

# **Randomised Trials in Child and Adolescent Health in Developing Countries**

20<sup>th</sup> Edition  
July 2022-June 2023

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](mailto:trevor.duke@rch.org.au)

## Table of contents

Introduction.....	6
Search strategy .....	17
Acute respiratory infection.....	18
Treatment of ARI .....	18
Prevention of ARI.....	24
Oxygen therapy and CPAP for ALRI .....	24
Asthma .....	25
Adolescent health .....	28
Overall health and well-being.....	28
Adolescent mental health.....	29
Adolescent sexual and reproductive health .....	36
Adolescent pregnancy and child marriage.....	42
Adolescents and HIV prevention and treatment.....	43
Adolescent substance use .....	51
Anaemia and iron deficiency .....	53
Anaesthesia and intensive care .....	57
Intensive care .....	60
Antibiotics.....	62
Antibiotic resistance and stewardship .....	68
Cash transfers and family economic support.....	69
Community child health.....	71
Child development and parenting programs .....	76
Child protection and family violence .....	87
Dengue .....	90
Diarrhoea .....	90
Treatment of diarrhoea .....	90
Diarrhoea prevention .....	93
Ear disease and hearing loss .....	100
Ebola and viral haemorrhagic fever.....	101
Endocrine disorders and bone health.....	101
Diabetes .....	101
Bone health.....	101
Epilepsy and acute seizures .....	101
Fever.....	106
Fluid management.....	106
Fungal infections .....	110
Gastrointestinal problems.....	110
Hygiene, sanitation and environmental health.....	111
Indoor air pollution .....	111
Water, Sanitation and Hygiene .....	115
Health worker education.....	121
Haematological disorders .....	122
Sickle cell disease.....	122
Thalassaemia .....	128

Heart disease .....	130
Rheumatic heart disease .....	130
Congenital heart disease and cardiac surgery .....	131
HIV / AIDS.....	135
Antiretroviral therapy (ART) .....	135
Viral load monitoring.....	140
HIV diagnosis.....	143
Cotrimoxazole preventative therapy.....	145
HIV-exposed and uninfected infants .....	146
Nutrition, growth, and development of children with HIV .....	146
Prevention of mother to child transmission of HIV and maternal-infant HIV care.....	147
HIV vaccine.....	154
Helminth infections .....	154
Hepatitis and liver disease .....	156
Injury prevention .....	157
Integrated management of Childhood Illness (IMCI).....	158
Iodine deficiency.....	158
Kidney disease .....	158
Leishmaniasis .....	162
Lymphatic filariasis.....	162
Leprosy .....	164
Malaria.....	164
Insecticide-treated bed nets and other materials .....	164
Environmental prevention of malaria.....	168
Intermittent preventative treatment and seasonal malaria prophylaxis .....	172
Treatment of uncomplicated malaria .....	176
Community based malaria testing and management .....	180
Treatment of severe malaria.....	182
Malaria and comorbidities .....	183
Malnutrition.....	184
Environmental enteric dysfunction.....	189
Maternal health.....	192
Antenatal and maternal care during pregnancy.....	192
Maternal malaria prevention .....	198
Obstetric care and delivery .....	201
Maternal nutrition and micronutrient supplementation .....	209
Post-natal maternal care.....	221
Maternal mental health .....	223
Family planning and birth spacing.....	224
Meningitis and encephalitis.....	224
Mental health and child psychiatry.....	225
Mobile phones, text messages, and Apps .....	229
Mortality – post discharge .....	232
Neurocysticercosis .....	233
Neurodevelopmental conditions and cerebral palsy .....	234
Cerebral palsy .....	234
Autism .....	239

Newborn care .....	243
Essential newborn care .....	243
Avoiding hypothermia .....	243
Cord management.....	243
Kangaroo mother care / skin to skin contact.....	247
Neonatal sepsis .....	251
Low birth weight and prematurity - prevention .....	253
Management of the preterm infant .....	258
Neonatal intensive care .....	271
Neonatal resuscitation - perinatal asphyxia.....	279
Perinatal asphyxia.....	284
Neonatal seizures .....	287
Neonatal sepsis .....	288
Jaundice.....	289
Nutrition .....	290
Nutrition assessment and education .....	290
Growth monitoring .....	293
Micronutrients, multivitamins, and food fortification.....	294
Lipid-based nutrition supplements.....	297
Macronutrient nutrition and complementary feeding .....	299
Breastfeeding .....	303
Community and home nutrition programs .....	309
Obesity .....	315
Oncology .....	316
Ophthalmology and optometry .....	322
Trachoma.....	325
Oral health / dentistry .....	327
Pain.....	332
Poisoning and toxins.....	332
Refugee health and humanitarian settings.....	332
Research .....	338
Rheumatology .....	340
Quality of care.....	341
Safe sleeping practices.....	342
Schistosomiasis .....	342
School health and education .....	343
Sepsis and serious bacterial infection .....	347
Shock.....	349
Skin and hair disease .....	349
Snake bite and envenomation .....	351
Surgical problems .....	351
Trypanosomiasis.....	355
Tuberculosis .....	355
Treatment of tuberculosis .....	355
Prevention of tuberculosis, treatment of latent tuberculosis .....	358
Diagnosis of tuberculosis.....	361
Typhus.....	364



Typhoid .....	365
Ultrasound .....	367
Urinary tract infection.....	367
Urology.....	367
Vaccines and immunization .....	367
Vaccine coverage and administration.....	367
Vaccine-related adverse effects .....	369
BCG and other TB vaccines .....	369
Cholera vaccine.....	370
Covid-19 vaccine .....	371
Dengue vaccine .....	372
Ebola vaccine .....	372
Enterovirus 71 vaccine.....	373
Hepatitis A vaccine .....	374
Hepatitis B vaccine.....	374
HIV vaccine.....	375
HPV vaccine.....	375
Influenza vaccine.....	378
Japanese encephalitis virus vaccine .....	379
Malaria vaccine.....	379
Maternal immunization in pregnancy .....	382
Measles vaccine.....	382
Measles, mumps, rubella (MMR) vaccine.....	384
Meningococcal vaccine.....	385
Norovirus vaccine.....	387
Prentavalent vaccine (DTP-HepB-Hib).....	388
Pneumococcal vaccine.....	388
Polio vaccine .....	393
Rabies vaccine.....	398
Respiratory syncytial virus vaccine .....	399
Rotavirus vaccine .....	400
Salmonella typhi vaccine.....	402
Schistosomiasis vaccine .....	402
Tuberculosis vaccine .....	402
Typhoid vaccine .....	403
Varicella vaccine.....	410
Zika virus vaccine .....	410
Vitamin A .....	411
Vitamin D .....	412
Yaws .....	416
Zinc.....	416

## Introduction

Each year this booklet is compiled 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 resource poor settings where up-to-date information is hard to find. I hope that this information will be helpful in reviewing treatment policies, clinical practice, 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. 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>

Last year I used a simpler search, but several readers informed me of trials I had missed. This year I went back to using a more complex search strategy that had been used for 10 years, I re-did the search weekly and added a system of checking, so I am confident I have captured virtually all. If you know of a study not included, please let me know.

**This year 501 trial publications were identified.** These were conducted in countries from all regions of the world. Several trials from 2022-23 will lead to significant changes in child health recommendations. 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. 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.

**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 (2002-2022) are available at: <https://pngpaediatricsociety.org/research-2/>

I have been liberal in what is included as an RCT. Some papers are the reports of sub-studies within an RCT, rather than the primary results of the completed RCT. I have not included papers that only report the protocol for an RCTs.

Since 2002 there have been **3712 trial publications** summarized in the 20 editions of this book. This year, trials addressed the widest range of diseases and conditions that affect the health, development, and wellbeing of children, newborns, adolescents, and mothers. RCTs reflected old, new, and neglected problems, the rapidly changing epidemiology, social and economic circumstances in many countries, local and global priorities of low and middle-income countries, environmental causes of poor child health and inequities. They tested

new and refined treatments, diagnostics, vaccines, holistic management, and prevention approaches, and explored many outcomes, including mortality, nutrition, psychosocial measures, and development. The studies were conducted in numerous hospitals and primary health care clinics, schools, and communities, including among some of the world's most disadvantaged populations in humanitarian and refugee emergencies. Some studies are of the highest quality, and others fall short. A summary of some of the results from July 2022 to June 2023 is below:

- In a systematic review of studies of children with uncomplicated pneumonia, 5 days of amoxicillin as recommended by WHO was as effective as longer courses.<sup>1</sup> In Pakistan, 3 days of amoxicillin for clinical “fast-breathing” ARI, was as effective as longer courses of cotrimoxazole. These studies need to be understood in the context of the high proportion of cases of ALRI being viral, and the power of a study to detect a difference in outcomes for bacterial pneumonia is lower than the sample size suggests.<sup>2</sup>
- Assessment of risk is increasingly a focus to guide decisions about hospital admission, location and nature of care, and safety of discharge. In a systematic review of 27 RCTs and other trials, post-discharge mortality in children was significantly increased by anaemia (odds ratio 1.72, 95% CI 1.22-2.44), severe malnutrition (RR=3.12, 2.02-4.68;  $p<0.0001$ ), HIV, bacteraemia, and hypoxia.<sup>3</sup>
- In the Congo, probiotics added to ready-to-use therapeutic feeds for children with severe malnutrition had moderate effects on reduction in the number of days of diarrhoea, the risk of diarrhoea, and the proportion of children who had nutritional recovery at 6 weeks.<sup>4</sup> In a small RCT in Indian children, 3 months of a daily probiotic (*Bacillus clausii* UBBC-07) reduced upper respiratory infections; the mechanism seemed to be improving mucosal immunity with decreased IgE and increased salivary IgA.<sup>5</sup>
- Systematic reviews showed that CPAP can be effective in severe ALRI, with the strongest evidence in infants with bronchiolitis, and in a safe context (adequate staffing, including doctor oversight, intensive monitoring and supportive care, and technician and infrastructure capacity. At the other end of the ALRI spectrum, home management of what WHO calls “chest indrawing” ALRI can be effective, but again is only safe in certain contexts. To be safe there needs to be a system of risk assessment including clinical danger signs, oxygen saturation, and the presence of comorbidities such as undernutrition, anaemia, or HIV, and parental understanding of when to return and ability to do so.<sup>6,7</sup>
- Among Malaysian school children with asthma, interactive messages using a mobile phone App, increased asthma knowledge compared to face-to-face education.<sup>8</sup>
- Trials of adolescent leadership and community youth teams in rural India increased school participation, other positive impacts may have been undermined by household poverty.<sup>9</sup>

- Several studies in India aimed to evaluate interventions to improve adolescent mental health in India. Remote online interventions had limited acceptability, a school-based mixed-gender body image intervention with a trained psychologist resulted in sustained improvements in many areas,<sup>10</sup> and teaching of problem solving skills by a lay-counsellor resulted in such skills being sustained and generalized beyond the original presenting problems.<sup>11</sup>
- In a trial involving 157 schools in Zambia over 2 years, economic support in combination with comprehensive sexuality education and community dialogue can improve the sexual and reproductive health of adolescent girls. An essential factor was economic support.<sup>12</sup> In a trial in Uganda, family-based economic strengthening for 613 adolescents living with HIV improved school enrolment, reduced school dropouts, and improved anti-retroviral therapy adherence and savings.<sup>13 14</sup>
- In Zambia, among adolescent girls in a large cluster RCT of schools over 3 years, addressing the knowledge gaps in sexual and reproductive health through comprehensive sexuality education and improving access to sexual and reproductive health services significantly reduced in-school pregnancies.<sup>15</sup>
- In Tanzania, girl-friendly medicine shops increased access to sexual and reproductive health products and services, including HIV self-testing kits and contraception among adolescent girls.<sup>16</sup>
- Among Tibetan children aged 9-12 years from single-parent families, 6-week of mindfulness training effectively improve self-compassion and resilience, when added to the normal school education curriculum, compared to similar children who were randomised to normal education alone, although there was no difference in overall mental health scores.<sup>17</sup>
- In Cambodia, daily Spirulina, a nutritional supplement to enhance child nutrition, improved weight gain and reduced anaemia in a small RCT involving 173 pre-school children.<sup>18</sup>
- In a meta-analysis of studies in children undergoing surgery, supplemental intraoperative intravenous crystalloids substantially reduced postoperative vomiting, nausea, thirst, and the need for anti-emetics.<sup>19</sup>
- In children in India with ventilator associated Gram negative pneumonia, nebulized Colistin and systemic antibiotics compared systemic antibiotics alone reduced the duration of mechanical ventilation, postoperative ICU and hospital stay.<sup>20</sup>
- In a large trial of over 21,000 births in Burkina Faso, a single dose of azithromycin in the neonatal period did not influence all-cause mortality at 12 months. However the infant mortality rate overall was low at 5.3 per 1000 neonates enrolled.<sup>21</sup> Several studies further analysed the earlier trial from Niger which had shown a mortality benefit of biannual azithromycin in very high mortality settings.

- Among 29,278 women intending to have a vaginal birth, azithromycin resulted in a lower risk of sepsis or death compared to than in the placebo group (1.6% vs. 2.4%), with a relative risk of 0.67 (95% confidence interval, 0.56 to 0.79); there was no effect on neonatal sepsis, still birth, or neonatal death.<sup>22</sup>
- In a large RCT involving 34 villages in a poor rural area in Maharashtra state, India, village health volunteers that engaged in newborn care, disease management and behavior change communications resulted in large and sustained reductions in infant and child mortality.<sup>23</sup>
- The benefits of delayed cord clamping or umbilical cord milking in late-preterm and term infants who are active at birth was again shown in trials and systematic reviews, with improvements in haemoglobin at 48 hours and 6 weeks.<sup>24-26</sup> However, how best to manage non-vigorous infants where delayed cord clamping is made difficult by the need for some resuscitation was also studied this year. Two RCTs showing blood pressure in the first 6 hours, haemoglobin at 48 hours and 6 weeks and ferritin levels at 6 weeks were higher in babies who had umbilical cord milking after cutting, compared to those who had early cord cutting alone.<sup>27</sup> These results guide what to do for the baby who is not vigorous and needs some resuscitation.<sup>28</sup>
- In Kenya, within a RCT of diarrhoea prevention, handwashing after handling animals (adjusted odds ratio = 0.20; 95% CI=0.06 to 0.50) and before eating (adjusted odd ratio=0.44; 95% CI=0.26 to 0.73) were strongly associated with lower risk of diarrhoea. Living in a household with vinyl-covered dirt floors was associated with an increased risk of diarrheal pathogen isolation. Reducing animal cohabitation, improving flooring, and hand washing are important in diarrhoea prevention.<sup>29</sup> In other studies in Kenya, water, hygiene and sanitation, maternal, new-born and child health, nutrition and early childhood development programs reduced all-cause diarrhoea and lead to improvements in water quality.<sup>30</sup>
- Several other studies and a large meta-analysis proved that WASH interventions: sewer connections to houses, water purification at the point-of-use, and promotion of handwashing with soap consistently and substantially reduced diarrhoea risk.<sup>31</sup>
- In Brazil, reading aloud to children beginning in pregnancy and early childhood was associated with increased vocabulary and reduced screen time, for families with low parent literacy.<sup>32</sup>
- In a meta-analysis of studies of benzodiazepine-resistant status epilepticus, phenobarbital was the most effective agent for seizure cessation within 60 min of administration, more effective than phenytoin, but phenobarbitone was associated with increased need for intubation. High-dose levetiracetam, high-dose valproate and fosphenytoin were also effective.<sup>33</sup>
- In poor communities in India, for people living with epilepsy, home care with antiseizure medication provision, adherence reinforcement and epilepsy self- and stigma management by a trained primary health care worker was associated with

improved medication adherence and reduced seizures compared with routine clinic care.<sup>34</sup>

- In neonates with seizures in India, in a small RCT of the acute management with levetiracetam and phenobarbitone were equally efficacious for clinical neonatal seizure control, but need for increased respiratory support was found with phenobarbitone use.<sup>35</sup>
- In India, another trial of intravenous fluids comparing 0.45% sodium chloride (NaCl) and 0.9% NaCl resulted in significant falls in sodium levels in children in an emergency department treated with the hypotonic fluid at 12 and 24 hours, but no difference at 48 hours.<sup>36</sup> However in neonates >34 weeks gestation in intensive care, 0.9% NaCl was associated with hypernatraemia (serum sodium >145 mmol/L).<sup>37</sup> So isotonic fluid is the standard of care for children, but not for neonates in intensive care.
- In South African children with sickle cell disease during a vaso-occlusive pain crisis and acute chest syndrome, oral arginine improves cardiopulmonary hemodynamics, including a significant reduction in tricuspid regurgitant jet velocity, compared with placebo. Arginine administration may improve nitric oxide bioavailability and lead to pulmonary vasodilatation.<sup>38</sup>
- In Egypt, children with sickle-cell or thalassemia requiring regular blood transfusions in an RCT of oral deferiprone or subcutaneous infusions of deferoxamine as chelating therapy showed that long-term oral chelation with deferiprone led to continued and progressive reduction in iron load, and no safety concerns.<sup>39</sup>
- A number of trials this year, including the ODYSSEY in South Africa, Uganda, and Zimbabwe showed the greater efficacy of Dolutegravir (DTG)-based ART over previous standard of care (mainly protease inhibitor-based) and a lower risk of treatment failure in infants and young children living with HIV.<sup>40</sup> In children with HIV-TB coinfection, twice-daily is safe and overcomes the rifampicin enzyme-inducing effect in children that reduces DTG blood levels with once daily dosing.<sup>41</sup>
- Several studies evaluated point of care viral load testing for HIV,<sup>42</sup> and rapid early infant diagnosis of HIV with GeneXpert or other PCR testing.<sup>43 44</sup>
- In Papua New Guinea to eliminate lymphatic filariasis, widespread community administration of the addition of ivermectin to the standard two-drug regimen (diethylcarbamazine, and albendazole) was more effective in reducing microfilariae prevalence to below the target level of <1% at 12 and 24 months.<sup>45</sup>
- There has been a rise in pyrethroid-resistant mosquitoes, making many existing insecticide-treated bed nets less effective. Studies this year from Uganda and Benin have shown that chlorfenapyr-pyrethroid<sup>46</sup> or piperonyl butoxide<sup>47</sup> insecticide treated bed-nets provided greater protection from malaria than standard pyrethroid bed-nets.

