta Arenas (53°S, n = 99). Participants were allocated (1:1:1) to receive placebo, cholecalciferol (vitamin D3 (VD3)) 5600 IU/week (low-dose), or 11 200 IU/week (high-dose) for 6 months. Primary outcome was parent-reported number of ARI; secondary outcomes included number of ARI hospitalizations, change of serum 25-hydroxyvitamin D (25(OH)D) and LL-37/cathelicidin levels, and adverse events.

Results: The mean age of participants was 26 ± 6 months; 45% were female. Baseline 25(OH)D was 24.9 ± 6.1 ng/ml, with 23% having 25(OH)D <20 ng/ml. No significant baseline clinical or laboratory differences were observed among groups. Overall, 64% (n = 194) completed study participation, without baseline differences between subjects lost to follow-up vs those completing participation or differences in completion rates across groups. After 6 months, a dose-dependent increase in serum 25(OH)D was observed from the VD3 intervention (P < .001), with a higher proportion of subjects ending the trial with 25(OH)D <20 ng/ml in the placebo group (30.8%) vs the low-dose (7.4%) and high-dose groups (5.1%). However, no group differences were observed in number of ARI (P = .85), ARI hospitalizations (P = .20), LL-37/cathelicidin change (P = .30), or adverse events (P = .41).

Conclusions: While weekly VD3 supplementation, in doses equivalent to 800 IU and 1600 IU daily, was associated with improved 25(OH)D levels in preschoolers, we did not find a reduced number of ARI in this sample.

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Efficacy of high-dose vs. low-dose vitamin D₃ supplementation in children with chronic tic disorders: a randomized controlled trial

[Zakaria Ahmed Mohamed^{1,2}](#), [Miaoshui Bai^{1,2}](#), [Hanyu Dong^{1,2}](#), [Yang Xue^{1,2}](#), [Feiyong Jia^{1,2}](#), [Junyan Feng^{3,4}](#)

Abstract

Background: Vitamin D₃ has emerged as a potential therapeutic agent for alleviating tic symptoms in children with chronic tic disorders (CTDs). This study aims to evaluate the comparative efficacy of high-dose and low-dose vitamin D₃ supplementation on tic severity and serum 25-hydroxyvitamin D 25(OH)D levels in children with CTDs.

Methods: A randomized controlled trial was conducted with 83 children aged 4 to 15 years diagnosed with CTDs. Participants were randomly assigned to receive either high-dose vitamin D₃ (5,000 IU/day) or low-dose vitamin D₃ (1,000 IU/day) for three months. The primary outcome was tic severity, assessed using the Yale Global Tic Severity Scale (YGTSS), while secondary outcomes included changes in serum 25(OH)D and calcium levels. Tic severity and biochemical markers were measured at baseline and after the intervention to assess the effects of vitamin D₃ supplementation.

Results: Both the high-dose and low-dose groups showed significant improvements in tic severity and increases in serum 25(OH)D levels ($p < 0.05$). The high-dose group exhibited a significantly greater reduction in tic severity and a more substantial increase in serum 25(OH)D levels compared to the low-dose group ($p < 0.05$). No significant differences were observed in serum calcium levels between the group ($p > 0.05$). Furthermore, multivariate linear regression analysis revealed a significant negative association between increases in serum 25(OH)D levels and reductions in tic severity ($t = -2.816, p < 0.05$).

Conclusion: High-dose vitamin D₃ supplementation is more effective than low-dose supplementation in reducing tic severity and increasing serum 25(OH)D levels in children with CTDs. These findings suggest that high-dose vitamin D₃ may serve as a valuable adjunctive therapy for managing CTDs.

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Efficacy of daily 4,000 International Units (IU) Versus 6,000 IU of oral Vitamin D₃ in Vitamin D deficient children with overweight and obesity: An Open-Label Randomized Controlled Trial

[Priya Setia¹](#), [Anju Seth²](#), [Ritu Singh³](#), [Rajeev Kumar Malhotra⁴](#), [Preeti Singh⁵](#)

Abstract

Background and objectives: Children with overweight/obesity are at increased risk of vitamin D deficiency. This study compares the efficacy and safety of 4000 International Units (IU)/day vs. 6000 IU/day oral vitamin D₃ over 12 weeks for treating vitamin D deficiency and evaluates its impact on metabolic parameters.