- In Myanmar, regular, targeted text messages to pregnant women and mothers via mobile phones significantly improved breastfeeding practices (exclusive breastfeeding at 6 months 43% compared to controls 15%; bottle feeding much reduced, and significantly reduced infant diarrhoea during the first 6 months of life.<sup>48</sup>
- In children undergoing abdominal surgery in India, intraoperative fluid therapy based on the Plethysmographic Variability Index (PVI) derived from pulse oximetry significantly reduced the volume of intravenous crystalloids administered to children undergoing open bowel surgery. PVI is the percentage difference between the maximum and minimum plethysmographic wave on a pulse oximeter throughout the respiratory cycle.<sup>49</sup>
- In India, in the treatment of acute lymphoblastic leukaemia with high-dose methotrexate, the reduction of pre-hyperhydration duration (from 12 to 6 hours) did not affect the risk of nephrotoxicity and methotrexate levels over 136 cycles in 34 patients. Nephrotoxicity occurred in 1 and 2 per 68 cycles of methotrexate respectively given 12 or 6 hours of pre-hyperhydration.<sup>50</sup>
- A systematic review of physiotherapy in children with cerebral palsy showed that trunk-targeted exercises improve gross motor function, trunk control and balance, and help in greater functional recovery.<sup>51</sup>
- In an RCT in India involving 128 asphyxiated newborns who needed positive pressure respiratory support in the delivery room, using room air resulted in higher treatment failures (27 (46%) vs. 16 (25%); relative risk (RR) 1.9 (1.1-3.1)) and took longer time to establish regular respiration ( $230 \pm 231$  vs.  $182 \pm 261$ , mean difference = 48 (40, 136) seconds), than initiating resuscitation with 100% oxygen.<sup>52</sup>
- A systematic review of RCTS of neonates with perinatal asphyxia being managed with therapeutic hypothermia showed that enteral feeding is safe and does not increase the risk of necrotizing enterocolitis, hypoglycaemia, or feed intolerance. Enteral feeding during therapeutic hypothermia may reduce the incidence of sepsis and all-cause mortality until discharge.<sup>53</sup>
- In a RCT of a school feeding program among underprivileged children in northern Pakistan, there was an improvement in cognitive performance in children who received a school meal with and without micronutrient supplementation over a 12-month period, compared to those who did not receive a school meal.<sup>54</sup>
- In Uganda, a household solar lighting intervention had far-reaching social implications with improved social integration and social health. Participants felt that lighting mitigated the stigma of poverty, increased the duration and frequency of social interactions, improved household relationships because of reduced conflicts over light (previously kerosene) rationing. Participants also described a communal benefit of lighting due to improved feelings of safety, improved self-esteem, sense of well-being, and reduced stress.<sup>55</sup>

- An RCT of improved oral health and dental hygiene in children living with HIV showed improvements in overall dental health in those with focused teeth brushing, including reduced dental caries, reduced HIV viral load, and improved salivary flow and quality of life scores.<sup>56</sup>
- In rural Vietnam, community-based, multicomponent group programmes for mothers and their infants “Learning Clubs” improved early childhood development compared to the standardised mean.<sup>57</sup>
- In India, children aged 5-18 years with unilateral cerebral palsy given 6-Hz primed, low-frequency, repetitive transcranial magnetic stimulation improved upper limb function, dexterity, and strength.<sup>58</sup>
- Multiple studies of the Typhoid Vi-polysaccharide conjugate vaccine were published this year, from Malawi,<sup>59 60</sup> India,<sup>61 62</sup> Nepal,<sup>63 64</sup> and Bangladesh<sup>65</sup> and China,<sup>66</sup> showing a single dose of the vaccine results in very high levels of seroconversion among children aged 9 months to 12 years and sustained for up to 3 years, and no interference with measles or measles-mumps-rubella vaccines.

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 RCT 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.

RCTs often report the “average effect”, that is, the effect on the overall population. However, depending on how specifically that population is defined, within that population may be children who will benefit from the therapy or intervention, children for whom the therapy will have no effect, and some children for whom it may be harmful. The “average” of these effects may be “no overall effect”, but it is increasingly important that researchers try to understand the effects for individuals or sub-groups within trials, and the context in which benefit or not occurs.

Some of the context differences that influence the results of a trial include individual or population characteristics, comorbidities, the health care environment and health care providers, geographical factors, other interventions, the delivery mechanism for the drug, vaccine or other intervention, the disease stage and specific aetiology, economic, social, and cultural characteristics of the population and individuals within it...and other unknown factors.

It is heartening to see the evolution of RCTs in low and middle income countries in the last 2 decades, and the high quality evidence that these studies generate, much of which is relevant globally.



## References

1. R. Marques I, P. Calvi I, A. Cruz S, et al. Shorter versus longer duration of Amoxicillin-based treatment for pediatric patients with community-acquired pneumonia: a systematic review and meta-analysis. *Eur J Pediatr* 2022;181(11):3795-804.
2. Sheraz A, Shabina A, Sajid M, et al. Community case management of fast-breathing pneumonia with 3 days oral amoxicillin vs 5 days cotrimoxazole in children 2-59 months of age in rural Pakistan: A cluster randomized trial. *Journal of Global Health* 2022;12
3. Kwambai TK, Mori AT, Nevitt S, et al. Post-discharge morbidity and mortality in children admitted with severe anaemia and other health conditions in malaria-endemic settings in Africa: a systematic review and meta-analysis. *The Lancet Child & Adolescent Health* 2022
4. Kambale RM, Ntagazibwa JN, Kasengi JB, et al. Probiotics for children with uncomplicated severe acute malnutrition (PruSAMstudy): A randomized controlled trial in the Democratic Republic of Congo. *The American journal of clinical nutrition* 2023;117(5):976-84.
5. Madempudi R, Neelamraju J, Ahire J, et al. *Bacillus clausii* UBBC-07 in the symptom management of upper respiratory tract infections in children: a double blind, placebo-controlled randomised study. *Beneficial Microbes* 2022;13(4):331-39.
6. Wilkes C, Rami S, Graham HR, et al. Continuous Positive Airway Pressure (CPAP) for severe pneumonia in low- and middle-income countries: A systematic review of contextual factors. *Journal of Global Health* 2022;12
7. Wilkes C, Graham H, Walker P, et al. Which children with chest-indrawing pneumonia can be safely treated at home, and under what conditions is it safe to do so? A systematic review of evidence from low- and middle-income countries. *Journal of Global Health* 2022;12
8. Al Raimi AM, Chong MC, Tang LY, et al. The effect of mobile applications in enhancing asthma knowledge among school children with asthma in Malaysia. *J Pediatr Nurs* 2022;65:e63-e71.
9. Bhatia K, Rath S, Pradhan H, et al. Effects of community youth teams facilitating participatory adolescent groups, youth leadership activities and livelihood promotion to improve school attendance, dietary diversity and mental health among adolescent girls in rural eastern India (JIAH trial): A cluster-randomised controlled trial. *SSM-Population Health* 2023;21:101330.
10. Lewis-Smith H, Garbett KM, Chaudhry A, et al. Evaluating a body image school-based intervention in India: A randomized controlled trial. *Body Image* 2023;44:148-56.
11. Malik K, Parikh R, Sahu R, et al. "If there is a tension about something, I can solve it": A qualitative investigation of change processes in a trial of brief problem-solving interventions for common adolescent mental health problems in India. *Psychology and Psychotherapy: Theory, Research and Practice* 2023;96(1):189-208.
12. Hegdahl HK, Musonda P, Svanemyr J, et al. Effects of economic support, comprehensive sexuality education and community dialogue on sexual behaviour: Findings from a cluster-RCT among adolescent girls in rural Zambia. *Soc Sci Med* 2022;306:115125.
13. Kizito S, Nabayinda J, Kiyangi J, et al. The impact of an economic strengthening intervention on academic achievement among adolescents living with HIV: Findings from the Suubi+ adherence cluster-randomized trial in Uganda (2012–2018). *AIDS Behav* 2023;27(3):1013-23.
14. Brathwaite R, Ssewamala FM, Mutumba M, et al. The Long-term (5-year) impact of a family economic empowerment intervention on adolescents living with HIV in Uganda: analysis of longitudinal data from a cluster randomized controlled trial from the Suubi+ Adherence Study (2012–2018). *AIDS Behav* 2022;26(10):3337-44.
15. Mbizvo MT, Kasonda K, Muntalima N-C, et al. Comprehensive sexuality education linked to sexual and reproductive health services reduces early and unintended pregnancies among in-school adolescent girls in Zambia. *BMC Public Health* 2023;23(1):1-13.
16. Hunter LA, Rao A, Napierala S, et al. Reaching Adolescent Girls and Young Women With HIV Self-Testing and Contraception at Girl-Friendly Drug Shops: A Randomized Trial in Tanzania. *J Adolesc Health* 2023;72(1):64-72.

## Randomised trials in child health in developing countries July 2022 to June 2023

17. Guo T, Jiang D, Kuang J, et al. Mindfulness group intervention improved self-compassion and resilience of children from single-parent families in Tibetan areas. *Complement Ther Clin Pract* 2023;101743.
18. Barennes H, Houdart L, de Courville C, et al. Spirulina as a daily nutritional supplement of young pre-school Cambodian children of deprived settings: a single-blinded, placebo-controlled, cross-over trial. *BMC Pediatr* 2022;22(1):1-8.
19. Puri S, Bandyopadhyay A, Ashok V. Supplemental intraoperative crystalloids for pediatric postoperative nausea and vomiting—A systematic review and meta-analysis. *Pediatric Anesthesia* 2023;33(1):38-45.
20. Bharathi K, Bhat A, Pruthi G, et al. Randomized control study of nebulized colistin as an adjunctive therapy in ventilator-associated pneumonia in pediatric postoperative cardiac surgical population. *Ann Card Anaesth* 2022;25(4):435.
21. Sié A, Bountogo M, Zakane A, et al. Effect of Neonatal Azithromycin on All-Cause and Cause-Specific Infant Mortality: A Randomized Controlled Trial. *The American Journal of Tropical Medicine and Hygiene* 2022;107(6):1331.
22. Tita AT, Carlo WA, McClure EM, et al. Azithromycin to prevent sepsis or death in women planning a vaginal birth. *N Engl J Med* 2023;388(13):1161-70.
23. Satav AR, Satav KA, Bharadwaj A, et al. Effect of home-based childcare on childhood mortality in rural Maharashtra, India: a cluster randomised controlled trial. *BMJ Global Health* 2022;7(7):e008909.
24. Jeevan A, Ananthan A, Bhuwan M, et al. Umbilical cord milking versus delayed cord clamping in term and late-preterm infants: a systematic review and meta-analysis. *The Journal of Maternal-Fetal & Neonatal Medicine* 2022;35(25):5478-88.
25. Chaudhary P, Priyadarshi M, Singh P, et al. Effects of delayed cord clamping at different time intervals in late preterm and term neonates: a randomized controlled trial. *Eur J Pediatr* 2023:1-11.
26. Ramaswamy VV, Bandyopadhyay T, Abiramalatha T, et al. Placental Transfusion Strategies in Preterm Infants in Low-and Middle-Income Countries: A Systematic Review and Network Meta-Analysis. *Neonatology* 2023;120(1):118-33.
27. Bora RL, Bandyopadhyay S, Saha B, et al. Cut umbilical cord milking (C-UCM) as a mode of placental transfusion in non-vigorous preterm neonates: a randomized controlled trial. *Eur J Pediatr* 2023:1-9.
28. Katheria AC, Clark E, Yoder B, et al. Umbilical cord milking in nonvigorous infants: a cluster-randomized crossover trial. *Am J Obstet Gynecol* 2023;228(2):217. e1-17. e14.
29. Baker KK, Mumma JAO, Simiyu S, et al. Environmental and behavioural exposure pathways associated with diarrhoea and enteric pathogen detection in 5-month-old, periurban Kenyan infants: a cross-sectional study. *BMJ open* 2022;12(10):e059878.
30. Wandera EA, Muriithi B, Kathiiko C, et al. Impact of integrated water, sanitation, hygiene, health and nutritional interventions on diarrhoea disease epidemiology and microbial quality of water in a resource-constrained setting in Kenya: A controlled intervention study. *Trop Med Int Health* 2022;27(8):669-77.
31. Wolf J, Hubbard S, Brauer M, et al. Effectiveness of interventions to improve drinking water, sanitation, and handwashing with soap on risk of diarrhoeal disease in children in low-income and middle-income settings: a systematic review and meta-analysis. *The Lancet* 2022;400(10345):48-59.
32. Piccolo LR, Batista Araujo Oliveira J, Hirata G, et al. Supporting reading aloud beginning prenatally and in early infancy: a randomized trial in Brazil. *J Dev Behav Pediatr* 2022;43(9):e590-e97.
33. Jain P, Aneja S, Cunningham J, et al. Treatment of benzodiazepine-resistant status epilepticus: Systematic review and network meta-analyses. *Seizure* 2022
34. Singh G, Sharma S, Bansal N, et al. A cluster-randomized trial comparing home-based primary health care and usual clinic care for epilepsy in a resource-limited country. *Epilepsia Open* 2022;7(4):781-91.
35. Gyandeep G, Behura SS, Sahu SK, et al. Comparison between Phenobarbitone and Levetiracetam as the initial anticonvulsant in preterm neonatal seizures—a pilot randomized control trial in developing country setup. *Eur J Pediatr* 2023;182(5):2133-38.

## Randomised trials in child health in developing countries July 2022 to June 2023

36. Ratnjeet K, Pallavi P, Jhamb U, et al. 0.45% Versus 0.9% Saline in 5% Dextrose as Maintenance Fluids in Children Admitted With Acute Illness: A Randomized Control Trial. *Pediatr Emerg Care* 2022;38(9):436-41.
37. Dathan K, Sundaram M. Comparison of isotonic versus hypotonic intravenous fluid for maintenance fluid therapy in neonates more than or equal to 34 weeks of gestational age—a randomized clinical trial. *The Journal of Maternal-Fetal & Neonatal Medicine* 2022;35(25):6338-45.
38. Onalo R, Cilliers A, Cooper P, et al. Arginine therapy and cardiopulmonary hemodynamics in hospitalized children with sickle cell anemia: a prospective, double-blinded, randomized placebo-controlled clinical trial. *Am J Respir Crit Care Med* 2022;206(1):70-80.
39. Elalfy MS, Hamdy M, El-Beshlawy A, et al. Deferiprone for transfusional iron overload in sickle cell disease and other anemias: open-label study of up to 3 years. *Blood Advances* 2023;7(4):611-19.
40. Amuge P, Lugemwa A, Wynne B, et al. Once-daily dolutegravir-based antiretroviral therapy in infants and children living with HIV from age 4 weeks: results from the below 14 kg cohort in the randomised ODYSSEY trial. *The Lancet HIV* 2022;9(9):e638-e48.
41. Turkova A, Waalewijn H, Chan MK, et al. Dolutegravir twice-daily dosing in children with HIV-associated tuberculosis: a pharmacokinetic and safety study within the open-label, multicentre, randomised, non-inferiority ODYSSEY trial. *The Lancet HIV* 2022;9(9):e627-e37.
42. Patel RC, Oyaro P, Thomas KK, et al. Point-of-care HIV viral load and targeted drug resistance mutation testing versus standard care for Kenyan children on antiretroviral therapy (Opt4Kids): an open-label, randomised controlled trial. *The Lancet Child & Adolescent Health* 2022;6(10):681-91.
43. Mohamed Y, Htay H, Gare J, et al. The effect of the Xpert HIV-1 Qual test on early infant diagnosis of HIV in Myanmar and Papua New Guinea: a pragmatic, cluster-randomised, stepped-wedge, open-label trial. *The Lancet HIV* 2023;10(4):e220-e29.
44. Chibwesa CJ, Mollan KR, Ford CE, et al. A randomized trial of point-of-care early infant human immunodeficiency virus (HIV) diagnosis in Zambia. *Clin Infect Dis* 2022;75(2):260-68.
45. Laman M, Tavul L, Karl S, et al. Mass drug administration of ivermectin, diethylcarbamazine, plus albendazole compared with diethylcarbamazine plus albendazole for reduction of lymphatic filariasis endemicity in Papua New Guinea: a cluster-randomised trial. *The Lancet Infectious Diseases* 2022;22(8):1200-09.
46. Accrombessi M, Cook J, Dangbenon E, et al. Efficacy of pyriproxyfen-pyrethroid long-lasting insecticidal nets (LLINs) and chlorfenapyr-pyrethroid LLINs compared with pyrethroid-only LLINs for malaria control in Benin: a cluster-randomised, superiority trial. *The Lancet* 2023;401(10375):435-46.
47. Maiteki-Sebuguzi C, Gonahasa S, Kamya MR, et al. Effect of long-lasting insecticidal nets with and without piperonyl butoxide on malaria indicators in Uganda (LLINEUP): final results of a cluster-randomised trial embedded in a national distribution campaign. *The Lancet Infectious Diseases* 2023;23(2):247-58.
48. Hmone MP, Li M, Agho KE, et al. Tailored text messages to improve breastfeeding practices in Yangon, Myanmar: the M528 individually randomized controlled trial. *The American Journal of Clinical Nutrition* 2023;117(3):518-28.
49. Mathew PJ, Sharma S, Bhardwaj N, et al. Goal-directed fluid therapy guided by Plethysmographic Variability Index (PVI) versus conventional liberal fluid administration in children during elective abdominal surgery: A randomized controlled trial. *J Pediatr Surg* 2023;58(4):735-40.
50. Khera S, Mahajan D, Barbind K, et al. Impact of pre-hydration duration on high-dose methotrexate induced nephrotoxicity in childhood acute lymphoblastic leukaemia in resource constraint centers: a randomized crossover study. *Cancer Chemother Pharmacol* 2023:1-6.
51. Talgeri AJ, Nayak A, Karnad SD, et al. Effect of Trunk Targeted Interventions on Functional Outcomes in Children with Cerebral Palsy-A Systematic Review. *Dev Neurorehabil* 2023;26(3):193-205.
52. Liyakat NA, Kumar P, Sundaram V. Room air versus 100% oxygen for delivery room resuscitation of preterm neonates in low resource settings: A randomised, blinded, controlled trial. *J Paediatr Child Health* 2023
53. Kumar J, Anne RP, Meena J, et al. To feed or not to feed during therapeutic hypothermia in asphyxiated neonates: a systematic review and meta-analysis. *Eur J Pediatr* 2023:1-15.

## Randomised trials in child health in developing countries July 2022 to June 2023

54. Lowe NM, Qualter P, Sinclair JK, et al. School Feeding to Improve Cognitive Performance in Disadvantaged Children: A 3-Arm Parallel Controlled Trial in Northwest Pakistan. *Nutrients* 2023;15(7):1768.
55. Ponticiello M, Nuwagira E, Tayebwa M, et al. "If you have light, your heart will be at peace": A qualitative study of household lighting and social integration in southwestern Uganda. *Journal of Global Health* 2023;13
56. Kikuchi K, Tuot S, Yasuoka J, et al. Impact of oral intervention on the oral and overall health of children living with HIV in Cambodia: a randomized controlled trial. *BMC Med* 2023;21(1):1-15.
57. Fisher J, Tran T, Tran H, et al. Structured, multicomponent, community-based programme for women's health and infant health and development in rural Vietnam: a parallel-group cluster randomised controlled trial. *The Lancet Child & Adolescent Health* 2023;7(5):311-25.
58. Gupta J, Gulati S, Singh UP, et al. Brain Stimulation and Constraint Induced Movement Therapy in Children With Unilateral Cerebral Palsy: A Randomized Controlled Trial. *Neurorehabil Neural Repair* 2023:15459683231174222.
59. Liang Y, Driscoll AJ, Patel PD, et al. Typhoid conjugate vaccine effectiveness in Malawi: evaluation of a test-negative design using randomised, controlled clinical trial data. *The Lancet Global Health* 2023;11(1):e136-e44.
60. Nampota-Nkomba N, Nyirenda OM, Khonde L, et al. Safety and immunogenicity of a typhoid conjugate vaccine among children aged 9 months to 12 years in Malawi: a nested substudy of a double-blind, randomised controlled trial. *The Lancet Global Health* 2022;10(9):e1326-e35.
61. Thuluva S, Paradkar V, Matur R, et al. A multicenter, single-blind, randomized, phase-2/3 study to evaluate immunogenicity and safety of a single intramuscular dose of biological E's Vi-capsular polysaccharide-CRM197 conjugate typhoid vaccine (TyphiBEVTM) in healthy infants, children, and adults in comparison with a licensed comparator. *Hum Vaccin Immunother* 2022;18(5):2043103.
62. Vadrevu KM, Dugyala R, Mahantashetti NS, et al. Safety, immunogenicity and non-interference of concomitant Typhoid Vi capsular polysaccharide-tetanus toxoid conjugate vaccine (Typbar-TCV<sup>®</sup>) and measles or measles-mumps-rubella vaccines in 8–9 months-old Indian children. *Hum Vaccin Immunother* 2022:2150030.
63. Chaudhary S, Shah GS, Bhatta NK, et al. A randomized, observer-blind, controlled phase III clinical trial assessing safety and immunological non-inferiority of Vi-diphtheria toxoid versus Vi-tetanus toxoid typhoid conjugate vaccine in healthy volunteers in eastern Nepal. *Hum Vaccin Immunother* 2023;19(1):2203634.
64. Saluja T, Rai GK, Chaudhary S, et al. Immune non-interference and safety study of Vi-DT typhoid conjugate vaccine with a measles, mumps and rubella containing vaccine in 9–15 months old Nepalese infants. *Vaccine* 2022;40(40):5828-34.
65. Khanam F, Babu G, Rahman N, et al. Immune responses in children after vaccination with a typhoid Vi-tetanus toxoid conjugate vaccine in Bangladesh. *Vaccine* 2023;41(19):3137-40.
66. Baik YO, Lee Y, Lee C, et al. A Phase II/III, Multicenter, Observer-blinded, Randomized, Non-inferiority and Safety, study of typhoid conjugate vaccine (EuTCV) compared to Typbar-TCV<sup>®</sup> in healthy 6 Months-45 years aged participants. *Vaccine* 2023;41(10):1753-59.

## Search strategy

Pubmed Advanced strategy, search: ("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]))): Publication date between July 1 2022 and June 30 2023.

## Acute respiratory infection

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

### Treatment of ARI

Eur J Pediatr. 2022 Nov;181(11):3795-3804.

doi: 10.1007/s00431-022-04603-8. Epub 2022 Sep 6.

#### [Shorter versus longer duration of Amoxicillin-based treatment for pediatric patients with community-acquired pneumonia: a systematic review and meta-analysis](#)

[Isabela R Marques<sup>1</sup>](#), [Izabela P Calvi<sup>2</sup>](#), [Sara A Cruz<sup>2</sup>](#), [Luana M F Sanchez<sup>3</sup>](#), [Isis F Baroni<sup>4</sup>](#), [Christi Oommen<sup>5</sup>](#), [Eduardo M H Padrao<sup>5</sup>](#), [Paula C Mari<sup>6</sup>](#)

#### Abstract

*Streptococcus pneumoniae* is the most common typical bacterial cause of pneumonia among children. The World Health Organization (WHO) recommends a 5-day Amoxicillin-based empiric treatment. However, longer treatments are frequently used. This study aimed to compare shorter and longer Amoxicillin regimens for children with uncomplicated community-acquired pneumonia (CAP). A search of PubMed, EMBASE, and Cochrane Central was conducted to identify randomized controlled trials (RCTs) comparing 5-day and 10-day courses of Amoxicillin for the treatment of CAP in children older than 6 months in an outpatient setting. Studies involving overlapping populations, lower-than-standard antibiotic doses, and hospitalized patients were excluded. The outcome of interest was clinical cure. Statistical analysis was performed using RevMan 5.4. Heterogeneity was assessed using the Cochran Q test and  $I^2$  statistics. Two independent authors conducted the critical appraisal of the included studies according to the RoB-2 tool for assessing the risk of bias in randomized trials, and disagreements were resolved by consensus. We used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) tool to evaluate the certainty of evidence of our results. **Three RCTs and 789 children aged from 6 months to 10 years were included, of whom 385 (48.8%) underwent a 5-day regimen. Amoxicillin-based therapy was used in 774 (98%) patients. No differences were found between 5-day and 10-day therapy regarding clinical cure (RR 1.01; 95% CI 0.98-1.05;  $p = 0.49$ ;  $I^2 = 0\%$ ). Subgroup analysis of children aged 6-71 months showed no difference in the rates of the same outcome (RR 1.01; 95% CI 0.98-1.05;  $p = 0.38$ ;  $I^2 = 0\%$ ).** The GRADE tool suggested moderate certainty of evidence.

J Glob Health. 2022 Dec 29;12:04097.

doi: 10.7189/jogh.12.04097.

#### [Community case management of fast-breathing pneumonia with 3 days oral amoxicillin vs 5 days cotrimoxazole in children 2-59 months of age in rural Pakistan: A cluster randomized trial](#)

[Sheraz Ahmed<sup>1</sup>](#), [Shabina Ariff<sup>1</sup>](#), [Sajid Muhammed<sup>2</sup>](#), [Arjumand Rizvi<sup>2</sup>](#), [Imran Ahmed<sup>2</sup>](#), [Sajid Bashir Soofi<sup>1,2</sup>](#), [Zulfiqar A Bhutta<sup>2,3</sup>](#)

#### Abstract

**Background:** Pneumonia is the leading cause of mortality in under-five children and most of these deaths occur in South-East Asia and Africa. Fast breathing pneumonia if not treated can progress to lower chest indrawing pneumonia. Treatment recommendation by the World

Health Organization (WHO) for fast-breathing pneumonia includes oral amoxicillin and cotrimoxazole (as an alternative). Due to limited access to health care facilities and skilled health care workers, many children are unable to receive antibiotics. Algorithm-based community case management of pneumonia through trained community health workers has resulted in a decline in morbidity and mortality in low- and middle-income countries (LMIC).

**Methods:** It was a cluster-randomized, unblinded, community-based trial conducted in the Matiari district of Sindh province, Pakistan. Lady Health Workers (LHWs) were trained in assessing, classifying, and managing fast-breathing pneumonia cases (Respiratory rate of >50 breaths/min) at home with oral amoxicillin for three days and with co-trimoxazole for five days in the intervention and control arms respectively. Children with fast-breathing pneumonia were screened by LHWs and were validated by the study by Community Health Workers (CHWs) within 48 hours. They were followed by the LHWs on days 2, 4, and 14 in intervention and on days 2, 6, and 14 in the control arm. Primary treatment failure was assessed on day 4 in intervention and day 6 in the control arm. A severe pneumonia trial was registered with ClinicalTrials.gov, number [NCT01192789](https://clinicaltrials.gov/ct2/show/study/NCT01192789).

**Results:** From February 2008 to March 2010, a total of 5876 children were enrolled by Lady Health Workers as fast breathing pneumonia. On validation visits of the CHWs, 728 (12%) children were excluded. A total of 4984 children were analysed as per protocol: 2480 in intervention and 2504 in control. There were 72 (2.9%) primary treatment failures in the intervention arm as compared to 102 (4%) in the control arm with a risk difference of -0.94 (-2.84%, 0.96%). Secondary treatment failures were almost equal in both arms (4 vs 7 cases). No deaths or serious adverse events were recorded.

**Conclusions:** This study shows that amoxicillin can be as effective as cotrimoxazole to treat fast-breathing pneumonia cases at the domiciliary level.

Lancet Infect Dis. 2023 Mar;23(3):341-351.

doi: 10.1016/S1473-3099(22)00668-5. Epub 2022 Nov 14.

### [Effect of systematic tuberculosis detection on mortality in young children with severe pneumonia in countries with high incidence of tuberculosis: a stepped-wedge cluster-randomised trial](#)

[Olivier Marcy<sup>1</sup>](#), [Eric Wobudeya<sup>2</sup>](#), [Hélène Font<sup>3</sup>](#), [Aurélia Vessière<sup>3</sup>](#), [Chishala Chabala<sup>4</sup>](#), [Celso Khosa<sup>5</sup>](#), [Jean-Voisin Taguebue<sup>6</sup>](#), [Raoul Moh<sup>7</sup>](#), [Juliet Mwanga-Amumpaire<sup>8</sup>](#), [Manon Lounnas<sup>9</sup>](#), [Veronica Mulenga<sup>4</sup>](#), [Sandra Mavale<sup>10</sup>](#), [Josina Chilundo<sup>10</sup>](#), [Dalila Rego<sup>11</sup>](#), [Bwendo Nduna<sup>12</sup>](#), [Perfect Shankalala<sup>4</sup>](#), [Uzima Chirwa<sup>13</sup>](#), [Agathe De Lauzanne<sup>14</sup>](#), [Bunnet Dim<sup>14</sup>](#), [Emeline Tiogouo Ngouana<sup>15</sup>](#), [Madeleine Folquet Amorrissani<sup>16</sup>](#), [Lassina Cisse<sup>17</sup>](#), [Flore Amon Tanoh Dick<sup>18</sup>](#), [Eric A Komona<sup>7</sup>](#), [Sylvie Kwedi Nolna<sup>19</sup>](#), [Gerald Businge<sup>2</sup>](#), [Naome Natukunda<sup>8</sup>](#), [Saniata Cumbe<sup>5</sup>](#), [Prossy Mbekeka<sup>20</sup>](#), [Ang Kim<sup>21</sup>](#), [Chanrithea Kheang<sup>22</sup>](#), [Sokha Pol<sup>23</sup>](#), [Elizabeth Maleche-Obimbo<sup>24</sup>](#), [James A Seddon<sup>25</sup>](#), [Tan Eang Mao<sup>26</sup>](#), [Stephen M Graham<sup>27</sup>](#), [Christophe Delacourt<sup>28</sup>](#), [Laurence Borand<sup>14</sup>](#), [Maryline Bonnet<sup>19</sup>](#); [TB-Speed Pneumonia Study Group](#)

#### **Abstract**

**Background:** Tuberculosis diagnosis might be delayed or missed in children with severe pneumonia because this diagnosis is usually only considered in cases of prolonged symptoms or antibiotic failure. Systematic tuberculosis detection at hospital admission could increase case detection and reduce mortality.

**Methods:** We did a stepped-wedge cluster-randomised trial in 16 hospitals from six countries (Cambodia, Cameroon, Côte d'Ivoire, Mozambique, Uganda, and Zambia) with high

incidence of tuberculosis. Children younger than 5 years with WHO-defined severe pneumonia received either the standard of care (control group) or standard of care plus Xpert MTB/RIF Ultra (Xpert Ultra; Cepheid, Sunnyvale, CA, USA) on nasopharyngeal aspirate and stool samples (intervention group). Clusters (hospitals) were progressively switched from control to intervention at 5-week intervals, using a computer-generated random sequence, stratified on incidence rate of tuberculosis at country level, and masked to teams until 5 weeks before switch. We assessed the effect of the intervention on primary (12-week all-cause mortality) and secondary (including tuberculosis diagnosis) outcomes, using generalised linear mixed models. The primary analysis was by intention to treat. We described outcomes in children with severe acute malnutrition in a post hoc analysis. This study is registered with ClinicalTrials.gov ([NCT03831906](https://clinicaltrials.gov/ct2/show/study/NCT03831906)) and the Pan African Clinical Trial Registry (PACTR202101615120643).

**Findings:** From March 21, 2019, to March 30, 2021, we enrolled 1401 children in the control group and 1169 children in the intervention group. In the intervention group, 1140 (97.5%) children had nasopharyngeal aspirates and 942 (80.6%) had their stool collected; 24 (2.1%) had positive Xpert Ultra. At 12 weeks, 110 (7.9%) children in the control group and 91 (7.8%) children in the intervention group had died (adjusted odds ratio [OR] 0.986, 95% CI 0.597-1.630,  $p=0.957$ ), and 74 (5.3%) children in the control group and 88 (7.5%) children in the intervention group had tuberculosis diagnosed (adjusted OR 1.238, 95% CI 0.696-2.202,  $p=0.467$ ). In children with severe acute malnutrition, 57 (23.8%) of 240 children in the control group and 53 (17.8%) of 297 children in the intervention group died, and 36 (15.0%) of 240 children in the control group and 56 (18.9%) of 297 children in the intervention group were diagnosed with tuberculosis. The main adverse events associated with nasopharyngeal aspirates were samples with blood in 312 (27.3%) of 1147 children with nasopharyngeal aspirates attempted, dyspnoea or SpO<sub>2</sub> less than 95% in 134 (11.4%) of children, and transient respiratory distress or SpO<sub>2</sub> less than 90% in 59 (5.2%) children. There was no serious adverse event related to nasopharyngeal aspirates reported during the trial.

**Interpretation:** Systematic molecular tuberculosis detection at hospital admission did not reduce mortality in children with severe pneumonia. High treatment and microbiological confirmation rates support more systematic use of Xpert Ultra in this group, notably in children with severe acute malnutrition.

J Glob Health. 2022 Aug 31;12:10008.

doi: 10.7189/jogh.12.10008.