Methods: In this open-label randomized controlled trial, 90 children (5-18 years) with overweight/obesity and vitamin D deficiency (25[OH]D <50 nmol/L) were randomized to receive 4000 IU/day (Group A, n=45) or 6000 IU/day (Group B, n=45) along with calcium. Efficacy (25[OH]D ≥50 nmol/L), safety (hypercalcemia, hypercalciuria, hypervitaminosis D), and metabolic impact (HbA1c, lipids) were assessed over 12 weeks. Trial registered with CTRI/2021/02/031591.

Results: Sixty-eight children completed the study. Both groups showed significant increases in serum calcium and reductions in alkaline phosphatase and parathormone, with no inter-group differences. Group B showed a faster rise in 25(OH)D levels, with higher means at 4 weeks [66.3 (3.12) vs. 55.6 (2.92)] and 12 weeks [100.6 (3.42) vs. 79.3 (3.17) nmol/L]. At 12 weeks, sufficiency was achieved in 91.4% (Group A) and 93.4% (Group B). Mild, asymptomatic hypercalcemia was noted in 7 children (Group A-3, Group B-4; $p=0.70$) and resolved spontaneously. No significant metabolic changes were observed in either group.

Conclusions: Both 4000 IU/day and 6000 IU/day of vitamin D₃ were effective and safe for treating vitamin D deficiency in overweight or obese children, with no observed effect on metabolic parameters in either group. Higher doses may accelerate sufficiency; however, standard dosing remains effective, emphasizing the need for individualized treatment and monitoring.

Impact statement: Comparing 4000 IU/day to 6000 IU/day of vitamin D₃ in children with overweight or obesity showed that both regimens were safe and effective in achieving sufficiency without either regimen influencing metabolic parameters. The higher doses allowed for a quicker attainment of optimal levels. While both doses effectively establish vitamin D sufficiency in the short term, long-term data are necessary to confirm their ongoing efficacy and safety over extended periods.

Yaws

Zinc

(see also: Acute respiratory infection, Diarrhoea, Nutrition – micronutrients, Vitamin A, Cholera vaccine)

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[Zinc absorption from maize-based meals enriched with edible house crickets: a randomized crossover stable-isotope study in Kenyan pre-school children](#)

[Nikolin Hilaj](#)^{1,2}, [Tele Boit](#)^{3,4}, [Pauline Andang'o](#)⁵, [Christophe Zeder](#)¹, [Martin N Mwangi](#)^{3,6}, [Marijke Hummel](#)³, [Ornella Necochea Velazco](#)^{7,8}, [Joop J A van Loon](#)⁹, [Marcel Dicke](#)⁹, [Michael B Zimmermann](#)^{1,10}, [Alida Melse-Boonstra](#)¹¹

Abstract

Edible insects have been proposed as a novel and sustainable source of protein and other essential nutrients for human consumption but nutrient absorption efficiency is still uncertain. We investigated zinc absorption from house crickets (*Acheta domesticus*) in a single-center and single-blinded cross-over study with children aged 24-36 months old in Kenya from September-November 2021. For this, children were randomized to consume two different experimental meals labeled with stable isotopes of zinc (Zn) at two different days, separated by a wash-out period of one month. Primary endpoints were the differences in amount of absorbed zinc (AZ) from maize-based meals enriched with intrinsically ⁶⁷Zn-labeled house crickets (2.61 mg Zn, n = 28) in comparison with meals enriched with ⁶⁸Zn (low-enriched: 0.90 mg Zn, n = 29); high-enriched: 3.24 mg Zn, n = 28) or with intrinsically ⁶⁷Zn-labeled low-chitin cricket flour (2.51 mg Zn, n = 25), whereas the secondary endpoints were the differences in fractional zinc absorption. We found that AZ from meals with whole crickets (geometric mean: 0.36 mg; 95%CI: 0.30, 0.43) was 2.6 times higher than from low-enriched maize meals (0.14 mg; 0.11, 0.16; P < 0.001), while it was not different from low-chitin cricket flour meals. Absorbed zinc from both cricket meals was higher than that from high-enriched meals. No severe adverse side events were reported. We conclude that edible house crickets are a good source of well-absorbable zinc, and their increased consumption could contribute to the alleviation of zinc deficiency.