[\*\*Which children with chest-indrawing pneumonia can be safely treated at home, and under what conditions is it safe to do so? A systematic review of evidence from low- and middle-income countries\*\*](#)

[Chris Wilkes](#), [Hamish Graham](#), [Patrick Walker](#), [Trevor Duke](#), [ARI Review group](#)

### **Abstract**

**Background:** WHO pneumonia guidelines recommend that children (aged 2-59 months) with chest indrawing pneumonia and without any "general danger sign" can be treated with oral amoxicillin without hospital admission. This recommendation was based on trial data from limited contexts whose generalisability is unclear. This review aimed to identify which children with chest-indrawing pneumonia in low- and middle-income countries can be safely treated at home, and under what conditions is it safe to do so.



**Methods:** We searched MEDLINE, EMBASE, and PubMed for observational and interventional studies of home-based management of children (aged 28 days to four years) with chest-indrawing pneumonia in low- or middle-income countries.

**Results:** We included 14 studies, including seven randomised trials, from a variety of urban and rural contexts in 11 countries. Two community-based and two hospital-based trials in Pakistan and India found that home treatment of chest-indrawing pneumonia was associated with similar or superior treatment outcomes to hospital admission. Evidence from trials (n = 3) and observational (n = 6) studies in these and other countries confirms the acceptability and feasibility of home management of chest-indrawing pneumonia in low-risk cases, so long as safeguards are in place. Risk assessment includes clinical danger signs, oxygen saturation, and the presence of comorbidities such as undernutrition, anaemia, or HIV. Pulse oximetry is a critical risk-assessment tool that is currently not widely available and can identify severely ill patients with hypoxaemia otherwise possibly missed by clinical assessment alone. Additional safeguards include caregiver understanding and ability to return for review.

**Conclusions:** Home treatment of chest-indrawing pneumonia can be safe but should only be recommended for children confirmed to be low-risk and in contexts where appropriate care and safety measures are in place.

Cochrane Database Syst Rev. 2023 Jan 12;1(1):CD011597.

doi: 10.1002/14651858.CD011597.pub3.

[Vitamin D as an adjunct to antibiotics for the treatment of acute childhood pneumonia](#)

[Rashmi R Das<sup>1</sup>](#), [Meenu Singh<sup>2</sup>](#), [Sushree S Naik<sup>3</sup>](#)

### Abstract

**Background:** Children with acute pneumonia may be vitamin D deficient. Clinical trials have found that prophylactic vitamin D supplementation decreases children's risk of developing pneumonia. Data on the therapeutic effects of vitamin D in acute childhood pneumonia are limited. This is an update of a Cochrane Review first published in 2018.

**Objectives:** To evaluate the efficacy and safety of vitamin D supplementation as an adjunct to antibiotics for the treatment of acute childhood pneumonia.

**Search methods:** We searched CENTRAL, MEDLINE, Embase, and two trial registries on 28 December 2021. We applied no language restrictions.

**Selection criteria:** We included randomised controlled trials (RCTs) that compared vitamin D supplementation with placebo in children (aged one month to five years) hospitalised with acute community-acquired pneumonia, as defined by the World Health Organization (WHO) acute respiratory infection guidelines. For this update, we reappraised eligible trials according to research integrity criteria, excluding RCTs published from April 2018 that were not prospectively registered in a trials registry according to WHO or Clinical Trials Registry - India (CTRI) guidelines (it was not mandatory to register clinical trials in India before April 2018).

**Data collection and analysis:** Two review authors independently assessed trials for inclusion and extracted data. For dichotomous data, we extracted the number of participants experiencing the outcome and the total number of participants in each treatment group. For continuous data, we used the arithmetic mean and standard deviation (SD) for each treatment group together with number of participants in each group. We used standard methodological procedures expected by Cochrane.

**Main results:** In this update, we included three new trials involving 468 children, bringing the total number of trials to seven, with 1601 children (631 with pneumonia and 970 with severe or very severe pneumonia). We categorised three previously included studies and three new studies as 'awaiting classification' based on the research integrity screen. Five trials used a single bolus dose of vitamin D (300,000 IU in one trial and 100,000 IU in four trials) at the onset of illness or within 24 hours of hospital admission; one used a daily dose of oral vitamin D (1000 IU for children aged up to one year and 2000 IU for children aged over one year) for five days; and one used variable doses (on day 1, 20,000 IU in children younger than six months, 50,000 IU in children aged six to 12 months, and 100,000 IU in children aged 13 to 59 months; followed by 10,000 IU/day for four days or until discharge). Three trials performed microbiological diagnosis of pneumonia, radiological diagnosis of pneumonia, or both. Vitamin D probably has little or no effect on the time to resolution of acute illness (mean difference (MD) -1.28 hours, 95% confidence interval (CI) -5.47 to 2.91; 5 trials, 1188 children; moderate-certainty evidence). We do not know if vitamin D has an effect on the duration of hospitalisation (MD 4.96 hours, 95% CI -8.28 to 18.21; 5 trials, 1023 children; very low-certainty evidence). We do not know if vitamin D has an effect on mortality rate (risk ratio (RR) 0.69, 95% CI 0.44 to 1.07; 3 trials, 584 children; low-certainty evidence). The trials reported no major adverse events. According to GRADE criteria, the evidence was of very low-to-moderate certainty for all outcomes, owing to serious trial limitations, inconsistency, indirectness, and imprecision. Three trials received funding: one from the New Zealand Aid Corporation, one from an institutional grant, and one from multigovernment organisations (Bangladesh, Sweden, and UK). The remaining four trials were unfunded.

**Authors' conclusions:** Based on the available evidence, we are uncertain whether vitamin D supplementation has important effects on outcomes of acute pneumonia when used as an adjunct to antibiotics. The trials reported no major adverse events. Uncertainty in the evidence is due to imprecision, risk of bias, inconsistency, and indirectness.

Cochrane Database Syst Rev. 2023 Apr 4;4(4):CD006458.

doi: 10.1002/14651858.CD006458.pub5.

### [Nebulised hypertonic saline solution for acute bronchiolitis in infants](#)

[Linjie Zhang](#)<sup>1</sup>, [Raúl Andrés Mendoza-Sassi](#)<sup>1</sup>, [Claire E Wainwright](#)<sup>2</sup>, [Alex Aregbesola](#)<sup>3</sup>, [Terry P Klassen](#)<sup>3</sup>

#### **Abstract**

**Background:** Airway oedema (swelling) and mucus plugging are the principal pathological features in infants with acute viral bronchiolitis. Nebulised hypertonic saline solution ( $\geq 3\%$ ) may reduce these pathological changes and decrease airway obstruction. This is an update of a review first published in 2008, and updated in 2010, 2013, and 2017.

**Objectives:** To assess the effects of nebulised hypertonic ( $\geq 3\%$ ) saline solution in infants with acute bronchiolitis.

**Search methods:** We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily, Embase, CINAHL, LILACS, and Web of Science on 13 January 2022. We also searched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov on 13 January 2022.

**Selection criteria:** We included randomised controlled trials (RCTs) and quasi-RCTs using nebulised hypertonic saline alone or in conjunction with bronchodilators as an active

intervention and nebulised 0.9% saline or standard treatment as a comparator in children under 24 months with acute bronchiolitis. The primary outcome for inpatient trials was length of hospital stay, and the primary outcome for outpatients or emergency department (ED) trials was rate of hospitalisation.

**Data collection and analysis:** Two review authors independently performed study selection, data extraction, and assessment of risk of bias in included studies. We conducted random-effects model meta-analyses using Review Manager 5. We used mean difference (MD), risk ratio (RR), and their 95% confidence intervals (CI) as effect size metrics.

**Main results:** We included six new trials (N = 1010) in this update, bringing the total number of included trials to 34, involving 5205 infants with acute bronchiolitis, of whom 2727 infants received hypertonic saline. Eleven trials await classification due to insufficient data for eligibility assessment. All included trials were randomised, parallel-group, controlled trials, of which 30 were double-blinded. Twelve trials were conducted in Asia, five in North America, one in South America, seven in Europe, and nine in Mediterranean and Middle East regions. The concentration of hypertonic saline was defined as 3% in all but six trials, in which 5% to 7% saline was used. Nine trials had no funding, and five trials were funded by sources from government or academic agencies. The remaining 20 trials did not provide funding sources. Hospitalised infants treated with nebulised hypertonic saline may have a shorter mean length of hospital stay compared to those treated with nebulised normal (0.9%) saline or standard care (mean difference (MD) -0.40 days, 95% confidence interval (CI) -0.69 to -0.11; 21 trials, 2479 infants; low-certainty evidence). Infants who received hypertonic saline may also have lower postinhalation clinical scores than infants who received normal saline in the first three days of treatment (day 1: MD -0.64, 95% CI -1.08 to -0.21; 10 trials (1 outpatient, 1 ED, 8 inpatient trials), 893 infants; day 2: MD -1.07, 95% CI -1.60 to -0.53; 10 trials (1 outpatient, 1 ED, 8 inpatient trials), 907 infants; day 3: MD -0.89, 95% CI -1.44 to -0.34; 10 trials (1 outpatient, 9 inpatient trials), 785 infants; low-certainty evidence). Nebulised hypertonic saline may reduce the risk of hospitalisation by 13% compared with nebulised normal saline amongst infants who were outpatients and those treated in the ED (risk ratio (RR) 0.87, 95% CI 0.78 to 0.97; 8 trials, 1760 infants; low-certainty evidence). However, hypertonic saline may not reduce the risk of readmission to hospital up to 28 days after discharge (RR 0.83, 95% CI 0.55 to 1.25; 6 trials, 1084 infants; low-certainty evidence). We are uncertain whether infants who received hypertonic saline have a lower number of days to resolution of wheezing compared to those who received normal saline (MD -1.16 days, 95% CI -1.43 to -0.89; 2 trials, 205 infants; very low-certainty evidence), cough (MD -0.87 days, 95% CI -1.31 to -0.44; 3 trials, 363 infants; very low-certainty evidence), and pulmonary moist crackles (MD -1.30 days, 95% CI -2.28 to -0.32; 2 trials, 205 infants; very low-certainty evidence). Twenty-seven trials presented safety data: 14 trials (1624 infants; 767 treated with hypertonic saline, of which 735 (96%) co-administered with bronchodilators) did not report any adverse events, and 13 trials (2792 infants; 1479 treated with hypertonic saline, of which 416 (28%) co-administered with bronchodilators and 1063 (72%) hypertonic saline alone) reported at least one adverse event such as worsening cough, agitation, bronchospasm, bradycardia, desaturation, vomiting and diarrhoea, most of which were mild and resolved spontaneously (low-certainty evidence).

**Authors' conclusions:** Nebulised hypertonic saline may modestly reduce length of stay amongst infants hospitalised with acute bronchiolitis and may slightly improve clinical severity score. Treatment with nebulised hypertonic saline may also reduce the risk of hospitalisation amongst outpatients and ED patients. Nebulised hypertonic saline seems to

be a safe treatment in infants with bronchiolitis with only minor and spontaneously resolved adverse events, especially when administered in conjunction with a bronchodilator. The certainty of the evidence was low to very low for all outcomes, mainly due to inconsistency and risk of bias.

## Prevention of ARI

Benef Microbes. 2022 Oct 4;13(4):331-339.

doi: 10.3920/BM2021.0187. Epub 2022 Aug 25.

### [\*\*Bacillus clausii UBBC-07 in the symptom management of upper respiratory tract infections in children: a double blind, placebo-controlled randomised study\*\*](#)

[R S Madempudi<sup>1</sup>, J Neelamraju<sup>1</sup>, J J Ahire<sup>1</sup>, M Muthukumar<sup>1</sup>, S Rudrappa<sup>2</sup>, G Gopal<sup>2</sup>, K Nagendra<sup>2</sup>](#)

#### **Abstract**

In children, upper respiratory tract infections (URTIs) are one of the most common causes of infections which often require outpatient consultations with the doctor. The purpose of this study was to evaluate the effect of probiotic *Bacillus clausii* UBBC-07 on symptom management of URTIs in children. In this double blind, randomised, placebo-controlled study, 90 children (age 4-7 years) with URTIs were equally divided into two groups, the probiotic and placebo. The children were instructed to take *B. clausii* UBBC-07 spores ( $2 \times 10^9$  per 5 ml vial) or placebo suspension daily twice for three months. The total duration of the study was 6 months, 3 months treatment and 3 months follow-up period. The parameters assessed were the mean number of URTIs, duration and severity of URTIs, absenteeism from school/childcare and immunity parameters, such as immunoglobulin (Ig)M, IgG, IgE and salivary IgA levels. At the end of treatment, there was a significant decrease in the number, duration and severity of URTIs in the probiotic treated group as compared to the baseline and placebo. IgE levels were significantly decreased and salivary IgA levels were significantly increased in the probiotic treated group suggesting probiotic mediated Th1/Th2 immune homeostasis to alleviate URTIs in children. In conclusion, *B. clausii* UBBC-07 may help in the reduction of symptoms of URTIs.

## Oxygen therapy and CPAP for ALRI

J Glob Health. 2022 Oct 30;12:10012.

doi: 10.7189/jogh.12.10012.

### [\*\*Continuous Positive Airway Pressure \(CPAP\) for severe pneumonia in low- and middle-income countries: A systematic review of contextual factors\*\*](#)

[Chris Wilkes<sup>#1</sup>, Rami Subhi<sup>1,2</sup>, Hamish R Graham<sup>#1,2</sup>, Trevor Duke<sup>1,2</sup>, ARI Review group](#)

#### **Abstract**

**Background:** Continuous positive airway pressure (CPAP) may have a role in reducing the high mortality in children less than 5 years with World Health Organization (WHO) severe pneumonia. More evidence is needed to understand important contextual factors that impact on implementation, effectiveness, and safety in low resource settings.

**Methods:** We conducted a systematic review of Medline, Embase and Pubmed (January 2000 to August 2020) with terms of "pneumonia", "CPAP" and "child". We included studies that provided original clinical or non-clinical data on the use of CPAP in children (28 days-4 years) with pneumonia in low- or middle-income countries. We used standardised tools to assess study quality, and grade levels of evidence for clinical conclusions. Results are presented as a narrative synthesis describing context, intervention, and population alongside outcome data.

**Results:** Of 902 identified unique references, 23 articles met inclusion criteria, including 6 randomised controlled trials, one cluster cross over trial, 12 observational studies, 3 case reports and 1 cost-effectiveness analysis. There was significant heterogeneity in patient population, with wide range in mortality among participants in different studies (0%-55%). Reporting of contextual factors, including staffing, costs, and details of supportive care was patchy and non-standardised. Current evidence suggests that CPAP has a role in the management of infants with bronchiolitis and as escalation therapy for children with pneumonia failing standard-flow oxygen therapy. However, CPAP must be implemented with appropriate staffing (including doctor oversight), intensive monitoring and supportive care, and technician and infrastructure capacity. We provide practical guidance and recommendations based on available evidence and published expert opinion, for the adoption of CPAP into routine care in low resource settings and for reporting of future CPAP studies.

**Conclusions:** CPAP is a safe intervention in settings that can provide intensive monitoring and supportive care, and the strongest evidence for a benefit of CPAP is in infants (aged less than 1 year) with bronchiolitis. The available published evidence and clinical experience can be used to help facilities assess appropriateness of implementing CPAP, guide health workers in refining selection of patients most likely to benefit from it, and provide a framework for components of safe and effective CPAP therapy.

## Asthma

Adv Ther. 2022 Nov 8.

doi: 10.1007/s12325-022-02356-2. Online ahead of print.

### [Safety of SABA Monotherapy in Asthma Management: a Systematic Review and Meta-analysis](#)

[Thitiwat Sriprasart<sup>1</sup>](#), [Grant Waterer<sup>2</sup>](#), [Gabriel Garcia<sup>3</sup>](#), [Adalberto Rubin<sup>4</sup>](#), [Marco Antonio Loustaunau Andrade<sup>5</sup>](#), [Agnieszka Roguska<sup>6</sup>](#), [Abhay Phansalkar<sup>7</sup>](#), [Sourabh Fulmali<sup>7</sup>](#), [Amber Martin<sup>8</sup>](#), [Lalith Mittal<sup>9</sup>](#), [Bhumika Aggarwal<sup>10</sup>](#), [Gur Levy<sup>11</sup>](#)

#### **Abstract**

**Introduction:** Short-acting  $\beta_2$ -agonist (SABA) reliever overuse is common in asthma, despite availability of inhaled corticosteroid (ICS)-based maintenance therapies, and may be associated with increased risk of adverse events (AEs). This systematic literature review (SLR) and meta-analysis aimed to investigate the safety and tolerability of SABA reliever

monotherapy for adults and adolescents with asthma, through a analysis of randomized controlled trials (RCTs) and real-world evidence.

**Methods:** An SLR of English-language publications between January 1996 and December 2021 included RCTs and observational studies of patients aged  $\geq 12$  years treated with inhaled SABA reliever monotherapy (fixed dose or as needed) for  $\geq 4$  weeks. Studies of terbutaline and fenoterol were excluded. Meta-analysis feasibility was dependent on cross-trial data comparability. A random-effects model estimated rates of mortality, serious AEs (SAEs), and discontinuation due to AEs (DAEs) for as-needed and fixed-dose SABA treatment groups. ICS monotherapy and SABA therapy were compared using a fixed-effects model.

**Results:** Forty-two studies were identified by the SLR for assessment of feasibility. Final meta-analysis included 24 RCTs. Too few observational studies ( $n = 2$ ) were available for inclusion in the meta-analysis. One death unrelated to treatment was reported in each of the ICS, ICS + LABA, and fixed-dose SABA groups. No other treatment-related deaths were reported. SAE and DAE rates were  $< 4\%$ . DAEs were reported more frequently in the SABA treatment groups than with ICS, potentially owing to worsening asthma symptoms being classified as an AE. SAE risk was comparable between SABA and ICS treatments.

**Conclusions:** Meta-analysis of data from RCTs showed that deaths were rare with SABA reliever monotherapy, and rates of SAEs and DAEs were comparable between SABA reliever and ICS treatment groups. When used appropriately within prescribed limits as reliever therapy, SABA does not contribute to excess rates of mortality, SAEs, or DAEs.

Mymensingh Med J. 2023 Jan;32(1):10-17.

### [Comparative Efficacy of Levosalbutamol and Racemic Salbutamol in the Treatment of Acute Exacerbation of Asthma](#)

[M A Rabbany<sup>1</sup>](#), [B K Saha](#), [N Subha](#), [I Sultana](#), [M S Islam](#), [A J Hossain](#), [S Seraj](#), [S Farzana](#), [M Sharmin](#), [M M Ali](#), [A Nahar](#), [K A Siddiqui](#)

#### **Abstract**

Asthma is a major noncommunicable disease (NCD), affecting both children and adults, and is the most common chronic disease among children. It is common in all ages and the prevalence is increasing in most countries, especially among children as because of urbanization. Multiple therapeutic modalities are available for management of acute asthma. The commonly used formulation is Racemic Salbutamol which contains equal amounts of both R and S isomers. Levosalbutamol contains only R isomer. The aim of the study was to compare the efficacy of levosalbutamol and racemic salbutamol for the treatment of acute exacerbation of asthma in children (5 to 15 years). A randomized double blind clinical trial was conducted in the Department of Paediatrics, Sylhet MAG Osmani Medical College Hospital, Sylhet, Bangladesh from October 2013 to March 2014. In this study randomization was done in two groups. Group A received nebulized levosalbutamol (LEV) and Group B received nebulized racemic salbutamol (RAC). The study parameters were respiratory rate (RR), heart rate (HR), oxygen saturation in room air ( $SpO_2$ ), PEFR, asthma score and serum  $K^+$  level. The results of treatment outcome were compared between two groups. After treatment the respiratory rate was  $24.4 \pm 5.6$  per minute versus  $27.6 \pm 5.3$  per minute ( $p < 0.05$ ); heart rate was  $115.5 \pm 16.4$  per minute versus  $124.5 \pm 12.0$  per minute ( $p < 0.05$ );  $SpO_2$  was  $97.2 \pm 1.8\%$  vs  $95.0 \pm 1.6\%$  ( $p < 0.05$ ); PEFR was found  $159.6 \pm 30.7$  L/min versus  $143.8 \pm 27.1$  L/min ( $p < 0.05$ ) in the LEV and RAC group respectively. LEV is more effective than RAC in respect to significant improvement of asthma score. Regarding adverse events



racemic salbutamol causes significant tachycardia. The study concluded that nebulized levosalbutamol is superior to racemic salbutamol in children in the treatment of acute exacerbation of asthma.

J Pediatr Nurs. 2022 Jul-Aug;65:e63-e71.

doi: 10.1016/j.pedn.2022.02.012. Epub 2022 Mar 9.

### [The effect of mobile applications in enhancing asthma knowledge among school children with asthma in Malaysia](#)

[Abdulaziz Mansoor Al Raimi<sup>1</sup>](#), [Mei Chan Chong<sup>2</sup>](#), [Li Yoong Tang<sup>3</sup>](#), [Yan Piaw Chua<sup>4</sup>](#), [Latifa Yahya Al Ajeel<sup>5</sup>](#)

#### **Abstract**

**Purpose:** This study set out to evaluate the impact of health education provided on mobile applications (app) to urban-living school children with asthma in Malaysia to improve their asthma-related knowledge.

**Design and methods:** This was a quasi-experimental study with pre-and post-intervention involving 214 respondents from six schools were selected randomly and assigned to the experimental and control groups. The intervention, i.e. the health education via mobile apps was given to the experimental group while the control group received the routine face-to-face education.

**Results:** The mean knowledge score increased post-intervention in the experimental group from  $15.5 \pm 8.77$  to  $24.6 \pm 6.69$ . Children with a moderate level of knowledge accounted for the biggest proportion in both group control and experimental groups in the pre-intervention stage. In contrast, the proportion of children with a high level of knowledge was the highest in the experimental group post-intervention. Therefore, health education delivered via mobile apps led to a statistically significant improvement in the asthma knowledge of the children ( $F [1, 288] = 22.940, p \leq 0.01$ ).

**Conclusion:** Compared to the conventional face-to-face education methods of lectures or handbooks, mobile technology is more effective in delivering health education and improving the knowledge of school children with asthma. Therefore, educational modules aimed at improving knowledge should be modified to incorporate mobile apps.

**Practice implications:** Health education via mobile applications is considered a great innovation in school children with asthma education, or as a supplement to conventional learning methods. It is necessary to place health education via mobile applications as a prominent learning strategy for school children with asthma.

Front Pediatr. 2023 Apr 28;11:1167506.

doi: 10.3389/fped.2023.1167506. eCollection 2023.

### [Noninvasive positive-pressure ventilation for children with acute asthma: a meta-analysis of randomized controlled trials](#)

[Jijia Dai<sup>1</sup>](#), [Libo Wang<sup>1</sup>](#), [Fang Wang<sup>2</sup>](#), [Lu Wang<sup>1</sup>](#), [Qingfen Wen<sup>2</sup>](#)

#### **Abstract**

**Background:** Noninvasive positive-pressure ventilation (NPPV) can be effective in children with acute asthma. However, clinical evidence remains limited. The objective of the meta-analysis was to systematically assess NPPV's effectiveness and safety in treating children with acute asthma.

**Methods:** Relevant randomized controlled trials were obtained from electronic resources, including PubMed, Embase, Cochrane's Library, Wanfang, and CNKI databases. The influence of potential heterogeneity was taken into account before using a random-effect model to pool the results.

**Results:** A total of 10 RCTs involving 558 children with acute asthma were included in the meta-analysis. Compared to conventional treatment alone, additional use of NPPV significantly improved early blood gas parameters such as the oxygen saturation (mean difference [MD]: 4.28%, 95% confidence interval [CI]: 1.51 to 7.04,  $p = 0.002$ ;  $I^2 = 80\%$ ), partial pressure of oxygen (MD: 10.61 mmHg, 95% CI: 6.06 to 15.16,  $p < 0.001$ ;  $I^2 = 89\%$ ), and partial pressure of carbon dioxide (MD: -6.29 mmHg, 95% CI: -9.81 to -2.77,  $p < 0.001$ ;  $I^2 = 85\%$ ) in the arterial blood. Moreover, NPPV was also associated with early reduced respiratory rate (MD: -12.90, 95% CI: -22.21 to -3.60,  $p = 0.007$ ;  $I^2 = 71\%$ ), improved symptom score (SMD: -1.85, 95% CI: -3.65 to -0.07,  $p = 0.04$ ;  $I^2 = 92\%$ ), and shortened hospital stay (MD: -1.82 days, 95% CI: -2.32 to -1.31,  $p < 0.001$ ;  $I^2 = 0\%$ ). No severe adverse events related to NPPV were reported.

**Conclusions:** NPPV in children with acute asthma is associated with improved gas exchange, decreased respiratory rates, a lower symptom score, and a shorter hospital stay. These results suggest that NPPV may be as effective and safe as conventional treatment for pediatric patients with acute asthma.

## Adolescent health

### Overall health and well-being

SSM Popul Health. 2022 Dec 27;21:101330.

doi: 10.1016/j.ssmph.2022.101330. eCollection 2023 Mar.

[Effects of community youth teams facilitating participatory adolescent groups, youth leadership activities and livelihood promotion to improve school attendance, dietary diversity and mental health among adolescent girls in rural eastern India \(JIAH trial\): A cluster-randomised controlled trial](#)

[Komal Bhatia<sup>1</sup>, Suchitra Rath<sup>2</sup>, Hemanta Pradhan<sup>2</sup>, Subhashree Samal<sup>2</sup>, Andrew Copas<sup>1</sup>, Sumitra Gagrai<sup>2</sup>, Shiband Rath<sup>2</sup>, Raj Kumar Gope<sup>2</sup>, Nirmala Nair<sup>2</sup>, Prasanta Tripathy<sup>2</sup>, Kelly Rose-Clarke<sup>3</sup>, Audrey Prost<sup>1</sup>](#)

#### Abstract

**Objectives:** To evaluate whether and how community youth teams facilitating participatory adolescent groups, youth leadership and livelihood promotion improved school attendance, dietary diversity, and mental health among adolescent girls in rural India.

**Design:** A parallel group, two-arm, superiority, cluster-randomised controlled trial with an embedded process evaluation.

**Setting intervention and participants:** 38 clusters (19 intervention, 19 control) in West Singhbhum district in Jharkhand, India. The intervention included participatory adolescent groups and youth leadership for boys and girls aged 10-19 (intervention clusters only), and family-based livelihood promotion (intervention and control clusters) between June 2017 and March 2020. We surveyed 3324 adolescent girls aged 10-19 in 38 clusters at baseline, and



1478 in 29 clusters at endline. Four intervention and five control clusters were lost to follow up when the trial was suspended due to the COVID-19 pandemic. Adolescent boys were included in the process evaluation only.

**Primary and secondary outcome measures:** Primary: school attendance, dietary diversity, and mental health; 12 secondary outcomes related to education, empowerment, experiences of violence, and sexual and reproductive health.

**Results:** In intervention vs control clusters, mean dietary diversity score was 4.0 (SD 1.5) vs 3.6 (SD 1.2) (adjDiff 0.34; 95%CI -0.23, 0.93,  $p = 0.242$ ); mean Brief Problem Monitor-Youth (mental health) score was 12.5 (SD 6.0) vs 11.9 (SD 5.9) (adjDiff 0.02, 95%CI -0.06, 0.13,  $p = 0.610$ ); and school enrolment rates were 70% vs 63% (adjOR 1.39, 95%CI 0.89, 2.16,  $p = 0.142$ ). Uptake of school-based entitlements was higher in intervention clusters (adjOR 2.01; 95%CI 1.11, 3.64,  $p = 0.020$ ). Qualitative data showed that the community youth team had helped adolescents and their parents navigate school bureaucracy, facilitated re-enrolments, and supported access to entitlements. Overall intervention delivery was feasible, but positive impacts were likely undermined by household poverty.

**Conclusions:** Participatory adolescent groups, leadership training and livelihood promotion delivered by a community youth team did not improve adolescent girls' mental health, dietary diversity, or school attendance in rural India, but may have increased uptake of education-related entitlements.

## Adolescent mental health

Psychol Psychother. 2022 Nov 9.

doi: 10.1111/papt.12433. Online ahead of print.

### ["If there is a tension about something, I can solve it": A qualitative investigation of change processes in a trial of brief problem-solving interventions for common adolescent mental health problems in India](#)

[Kanika Malik<sup>1,2</sup>](#), [Rachana Parikh<sup>3,4</sup>](#), [Rooplata Sahu<sup>1</sup>](#), [Paulomi Sudhir<sup>5</sup>](#), [Christopher G Fairburn<sup>6</sup>](#), [Vikram Patel<sup>1,7,8</sup>](#), [Daniel Michelson<sup>9,10</sup>](#)

#### Abstract

**Objectives:** There is limited understanding of change processes and long-term effects of low-intensity psychosocial interventions. We investigated these aspects in two brief problem-solving intervention formats for adolescents with elevated mental health symptoms and associated distress/impairment.

**Methods:** This qualitative study was nested within a school-based randomized controlled trial in New Delhi, India, which compared two problem-solving intervention formats: a lay counsellor-led format supported by printed materials (intervention arm) and printed problem-solving materials alone ("bibliotherapy" control arm). A total of 32 participants, ranging in age from 14 to 20 years (mean = 16.4 years, SD = 1.9) and comprising 21 males and 11 females, were interviewed across both trial arms at 12-month follow-up.

**Results:** Five themes were derived using thematic framework analysis. The "impacts on symptoms and functioning" theme described symptomatic improvements and functional gains. "Processes underlying problem solving" reflected changes in positive beliefs, attitudes and emotions when confronted with problems, and the use of a more effective problem-

solving coping style. "Experiences of problem-solving materials" covered benefits (e.g. access to relatable stories and readymade solutions) and limitations (e.g. diminishing use over time) of printed problem-solving handouts. "Role of supporting figures" accounted for the facilitating roles played by counsellors and trusted others. There were also accounts of researchers functioning as de facto counsellors in the bibliotherapy arm. "Recommended modifications for intervention delivery" included more flexible and private ways to access the interventions, greater personalization of the counselling process, more engaging and relevant supporting materials, and suggestions for widening access to the interventions in schools and community settings.

**Conclusions:** We infer from our qualitative analysis that changes in problem-solving style and problem orientation underpinned long-term symptomatic and functional improvements. Participants in the counsellor-led intervention appeared better able to sustain the use of problem-solving skills and generalize this approach beyond the original presenting problems. We attribute the differences between arms to the influence of direct advice and supportive interactions with counsellors. Practice implications are discussed.

BJPsych Open. 2022 Dec 27;9(1):e7.

doi: 10.1192/bjo.2022.624.

**[Pilot randomised controlled trial of a remotely delivered online intervention for adolescent mental health problems in India: lessons learned about low acceptability and feasibility during the COVID-19 pandemic](#)**

[Pattie P Gonsalves](#)<sup>1</sup>, [Bhargav Bhat](#)<sup>2</sup>, [Rhea Sharma](#)<sup>2</sup>, [Abhijeet Jambhale](#)<sup>2</sup>, [Bindiya Chodankar](#)<sup>2</sup>, [Mamta Verma](#)<sup>2</sup>, [Eleanor Hodgson](#)<sup>2</sup>, [Helen A Weiss](#)<sup>3</sup>, [Baptiste Leurent](#)<sup>3</sup>, [Kate Cavanagh](#)<sup>4</sup>, [Christopher G Fairburn](#)<sup>5</sup>, [Pim Cuijpers](#)<sup>6</sup>, [Daniel Michelson](#)<sup>7</sup>, [Vikram Patel](#)<sup>8</sup>

**Abstract**

**Background:** 'POD Adventures' is a gamified problem-solving intervention delivered via smartphone app, and supported by non-specialist counsellors for a target population of secondary school students in India during the COVID-19 pandemic.

**Aims:** To evaluate the feasibility and acceptability of undertaking a randomised controlled trial of POD Adventures when delivered online with telephone support from counsellors.

**Method:** We conducted a parallel, two-arm, individually randomised pilot-controlled trial with 11 secondary schools in Goa, India. Participants received either the POD Adventures intervention delivered over 4 weeks or usual care comprising information about local mental health services and national helplines. Outcomes were assessed at two timepoints: baseline and 6 weeks post-randomisation.

**Results:** Seventy-nine classroom sensitisation sessions reaching a total of 1575 students were conducted. Ninety-two self-initiated study referrals (5.8%) were received, but only 11 participants enrolled in the study. No intervention arm participants completed the intervention. Outcomes at 6 weeks were not available for intervention arm participants ( $n = 5$ ), and only four control arm participants completed outcomes. No qualitative interviews or participant satisfaction measures were completed because participants could not be reached by the study team.

**Conclusions:** Despite modifications to address barriers arising from COVID-19 restrictions, online delivery was not feasible in the study context. Low recruitment and missing feasibility and acceptability data make it difficult to draw conclusions about intervention engagement

and indicative clinical outcomes. Prior findings showing high uptake, adherence and engagement with POD Adventures when delivered in a school-based context suggest that an online study and delivery posed the biggest barriers to study participation and engagement.

Body Image. 2023 Jan 4;44:148-156.

doi: 10.1016/j.bodyim.2022.12.006. Online ahead of print.

### [Evaluating a body image school-based intervention in India: A randomized controlled trial](#)

[Helena Lewis-Smith<sup>1</sup>](#), [Kirsty May Garbett<sup>2</sup>](#), [Anshula Chaudhry<sup>3</sup>](#), [Megha Dhillon<sup>3</sup>](#), [Hemal Shroff<sup>4</sup>](#), [Paul White<sup>5</sup>](#), [Phillippa Claire Diedrichs<sup>2</sup>](#)

#### **Abstract**

Body dissatisfaction is highly prevalent among adolescents in low- and middle- income countries, including in India. However, evidence-based interventions are lacking. This study evaluated the efficacy of a school-based mixed-gender body image intervention among adolescents in India. A randomized controlled trial was conducted among 568 (43 % girls) Year 7 students (aged 11-14; 94 % aged 12-13) in six schools in Delhi. Each school was randomly allocated to receive five 45-minute intervention sessions delivered by trained psychologists or a wait-list control condition. The primary outcome of body image and related secondary outcomes were assessed at pre-intervention, post-intervention, and 3-month follow-up. Intention-to-treat linear mixed models analyses showed improvements in body image relative to the control group at post-intervention and 3-month follow-up. Significant improvements were identified at post-intervention for internalization, life disengagement, disordered eating, self-esteem, and negative affect, with effects maintained in nearly all outcomes (girls only - internalization, boys only - life disengagement) at 3-month follow-up. This study presents the first mixed-gender school-based body image intervention in India, which was efficacious in improving urban adolescents' body image, disordered eating, and related outcomes.

BMC Psychiatry. 2023 Mar 1;23(1):131.

doi: 10.1186/s12888-023-04571-9.

### [Feasibility randomised controlled trial of the Early Adolescent Skills for Emotions psychological intervention with young adolescents in Lebanon](#)

[Felicity L Brown<sup>1,2</sup>](#), [Karine Taha<sup>3,4</sup>](#), [Frederik Steen<sup>3</sup>](#), [Jeremy Kane<sup>5</sup>](#), [Aviva Gillman<sup>6</sup>](#), [May Aoun<sup>3,4</sup>](#), [Aiysha Malik<sup>7</sup>](#), [Richard Bryant<sup>8</sup>](#), [Marit Sijbrandij<sup>9</sup>](#), [Rabih El Chammay<sup>10,11</sup>](#), [Chiara Servili<sup>7</sup>](#), [Mark van Ommeren<sup>7</sup>](#), [Aemal Akhtar<sup>8,12</sup>](#), [Edwina Zoghbi<sup>13</sup>](#); [EASE Intervention Development, Training Team](#); [Mark J D Jordans<sup>14,15</sup>](#); [STRENGTHS Consortium](#)

#### **Abstract**

**Background:** Globally, there is a vast mental health treatment gap, whereby the majority of adolescents living in low- and middle-income countries requiring mental health services, do not have access to adequate care. To improve access, the World Health Organization (WHO) developed a range of interventions, designed to be low-cost and delivered by non-specialists. We conducted a two-arm, individually randomised group treatment feasibility trial of a new WHO group intervention for young adolescents with emotional distress ('Early Adolescent Skills for Emotions'; EASE) in Lebanon.

**Method:** The aim of this study was to determine the feasibility of the intervention and study procedures. Adolescents aged 10 to 14 years were eligible to take part if they scored above a validated cut-off on the Child Psychosocial Distress Screener. Participants were randomized to EASE or enhanced treatment as usual (ETAU) control using a 1:1 ratio. EASE consisted of seven group sessions with adolescents and three sessions with caregivers. ETAU consisted of a single brief psychoeducation home visit. Child and caregiver outcomes were measured by blind assessors at baseline, endline (8 weeks post-randomisation), and three month follow-up (20 weeks post-randomisation), with the primary outcome measure being child psychological symptoms on the Pediatric Symptom Checklist. Qualitative interviews were conducted with adolescents (n = 13), caregivers (n = 17), facilitators (n = 6), trainers (n = 3), and outreach staff (n = 1) at endline to assess barriers and facilitators related to the feasibility and delivery of EASE and study procedures.

**Results:** Of 154 adolescents screened, 67 (43%) were eligible, completed baseline, and were randomized. Sixty adolescents (90%) completed endline assessments (31 EASE, 29 ETAU), and fifty-nine (88%) completed three-month assessments (29 EASE, 30 ETAU). Qualitatively, participants provided overall positive feedback about the intervention. Several challenges and suggestions for improvement were raised around logistics, intervention content, and acceptability of assessment measures. Implementation data highlighted challenges with intervention uptake and attendance. Outcome measures generally had strong psychometric properties (range:  $\alpha = 0.77$  to  $\alpha = 0.87$ ), however did not demonstrate change over time in either group.

**Conclusions:** The EASE intervention and study procedures are acceptable and feasible for implementation with vulnerable adolescents in Lebanon, however several improvements are necessary prior to full-scale evaluation.

J Adolesc Health. 2022 Sep;71(3):301-307.

doi: 10.1016/j.jadohealth.2022.04.008. Epub 2022 Jun 1.

**[The Short-Term Impact of a Combination Intervention on Depressive Symptoms Among School-Going Adolescent Girls in Southwestern Uganda: The Suubi4Her Cluster Randomized Trial](#)**

[William Byansi](#)<sup>1</sup>, [Fred M Ssewamala](#)<sup>2</sup>, [Torsten B Neilands](#)<sup>3</sup>, [Ozge Sensoy Bahar](#)<sup>2</sup>, [Proscovia Nabunya](#)<sup>2</sup>, [Flavia Namuwonge](#)<sup>4</sup>, [Mary M McKay](#)<sup>2</sup>

**Abstract**

**Purpose:** This study aims to examine the short-term impact of a combined intervention consisting of evidence-based family economic empowerment (FEE) and multiple family group (MFG) interventions on depressive symptoms among school-going adolescent girls in southwestern Uganda.

**Methods:** We analyzed longitudinal data from a cluster randomized trial. The sample consisted of 1,260 adolescent girls (aged 14-17 years at enrollment) recruited from senior one and senior two classes across 47 secondary schools in the southwestern region of Uganda. Participants were randomized at the school level to either the control condition receiving bolstered standard of care or one of the two treatment conditions-the treatment one condition receiving the FEE intervention or the treatment two conditions receiving both the FEE plus MFG interventions. Descriptive statistics and a three-level mixed-effects model

were conducted to examine the effect of a combination intervention on depressive symptoms.

**Results:** At baseline, there were no significant differences between the control condition and both treatment conditions. While all three groups experienced a substantial reduction in depressive symptoms from baseline to 12 months, the reductions were stronger for the two intervention groups. However, FEE + MFG was not significantly different from FEE at 12 months.

**Discussion:** Results imply that the FEE intervention may be a promising tool in addressing depressive symptoms among adolescent girls. Therefore, to reduce the long-term implications of adverse psychosocial health during adolescence, policymakers and program implementers should explore scaling up economic empowerment interventions in similar settings to bridge the mental health treatment gap for adolescent girls.

J Adolesc Health. 2023 May;72(5S):S33-S40.

doi: 10.1016/j.jadohealth.2022.11.250.

**[Effects of a Combination Economic Empowerment and Family Strengthening Intervention on Psychosocial Well-being Among Ugandan Adolescent Girls and Young Women: Analysis of a Cluster Randomized Controlled Trial \(Suubi4Her\)](#)**

[Lindsey M Filiatreau](#)<sup>1</sup>, [Nhial Tutlam](#)<sup>2</sup>, [Rachel Brathwaite](#)<sup>2</sup>, [William Byansi](#)<sup>3</sup>, [Flavia Namuwonge](#)<sup>2</sup>, [Abel Mwebembezi](#)<sup>4</sup>, [Ozge Sensoy-Bahar](#)<sup>2</sup>, [Proscovia Nabunya](#)<sup>2</sup>, [Torsten B Neilands](#)<sup>5</sup>, [Patricia Cavazos-Rehg](#)<sup>1</sup>, [Mary McKay](#)<sup>6</sup>, [Fred M Ssewamala](#)<sup>7</sup>

**Abstract**

**Purpose:** Economic empowerment and family strengthening interventions have shown promise for improving psychosocial well-being in a range of populations. This study investigates the effect of a combination economic and family strengthening intervention on psychosocial well-being among Ugandan adolescent girls and young women (AGYW).

**Methods:** We harnessed data from a three-arm cluster randomized controlled trial among AGYW aged 14-17 years in 47 Ugandan secondary schools. Schools were randomized to either a youth development account intervention (YDA) [N = 16 schools], YDA plus a multiple family group intervention (YDA + MFG) [N = 15 schools], or bolstered standard of care (BSOC) [N = 16 schools]. We estimated the effect of each intervention (BSOC = referent) on three measures of psychosocial well-being: hopelessness (Beck's Hopelessness Scale), self-concept (Tennessee Self-Concept Scale), and self-esteem (Rosenberg Self-Esteem Scale) at 12 months following enrollment using multi-level linear mixed models for each outcome.

**Results:** A total of 1,260 AGYW (mean age, 15.4) were enrolled-471 assigned to YDA (37%), 381 to YDA + MFG (30%), and 408 to usual care (32%). Over the 12-month follow-up, participants assigned to the YDA + MFG group had significantly greater reductions in hopelessness and improvements in self-esteem outcomes compared to BSOC participants. Those enrolled in the YDA arm alone also had significantly greater reductions in hopelessness compared to BSOC participants.

**Discussion:** Combination interventions, combining economic empowerment (represented here by YDA), and family-strengthening (represented by MFG) can improve the psychosocial well-being of AGYW. The long-term effects of these interventions should be further tested for potential scale-up in an effort to address the persistent mental health treatment gap in resource-constrained settings.

PLoS One. 2023 Mar 29;18(3):e0281800.

doi: 10.1371/journal.pone.0281800. eCollection 2023.

**[Mental health and gender-based violence: An exploration of depression, PTSD, and anxiety among adolescents in Kenyan informal settlements participating in an empowerment intervention](#)**

[Rina Friedberg](#)<sup>1</sup>, [Michael Baiocchi](#)<sup>2,3</sup>, [Evan Rosenman](#)<sup>4</sup>, [Mary Amuyunzu-Nyamongo](#)<sup>5</sup>, [Gavin Nyairo](#)<sup>5</sup>, [Clea Sarnquist](#)<sup>6</sup>

**Abstract**

**Objective:** This study examines the prevalence of depression, anxiety, and post-traumatic stress disorder (PTSD) among adolescents attending schools in several informal settlements of Nairobi, Kenya. Primary aims were estimating prevalence of these mental health conditions, understanding their relationship to gender-based violence (GBV), and assessing changes in response to an empowerment intervention.

**Methods:** Mental health measures were added to the final data collection point of a two-year randomized controlled trial (RCT) evaluating an empowerment self-defense intervention. Statistical models evaluated how past sexual violence, access to money to pay for a needed hospital visit, alcohol use, and self-efficacy affect both mental health outcomes as well as how the intervention affected female students' mental health.

**Findings:** Population prevalence of mental health conditions for combined male and female adolescents was estimated as: PTSD 12.2% (95% confidence interval 10.5-15.4), depression 9.2% (95% confidence interval 6.6-10.1) and anxiety 17.6% (95% confidence interval 11.2% - 18.7%). Female students who reported rape before and during the study-period reported significantly higher incidence of all mental health outcomes than the study population. No significant differences in outcomes were found between female students in the intervention and standard-of-care (SOC) groups. Prior rape and low ability to pay for a needed hospital visit were associated with higher prevalence of mental health conditions. The female students whose log-PTSD scores were most lowered by the intervention (effects between -0.23 and -0.07) were characterized by high ability to pay for a hospital visit, low agreement with gender normative statements, larger homes, and lower academic self-efficacy.

**Conclusion:** These data illustrate a need for research and interventions related to (1) mental health conditions among the young urban poor in low-income settings, and (2) sexual violence as a driver of poor mental health, leading to a myriad of negative long-term outcomes.

J Adolesc Health. 2023 May;72(5S):S3-S10.

doi: 10.1016/j.jadohealth.2022.09.035.

**[The Post-intervention Impact of Amaka Amasanyufu on Behavioral and Mental Health Functioning of Children and Adolescents in Low-Resource Communities in Uganda: Analysis of a Cluster-Randomized Trial From the SMART Africa-Uganda Study \(2016-2022\)](#)**

[Fred M Ssewamala](#)<sup>1</sup>, [Rachel Brathwaite](#)<sup>2</sup>, [Ozge Sensoy Bahar](#)<sup>2</sup>, [Phionah Namatovu](#)<sup>3</sup>, [Torsten B Neilands](#)<sup>4</sup>, [Joshua Kiyingi](#)<sup>5</sup>, [Keng-Yen Huang](#)<sup>6</sup>, [Mary M McKay](#)<sup>2</sup>

**Abstract**



**Purpose:** Disruptive behavioral disorders (DBDs) are common among children/adolescents in sub-Saharan Africa. A 16-week manualized multiple family group (MFG) intervention called Amaka Amasanyufu designed to reduce DBDs among school-going children/adolescents in low-resource communities in Uganda was efficacious in reducing symptoms of poor mental health relative to usual care in the short-term (4 months post-intervention-initiation). We examined whether intervention effects are sustained 6 months postintervention.

**Methods:** We used longitudinal data from 636 children positive for DBDs: (1) Control condition, 10 schools,  $n = 243$ ; (2) MFG delivered via parent peers (MFG-PP), eight schools,  $n = 194$  and; (3) MFG delivered via community healthcare workers (MFG-CHW), eight schools,  $n = 199$  from the SMART Africa-Uganda study (2016-2022). All participants were blinded. We estimated three-level linear mixed-effects models and pairwise comparisons at 6 months postintervention and time-within-group effects to evaluate the impact on Oppositional Defiant Disorder (ODD), impaired functioning, depressive symptoms, and self-concept.

**Results:** At 6 months postintervention, children in MFG-PP and MFG-CHW groups had significantly lower means for ODD (mean difference [MD] = -1.08 and -1.35) impaired functioning (MD = -1.19 and -1.16), and depressive symptoms (MD = -1.06 and -0.83), than controls and higher means for self-concept (MD = 3.81 and 5.14). Most outcomes improved at 6 months compared to baseline. There were no differences between the two intervention groups.

**Discussion:** The Amaka Amasanyufu intervention had sustained effects in reducing ODD, impaired functioning, and depressive symptoms and improving self-concept relative to usual care at 6 months postintervention. Our findings strengthen the evidence that the intervention effectively reduces DBDs and impaired functioning among young people in resource-limited settings and was sustained over time.

Int J Environ Res Public Health. 2022 Nov 4;19(21):14497.

doi: 10.3390/ijerph192114497.

### [Feasibility and Acceptability of a School-Based Emotion Regulation Prevention Intervention \(READY-Nepal\) for Secondary School Students in Post-Earthquake Nepal](#)

[Megan K Ramaiya<sup>1</sup>](#), [Caitlin L McLean<sup>2</sup>](#), [Manjila Pokharel<sup>3</sup>](#), [Kiran Thapa<sup>4</sup>](#), [M Andi Schmidt<sup>5</sup>](#), [Martha Berg<sup>6</sup>](#), [Jane M Simoni<sup>7</sup>](#), [Deepa Rao<sup>8</sup>](#), [Brandon A Kohrt<sup>9</sup>](#)

#### **Abstract**

**Background:** Child and adolescent mental health problems are major contributors to the global burden of disease in low- and middle-income country (LMIC) settings. To advance the evidence base for adolescent mental health interventions in LMICs, we evaluated the feasibility and acceptability of a school-based emotion regulation prevention intervention (READY-Nepal) for adolescents who had a recent exposure to a humanitarian disaster.

**Methods:** A mixed-method, non-randomized controlled trial was conducted with Nepali secondary school students in one heavily affected post-earthquake district. Students ( $N = 102$ ; aged 13 to 17 years) were enrolled in the intervention ( $n = 42$ ) and waitlist control ( $n = 60$ ) conditions. Feasibility and acceptability were examined via attendance, and by qualitative interviews with a subset of students ( $n = 15$ ), teachers ( $n = 2$ ), and caregivers ( $n = 3$ ). Preliminary efficacy was examined on primary outcome (emotion regulation) and secondary outcomes (anxiety symptoms, posttraumatic stress symptoms, functional

impairment, resilience, coping skills), which were measured at baseline and post-intervention (four weeks).

**Results:** Delivering the intervention was feasible and acceptable, as demonstrated by low dropout (8%) and high program attendance (6.7 of 8 sessions). Qualitative data suggested high uptake of anger regulation skills, but lower uptake of mindfulness skills. Despite this, there were no significant differences by condition on primary or secondary outcomes at four-week follow-up. Students provided suggestions for improvement of the program.

**Conclusion:** Further research on longitudinal outcome measurement, use of alternatives to retrospective self-report data, and rigorous development of culturally grounded models of emotion regulation is necessary to explore the utility of school-based emotion regulation interventions in Nepal and other LMICs.

J Adolesc Health. 2023 May;72(5S):S24-S32.

doi: 10.1016/j.jadohealth.2022.09.037.

**[Patterns of and Factors Associated With Mental Health Service Utilization Among School-Going Adolescent Girls in Southwestern Uganda: A Latent Class Analysis](#)**

[William Byansi](#)<sup>1</sup>, [Fred M Ssewamala](#)<sup>2</sup>, [Torsten B Neilands](#)<sup>3</sup>, [Abel Mwebembezi](#)<sup>4</sup>, [Gertrude Nakigozi](#)<sup>5</sup>

**Abstract**

**Purpose:** The study aimed to improve understanding of patterns of multiple family group intervention engagement and associated factors among adolescent girls in a low-resource country, Uganda.

**Methods:** The data used in this analysis were part of a larger cluster randomized controlled trial consisting of 1260 adolescent girls across 47 public secondary schools. The sample in the current study consisted of 317 adolescent girls (ages 14-17 at enrollment) recruited from senior one and senior two classes across 12 secondary schools in the southwestern region of Uganda. Participants in this study participated in the multiple family group intervention-a 16-week manualized intervention. Attendance data from 16 sessions were used to identify the heterogeneity of intervention engagement using latent class analysis modeling. Logistic regression analysis was conducted to assess the association between predisposing, enabling, need factors, and mental health utilization patterns.

**Results:** On average, participants attended 10 sessions (standard deviation = 5.90), 34.38% (N = 109) completed all 16 sessions, and 13.56% (N = 43) did not attend any of the sessions. Two attendance groups were identified: low and high attendants using latent class analysis. In addition, two family-level factors, the number of adults and the number of children in the family, were associated with an increase in the utilization of mental health services.

**Discussion:** Findings suggest that enhancing family support systems may be useful in promoting mental health utilization among adolescent girls with the potential to improve self-esteem, reduce feelings of inadequacy, and ultimately achieve better mental health outcomes

## Adolescent sexual and reproductive health



Int J Gynaecol Obstet. 2022 Jul 28.

doi: 10.1002/ijgo.14378. Online ahead of print.

**[Sustained impact of community-based interventions on contraceptive use among married adolescent girls in rural Niger: Results from a cluster randomized controlled trial](#)**

[Blake Erhardt-Ohren](#)<sup>1</sup>, [Mohamad Brooks](#)<sup>1</sup>, [Sani Aliou](#)<sup>2</sup>, [Akim Assani Osseni](#)<sup>2</sup>, [Alhassane Oumarou](#)<sup>2</sup>, [Sneha Challa](#)<sup>3</sup>, [Shweta Tomar](#)<sup>3</sup>, [Nicole Johns](#)<sup>3</sup>, [Jay Silverman](#)<sup>3</sup>

**Abstract**

**Objective:** To evaluate the sustained impact of community-based family planning (FP) interventions on current modern contraceptive and long-acting reversible contraceptive (LARC) use among married adolescent girls in rural Niger.

**Methods:** We used a cluster randomized controlled trial design following married adolescent girls and their husbands over 3 years. Villages were randomized to one of four arms: household visits, small group discussions, combined intervention, or control. For 1.5 years, couples were exposed to one intervention activity per month and 1.5 years after implementation ended, we used a multi-level mixed effects logistic regression model to evaluate changes in key FP outcomes.

**Results:** We analyzed survey data from 404 married adolescent girls with data at baseline and endline. Small group discussions (+35.6%; adjusted odds ratio [aOR] 7.94,  $P < 0.001$ ) and the combined intervention (+17.9%; aOR 4.53,  $P = 0.005$ ) led to statistically significant increases in the odds of using modern contraceptives at endline compared with the control. The combined intervention (+14.2%; aOR 7.98,  $P < 0.001$ ) and home visits (+12.6%; aOR 8.09,  $P < 0.001$ ) led to statistically significant increases in odds of using LARC methods at endline compared with the control. Increase in LARC use was driven by implant use across all intervention groups.

**Conclusion:** This study contributes to the empirical evidence base on the sustained impact of community-based interventions on increases in FP use among married adolescent girls in low- and middle-income countries.

Reprod Health. 2023 Jun 5;20(1):83.

doi: 10.1186/s12978-023-01609-9.

**[Effects of the reaching married adolescents program on modern contraceptive use and intimate partner violence: results of a cluster randomized controlled trial among married adolescent girls and their husbands in Dosso, Niger](#)**

[Jay G Silverman](#)<sup>1</sup>, [Mohamad I Brooks](#)<sup>2</sup>, [Sani Aliou](#)<sup>2</sup>, [Nicole E Johns](#)<sup>3</sup>, [Sneha Challa](#)<sup>3</sup>, [Abdoul Moumouni Nouhou](#)<sup>4</sup>, [Shweta Tomar](#)<sup>3</sup>, [Holly Baker](#)<sup>3</sup>, [Sabrina C Boyce](#)<sup>3</sup>, [Lotus McDougal](#)<sup>3</sup>, [Stephanie DeLong](#)<sup>3</sup>, [Anita Raj](#)<sup>3</sup>

**Abstract**

**Background:** Niger has the highest rate of adolescent fertility in the world, with early marriage, early childbearing and high gender inequity. This study assesses the impact of Reaching Married Adolescents (RMA), a gender-synchronized social behavioral intervention designed to improve modern contraceptive use and reduce intimate partner violence (IPV) among married adolescent couples in rural Niger.

**Methods:** We conducted a four-armed cluster-randomized trial in 48 villages across three districts in Dosso region, Niger. Married adolescent girls (ages 13-19) and their husbands were recruited within selected villages. Intervention arms included home visits by gender-

matched community health workers (CHWs) (Arm 1), gender-segregated, group discussion sessions (Arm 2), and both approaches (Arm 3). We used multilevel mixed-effects Poisson regression models to assess intervention effects for our primary outcome, current modern contraceptive use, and our secondary outcome, past year IPV.

**Results:** Baseline and 24-month follow-up data were collected April-June 2016 and April-June 2018. At baseline, 1072 adolescent wives were interviewed (88% participation), with 90% retention at follow-up; 1080 husbands were interviewed (88% participation), with 72% retention at follow-up. Adolescent wives had higher likelihood of modern contraceptive use at follow-up relative to controls in Arm 1 (aIRR 3.65, 95% CI 1.41-8.78) and Arm 3 (aIRR 2.99, 95% CI 1.68-5.32); no Arm 2 effects were observed. Relative to those in the control arm, Arm 2 and Arm 3 participants were significantly less likely to report past year IPV (aIRR 0.40, 95% CI 0.18-0.88 for Arm 2; aIRR 0.46, 95% CI 0.21-1.01 for Arm 3). No Arm 1 effects were observed.

**Conclusions:** The RMA approach blending home visits by CHWs and gender-segregated group discussion sessions is the optimal format for increasing modern contraceptive use and decreasing IPV among married adolescents in Niger

Glob Health Action. 2023 Dec 31;16(1):2160543.

doi: 10.1080/16549716.2022.2160543.

**[Effectiveness of peer-led education interventions on contraceptive use, unmet need, and demand among adolescent girls in Gedeo Zone, South Ethiopia. A cluster randomized controlled trial](#)**

[Yohannes Addisu Wondimagegne](#)<sup>1</sup>, [Gurmesa Tura Debelew](#)<sup>2</sup>, [Zewdie Birhanu Koricha](#)<sup>3</sup>

**Abstract**

**Background:** Peer-led education interventions are assumed to be an effective means of increasing contraceptive utilization and demand in adolescents. However evidence is lacking on whether peer-led education is effective in promoting the demand for and use of contraceptives in adolescent girls, especially in resource-limited settings.

**Objective:** The present study evaluated the effectiveness of peer-led education interventions in improving contraceptive use, unmet needs, and demand among sexually active secondary school adolescent girls in Gedeo Zone, South Ethiopia.

**Methods:** A single-blinded cluster randomised controlled trial study was performed in six randomly selected secondary schools in the Gedeo Zone, southern Ethiopia. A total of 224 participants were recruited and randomly assigned to the intervention and control groups. The intervention group received peer-led education intervention for six months. A pre-tested and validated questionnaire was used to measure contraceptive use, unmet need, and contraceptive demand. A generalised estimating equation (GEE) model was used to examine the effectiveness of the intervention.

**Result:** After six months of intervention, the Differences-in-difference in contraceptive use, unmet need, and contraceptive demand between the intervention and control groups were 25.1%, 7.4%, and 17.7%, respectively. There was a statistically significant difference in contraceptive use [AOR = 8.7, 95% CI: (3.66, 20.83)], unmet need for contraceptives [AOR = 6.2, 95% CI: (1.61, 24.36)] and contraceptive demand [AOR = 6.1, 95% CI: (2.43, 15.11)] between the intervention and control groups.

**Conclusions:** School-based peer education intervention effectively improved contraceptive use and unmet needs in a low-resource setting and created demand in sexually active adolescent girls. These results support the potential utility of this approach in similar settings for the promotion of contraception use and demand.

Soc Sci Med. 2022 Aug;306:115125.

doi: 10.1016/j.socscimed.2022.115125. Epub 2022 Jun 11.

**[Effects of economic support, comprehensive sexuality education and community dialogue on sexual behaviour: Findings from a cluster-RCT among adolescent girls in rural Zambia](#)**

[Hanne Keyser Hegdahl](#)<sup>1</sup>, [Patrick Musonda](#)<sup>2</sup>, [Joar Svanemyr](#)<sup>3</sup>, [Joseph Mumba Zulu](#)<sup>2</sup>, [Taran Grønvik](#)<sup>4</sup>, [Choolwe Jacobs](#)<sup>2</sup>, [Ingvild Fossgard Sandøy](#)<sup>4</sup>

**Abstract**

Adolescent girls in Sub-Saharan Africa are at high risk of poor sexual and reproductive health outcomes. We present findings from a cluster-randomised trial in rural Zambia on the effects of economic support, comprehensive sexuality education (CSE) and community dialogue on sexual activity, contraceptive use and beliefs among adolescent girls. We recruited 157 schools in 2016, and all girls in grade 7 were invited to participate. Schools were randomised to either economic support, combined economic support, CSE and community dialogue, or control. Economic support consisted of unconditional cash transfers to girls and their guardians, and payment of school fees for girls continuing to grades eight and nine. CSE and community dialogue meetings focused on practices around girls' fertility, marriage and education. The interventions lasted two years from 2016 to 2018, with follow-up for another two years. The effects on outcomes were measured in 2018 and 2019 and compared using generalised estimating equations. We found that economic support lowered sexual activity (risk ratio (RR) 0.70; 95% C.I. 0.54 to 0.91), with a small added benefit of CSE and community dialogue. Economic support and the additional CSE and community dialogue were effective in lowering unprotected sexual activity (RR 0.53 for combined support vs. control; 95% C.I. 0.37 to 0.75). There was no evidence of intervention effects on contraceptive use among those ever sexually active, but the addition of CSE and community dialogue improved contraceptive use among those recently sexually active (RR 1.26; 95% C.I. 1.06 to 1.50) and knowledge regarding contraceptives (RR 1.18; 95% C.I. 1.01 to 1.38) compared to economic support alone. Perceived community support regarding contraceptives was lower in both intervention arms compared to the control. These findings indicate that economic support in combination with CSE and community dialogue can improve the sexual and reproductive health of adolescent girls.

BMC Public Health. 2023 Feb 15;23(1):335.

doi: 10.1186/s12889-023-15199-5.

**[Experiences of teachers and community-based health workers in addressing adolescents' sexual reproductive health and rights problems in rural health systems: a case of the RISE project in Zambia](#)**

[Kunda Chilambe](#)<sup>1</sup>, [Chama Mulubwa](#)<sup>2,3</sup>, [Joseph Mumba Zulu](#)<sup>2</sup>, [Malizgani Paul Chavula](#)<sup>4,5</sup>

## Abstract

**Background:** Adolescents in low-and-middle-income countries like Zambia face a high burden of sexual, reproductive, health and rights problems including coerced sex, teenage pregnancies, and early marriages. The Zambia government through Ministry of Education has integrated comprehensive sexuality education (CSE) in the education and school system to contribute towards addressing Adolescents sexual, reproductive, health and rights (ASRHR) problems. This paper sought to explore teachers and community based health workers (CBHWs)' experiences in addressing ASRHR problems in rural health systems in Zambia.

**Methodology:** The study was conducted under Research Initiative to Support the Empowerment of Girls (RISE) community randomized trial that aims to measure the effectiveness of economic and community interventions in reducing early marriages, teenage pregnancies, and school dropout in Zambia. We conducted qualitative 21 in-depth interviews with teachers and CBHWs involved in the implementation of CSE in communities. Thematic analysis was used to analyse teachers and CBHWs' roles, challenges, and opportunities in promoting ASRHR services.

**Results:** The study identified teachers and CBHWs roles, and challenges experienced in promoting ASRHR and suggested strategies to enhance delivery of the intervention. The role of teachers and CBHWs in addressing ASRHR problems included mobilizing and sensitizing the community for meetings, providing SRHR counseling services to both adolescents and guardians, and strengthening referral to SRHR services if needed. The challenges experienced included stigmatization associated with difficult experiences such as sexual abuse and pregnancy, shyness among girls to participate when discussing SRHR in the presence of the boys and myths about contraception. The suggested strategies for addressing the challenges included creating safe spaces for adolescents to discuss SRHR issues and engaging adolescents in coming up with the solution.

**Conclusion:** This study provides significant insight on the important roles that teachers CBHWs can play in addressing adolescents SRHR related problems. Overall, the study emphasizes the need to fully engage adolescents in addressing adolescents SRHR problems.

BMC Public Health. 2023 Feb 16;23(1):348.

doi: 10.1186/s12889-023-15023-0.

## [Comprehensive sexuality education linked to sexual and reproductive health services reduces early and unintended pregnancies among in-school adolescent girls in Zambia](#)

[Michael T Mbizvo<sup>1</sup>](#), [Kondwani Kasonda<sup>2</sup>](#), [Nelly-Claire Muntalima<sup>2</sup>](#), [Joseph G Rosen<sup>2</sup>](#), [Sophie Inambwae<sup>2</sup>](#), [Edith S Namukonda<sup>2</sup>](#), [Ronald Mungoni<sup>2</sup>](#), [Natasha Okpara<sup>2</sup>](#), [Chifundo Phiri<sup>2</sup>](#), [Nachela Chelwa<sup>2</sup>](#), [Chabu Kangale<sup>2</sup>](#)

## Abstract

**Background:** Advancing the health of adolescents, particularly their sexual and reproductive health, including HIV prevention and care, is a development imperative. A critical part for improving their wellbeing and economic development is the social status accorded to adolescent girls and young women (AGYW). However, AGYW in many countries including Zambia, encounter health challenges that stem from gender inequalities, lack of empowerment, inaccurate knowledge on sexuality, and poor access to sexual and

reproductive health (SRH) services and information. Addressing the knowledge gaps through comprehensive sexuality education (CSE) and improving access to SRH services and appropriate information, should reduce school attrition from early and unintended pregnancies (EUP) and enhance realization of their full potential.

**Methods:** The aim was to reduce EUP and improve SRH outcomes among AGYW in Zambia through provision of CSE linked to receptive SRH services. A 3-Arm randomized control study collected cross-sectional data at baseline, midline and Endline. Schools where CSE was being routinely provided were randomized into a non-intervention arm (arm1), an intervention arm in which information on available SRH services was provided in schools by health workers to complement CSE, (arm 2), and arm 3 in which pupils receiving CSE were also encouraged or supported to access pre-sensitized, receptive SRH services.

**Results:** Following 3 years of intervention exposure (CSE-Health Facility linkages), findings showed a significant decline of in-school pregnancies amongst AGYW in both intervention arms, with arm two exhibiting a more significant decline, having recorded only 0.74% pregnancies at endline ( $p < 0.001$ ), as well as arm 3, which recorded 1.34% pregnancies ( $p < 0.001$ ). No significant decline was recorded in the CSE only control arm. Trends in decline of pregnancies started to show by midline, and persisted at endline (2020), and when difference in differences test was applied, the incident rate ratios (IRR) between the none and exposed arms were equally significant ( $p < 0.001$ ).

**Conclusion:** Linking provision of CSE with accessible SRH services that are receptive to needs of adolescents and young people reduces EUP, which provides the opportunity for higher retention in school for adolescent girls.

Ann Epidemiol. 2023 Jul;83:35-39.e1.

doi: 10.1016/j.annepidem.2023.04.005. Epub 2023 Apr 14.

**[Measuring sexual behavior among in-school youth in Rwanda: a cross-sectional analysis of self-reported timing of first sex and correlates of early sexual debut](#)**

[Rebecca Hémono](#)<sup>1</sup>, [Emmyson Gatara](#)<sup>2</sup>, [Laetitia Kayitesi](#)<sup>3</sup>, [Lauren A Hunter](#)<sup>4</sup>, [Jacqueline Kunesh](#)<sup>5</sup>, [Laura Packel](#)<sup>6</sup>, [Rebecca Hope](#)<sup>7</sup>, [Sandra I McCoy](#)<sup>8</sup>

**Abstract**

**Purpose:** Understanding the timing of sexual debut is critical for informing sexual and reproductive health interventions. We investigated sexual behavior and early sexual debut among Rwandan youth.

**Methods:** We conducted a cross-sectional analysis of data from a cluster-randomized trial with 6079 students ages 12-19 years in Rwanda. We examined predictors of early sexual debut (<15 years) using logistic regression to estimate odds ratios and factors associated with the timing of first sex using Cox models to estimate hazard ratios. Interpretations of sex were also explored.

**Results:** Participants were 15 years and 51.5% female on average; 1723 (28.3%) reported sexual activity. Among the 1320 participants who provided an age of sexual debut, 51.4% reported sex at  $\leq 12$  years and 75.7% at  $< 15$  years. Males had a higher odds of early sexual debut (adjusted odds ratio: 2.40; 95% CI: 1.99, 2.90) and a higher hazard of sex occurring at an earlier age than females (adjusted hazard ratio: 1.91; 95% CI: 1.67, 2.20). One-third of participants considered "sexual intercourse" to include kissing, touching, or masturbation.

**Conclusions:** Sex at  $\leq 12$  years was frequently reported, indicating that interventions facilitating access to youth-friendly sexual and reproductive health services are necessary

before age 12. Validation studies are needed to evaluate how interpretations of sexual intercourse influence the assessment of sexual activity.

## Adolescent pregnancy and child marriage

SSM Popul Health. 2023 Apr 17;22:101407.

doi: 10.1016/j.ssmph.2023.101407. eCollection 2023 Jun.

### [Impact of the CARE Tipping Point Program in Nepal on adolescent girls' agency and risk of child, early, or forced marriage: Results from a cluster-randomized controlled trial](#)

[Kathryn M Yount<sup>1,2</sup>](#), [Robert L Durr<sup>1</sup>](#), [Irina Bergenfeld<sup>1</sup>](#), [Sudhindra Sharma<sup>3</sup>](#), [Cari Jo Clark<sup>1</sup>](#), [Anne Laterra<sup>4</sup>](#), [Sadhvi Kalra<sup>4</sup>](#), [Anne Sprinkel<sup>4</sup>](#), [Yuk Fai Cheong<sup>5</sup>](#)

#### Abstract

**Background:** Girl child, early, and forced marriage (CEFM) persists in South Asia, with long-term effects on well-being. CARE's Tipping Point Initiative (TPI) sought to address the gender norms and inequalities underlying CEFM by engaging participant groups on programmatic topics and supporting community dialogue to build girls' agency, shift power relations, and change norms. We assessed impacts of the CARE TPI on girls' multifaceted agency and risk of CEFM in Nepal.

**Methods:** The quantitative evaluation was a three-arm, cluster-randomized controlled trial (control; Tipping Point Program [TPP]; Tipping Point Plus Program [TPP+] with emphasized social-norms change). Fifty-four clusters of ~200 households each were selected from two districts (27:27) with probability proportional to size and randomized evenly to study arms. A pre-baseline census identified unmarried girls 12-16 years (1,242) and adults 25 years or older (540). Questionnaires covered marriage; agency; social networks/norms; and discrimination/violence. Baseline participation was 1,140 girls and 540 adults. Retention was 1,124 girls and 531 adults. Regression-based difference-in-difference models assessed program effects on 15 agency-related secondary outcomes. Cox-proportional hazard models assessed program effects on time to marriage. Sensitivity analyses assessed the robustness of findings.

**Results:** At follow-up, marriage was rare for girls (<6.05%), and 10 secondary outcomes had increased. Except for sexual/reproductive health knowledge (coef.=.71, p=.036) and group membership (coef.=.48, p=.026) for TPP + versus control, adjusted difference-in-difference models showed no program effects on secondary outcomes. Results were mostly unmoderated by community mean: gender norms, household poverty, or women's schooling attainment. Cox proportional hazard models showed no program effect on time-to-marriage. Findings were robust.

**Discussion:** Null findings of the Nepal TPI may be attributable to low CEFM rates at follow-up, poor socio-economic conditions, COVID-19-related disruptions, and concurrent programming in control areas. As COVID-19 abates, impacts of TPP/TPP + on girls' agency and marriage, alone and with complementary programming, should be assessed.



doi: 10.1111/mcn.13456. Epub 2022 Nov 9.

**[Supplementary feeding and infection control in pregnant adolescents-A secondary analysis of a randomized trial among malnourished women in Sierra Leone](#)**

[Aminata S Koroma](#)<sup>1</sup>, [Mariama Ellie](#)<sup>1</sup>, [Kadiatu Bangura](#)<sup>1</sup>, [Per O Iversen](#)<sup>2,3,4</sup>, [David T Hendrixson](#)<sup>5</sup>, [Kevin Stephenson](#)<sup>6</sup>, [Mark J Manary](#)<sup>7</sup>

**Abstract**

Undernutrition during pregnancy in adolescence confers a high risk of maternal morbidity and adverse birth outcomes, particularly in low-resource settings. In a secondary analysis, we hypothesized that younger undernourished pregnant adolescents (<18 years) would benefit more than undernourished pregnant adults (>20 years) from the intervention of supplementary food and anti-infective treatments. The original trial in Sierra Leone enrolled 236 younger adolescents (<18 years), 454 older adolescents (aged 18-19 years), and 741 adults (≥20 years), all with a mid-upper arm circumference ≤23 cm. Younger adolescents had lower final fundal height as well as smaller newborns (-0.3 kg; 95% confidence interval [CI], -0.3, -0.2; p < 0.001) and shorter newborns (-1.1 cm; 95% CI, -1.5, -0.7; p < 0.001) than adults. The intervention's effect varied significantly between maternal age groups: adults benefited more than younger adolescents with respect to newborn birth weight (difference in difference, 166 g; 95% CI, 26, 306; interaction p = 0.02), birth length (difference in difference, 7.4 mm; 95% CI, 0.1, 14.8; interaction p = 0.047), and risk for low birth weight (<2.5 kg) (interaction p = 0.019). The differences in response persisted despite adjustments for maternal anthropometry, the number of prior pregnancies, and human immunodeficiency virus status. Older adolescents similarly benefited more than younger adolescents, though differences did not reach statistical significance. In conclusion, newborns born to younger adolescent mothers had worse outcomes than those born to adult mothers, and adults and their newborns benefited more from the intervention than younger adolescents.

## Adolescents and HIV prevention and treatment

Lancet HIV. 2022 Oct;9(10):e680-e689.

doi: 10.1016/S2352-3018(22)00195-3. Epub 2022 Sep 7.

**[Alignment of PrEP adherence with periods of HIV risk among adolescent girls and young women in South Africa and Zimbabwe: a secondary analysis of the HPTN 082 randomised controlled trial](#)**

[Jennifer Velloza](#)<sup>1</sup>, [Deborah Donnell](#)<sup>2</sup>, [Sybil Hosek](#)<sup>3</sup>, [Peter L Anderson](#)<sup>4</sup>, [Z Mike Chirenje](#)<sup>5</sup>, [Nyaradzo Mgodzi](#)<sup>5</sup>, [Linda-Gail Bekker](#)<sup>6</sup>, [Mark A Marzinke](#)<sup>7</sup>, [Sinead Delany-Moretlwe](#)<sup>8</sup>, [Connie Celum](#)<sup>9</sup>

**Abstract**

**Background:** Adolescent girls and young women in southern and eastern Africa have adherence challenges with daily oral HIV pre-exposure prophylaxis (PrEP). High adherence is most important during periods of HIV risk (prevention-effective adherence). We aimed to describe HIV risk behaviour and to understand patterns in PrEP adherence during periods of risk among adolescent girls and young women from sub-Saharan Africa.

**Methods:** We did a secondary analysis of the HPTN 082 trial, an open-label, interventional, randomised controlled trial of sexually active adolescent girls and young women (aged 16-25

years) testing negative for HIV in Johannesburg and Cape Town, South Africa, and in Harare, Zimbabwe. The primary outcomes were high cumulative PrEP adherence, dichotomised as intracellular tenofovir diphosphate concentrations of at least 700 fmol/punch in dried blood spots at weeks 13, 26, and 52, and high recent PrEP adherence, dichotomised as plasma tenofovir concentrations of at least 40 ng/mL at weeks 13, 26, and 52, among participants who accepted PrEP. We collected data on sexual behaviour every 3 months. We categorised visits into a binary variable of any HIV risk based on condomless sex, more than one sexual partner, primary partner's HIV status and antiretroviral use, transactional sex, drug or alcohol use around sexual activity, and laboratory-diagnosed STIs. We used generalised estimating equations to evaluate associations between HIV risk (reflecting behaviour during the previous 3 months) and high cumulative and recent adherence to PrEP and any PrEP use (quantifiable drug concentrations). The trial is registered with ClinicalTrials.gov, [NCT02732730](https://clinicaltrials.gov/ct2/show/study/NCT02732730).

**Findings:** Between Oct 12, 2016, and Oct 25, 2018, 451 women were recruited, and 427 participants (median age 21.0 years [IQR 19.0-22.0]) were eligible for inclusion in this analysis. The proportion of participants reporting at least one HIV risk factor decreased significantly over follow-up, from 364 (85%) participants at enrolment, 226 (60%) at week 13, and 243 (65%) at week 26, to 224 (61%) at week 52 ( $p < 0.0001$ ). Any HIV risk was significantly associated with high PrEP adherence, measured by both tenofovir diphosphate concentrations of at least 700 fmol/punch (adjusted relative risk 1.57 [95% CI 1.09-2.25];  $p = 0.014$ ) and plasma tenofovir concentrations of at least 40 ng/mL (1.36 [1.11-1.65];  $p = 0.0025$ ). Any HIV risk was also associated with quantifiable concentrations of tenofovir diphosphate (1.15 [1.03-1.29];  $p = 0.013$ ) and tenofovir (1.27 [1.09-1.49];  $p = 0.0022$ ). We observed significant dose-response relationships between number of HIV risk factors and PrEP drug concentrations.

**Interpretation:** The association between any HIV risk and high PrEP adherence suggests that adolescent girls and young women were able to use PrEP during periods of risk, an indicator of prevention-effective PrEP adherence. Our findings support a shift in the PrEP framework to acknowledge prevention-effective adherence practices, which might improve PrEP delivery and adherence support for adolescent girls and young women in HIV-endemic settings.

Am J Public Health. 2023 Jan 5;e1-e10.

doi: 10.2105/AJPH.2022.307169. Online ahead of print.

**[Economic Empowerment, HIV Risk Behavior, and Mental Health Among School-Going Adolescent Girls in Uganda: Longitudinal Cluster-Randomized Controlled Trial, 2017–2022](#)**

[Fred M Ssewamala](#)<sup>1</sup>, [Rachel Brathwaite](#)<sup>1</sup>, [Torsten B Neilands](#)<sup>1</sup>

**Abstract**

**Objectives.** To investigate the long-term (12- and 24-month) impact of an economic empowerment intervention on HIV risk behaviors and mental health among school-going adolescent girls in Uganda. **Methods.** A total of 1260 girls aged 14 to 17 years were randomized at the school level to (1) standard health and sex education (controls;  $n = 408$  students;  $n = 16$  schools), (2) 1-to-1 matched savings youth development account (YDA;  $n = 471$  students;  $n = 16$  schools), or (3) combination intervention (YDA and multiple family group



[YDA+MFG]; n = 15 schools; n = 381 students). Mixed-effects models were fitted. **Results.** YDA and YDA+MFG girls had significantly lower depressive symptoms and better self-concept than controls at 24 months. Only YDA+MFG girls had significantly lower hopelessness levels than controls. There were no significant study group differences at 12 and 24 months for sexual risk-taking behavior and attitudes. There was no significant difference between YDA and YDA+MFG groups for all outcomes. **Conclusions.** Providing YDA and MFG can positively improve adolescent girls' mental health, but our analyses showed no significant differences across groups on sexual risk-taking behaviors. Future studies may consider replicating these interventions and analyses in older populations, including those transitioning into young adults

J Adolesc Health. 2022 Oct 12;S1054-139X(22)00600-0.

doi: 10.1016/j.jadohealth.2022.08.013. Online ahead of print.

**[Reaching Adolescent Girls and Young Women With HIV Self-Testing and Contraception at Girl-Friendly Drug Shops: A Randomized Trial in Tanzania](#)**

[Lauren A Hunter](#)<sup>1</sup>, [Aarthi Rao](#)<sup>2</sup>, [Sue Napierala](#)<sup>3</sup>, [Atuganile Kalinjila](#)<sup>4</sup>, [Agatha Mnyippembe](#)<sup>4</sup>, [Kassim Hassan](#)<sup>4</sup>, [Stefano M Bertozzi](#)<sup>5</sup>, [Rashid Mfaume](#)<sup>6</sup>, [Prosper Njau](#)<sup>7</sup>, [Jenny X Liu](#)<sup>8</sup>, [Sandra I McCoy](#)<sup>5</sup>

**Abstract**

**Purpose:** We hypothesized that an intervention designed to create girl-friendly drug shops would increase access to sexual and reproductive health products and services among adolescent girls and young women (AGYW) (ages 15-24 years) in Tanzania.

**Methods:** We conducted a four-month randomized trial at 20 drug shops in Shinyanga, Tanzania from August-December 2019 to determine if the Malkia Klabu ("Queen Club") intervention increased AGYW patronage and the provision of HIV self-testing (HIVST), contraception, and health facility referrals to AGYW (primary outcomes). Drug shops were randomized 1:1 to the intervention or comparison arm. All shops were provided with OraQuick HIVST kits to give to AGYW for free. Intervention shops implemented Malkia Klabu, a loyalty program for AGYW created using human-centered design through which AGYW could also access free contraception. We compared outcomes in intention-to-treat analyses using shop observations and shopkeeper records.

**Results:** By endline, shops implementing Malkia Klabu had higher AGYW patronage than comparison shops (rate ratio: 4.4; 95% confidence interval: 2.0, 9.8). Intervention shops distributed more HIVST kits (median per shop: 130.5 vs. 58.5, P = .02) and contraceptives (325.5 vs. 7.0, P < .01) to AGYW and provided more referrals for HIV, family planning, or pregnancy services combined (3.5 vs. 0.5, P = .02) than comparison shops.

**Discussion:** The Malkia Klabu intervention increased AGYW patronage and the provision of HIVST kits, contraception, and referrals to AGYW at drug shops, despite HIVST kits being freely available at all participating shops. Enhancing drug shops with girl-friendly services may be an effective strategy to reach AGYW with sexual and reproductive health services.

Libyan J Med. 2022 Dec;17(1):2128414.

doi: 10.1080/19932820.2022.2128414.

## **Effects of a structured health education on prevention of HIV risky behaviours among adolescents in Nigeria - a pragmatic randomized controlled trial**

[Ijeoma O Maduakolam<sup>1</sup>](#), [Ngozi P Ogbonnaya<sup>1</sup>](#), [Ifeoma F Ndubuisi<sup>1</sup>](#), [Echezona N D Ekechukwu<sup>2</sup>](#), [Ijeoma L Okoronkwo<sup>1</sup>](#), [Obinna Onwujekwe<sup>3</sup>](#)

### **Abstract**

Infection with HIV/AIDS continues to be a major public health concern around the world, particularly in low- and middle-income nations. To assess the effectiveness of structured health education on the prevention of HIV/AIDS risky behaviours among adolescents in secondary school. A pretest-posttest-control group randomized controlled trial where a sample of 647 adolescents was drawn from the population of 2,890 secondary school students and was block-randomized into the intervention (n = 400) and control (n = 224) groups. Data were collected using a content-validated (CVI = 4.2/5) and reliable (k = 0.791) self-developed structured questionnaire. Data were analyzed using descriptive statistics and with inferential statistics of independent and paired t-tests at  $\alpha = 0.05$ . Pre-intervention risky behaviours in both groups were below average though lower in the intervention than in the control group. Pre-intervention risky behaviour was significantly higher among males than females in the rural school ( $p < 0.001$ ) and in both schools together ( $p < 0.001$ ). Health education significantly affected risky behaviour with the intervention group being associated with lesser risky behaviour than the control group. There was no significant difference in the post-intervention risky behaviour between males and females in the rural (0.285), urban (0.179) and both schools together ( $p = 0.956$ ). Post-intervention reduced risky behaviours more significantly in the intervention than in the control groups. HIV/AIDS health education should be part of schools' curriculum, guidance and counsellor teachers should be trained as HIV counsellors.

PLoS Med. 2023 Jan 3;20(1):e1004150.

doi: 10.1371/journal.pmed.1004150. eCollection 2023 Jan.

## **Effectiveness of a peer educator-coordinated preference-based differentiated service delivery model on viral suppression among young people living with HIV in Lesotho: The PEBRA cluster-randomized trial**

[Mathebe Kopo<sup>1</sup>](#), [Thabo Ishmael Lejone<sup>1,2,3</sup>](#), [Nadine Tschumi<sup>2,3</sup>](#), [Tracy Renée Glass<sup>3,4</sup>](#), [Mpho Kao<sup>1</sup>](#), [Jennifer Anne Brown<sup>2,3</sup>](#), [Olivia Seiler<sup>5</sup>](#), [Josephine Muhairwe<sup>6</sup>](#), [Ntoli Moletsane<sup>7</sup>](#), [Niklaus Daniel Labhardt<sup>2,3</sup>](#), [Alain Amstutz<sup>2,3</sup>](#)

### **Abstract**

**Background:** Southern and Eastern Africa is home to more than 2.1 million young people aged 15 to 24 years living with HIV. As compared with other age groups, this population group has poorer outcomes along the HIV care cascade. Young people living with HIV and the research team co-created the PEBRA (Peer Educator-Based Refill of ART) care model. In PEBRA, a peer educator (PE) delivered services as per regularly assessed patient preferences for medication pick-up, short message service (SMS) notifications, and psychosocial support. The cluster-randomized trial compared PEBRA model versus standard clinic care (no PE and ART refill done by nurses) in 3 districts in Lesotho.

**Methods and findings:** Individuals taking antiretroviral therapy (ART) aged 15 to 24 years at 20 clinics (clusters) were eligible. In the 10 clinics randomized to the intervention arm, participants were offered the PEBRA model, coordinated by a trained PE and supported by

an eHealth application (PEBApp). In the 10 control clusters, participants received standard nurse-coordinated care without any service coordination by a PE. The primary endpoint was 12-month viral suppression below 20 copies/mL. Analyses were intention-to-treat and adjusted for sex. From November 6, 2019 to February 4, 2020, we enrolled 307 individuals (150 intervention, 157 control; 218 [71%] female, median age 19 years [interquartile range, IQR, 17 to 22]). At 12 months, 99 of 150 (66%) participants in the intervention versus 95 of 157 (61%) participants in the control arm had viral suppression (adjusted odds ratio (OR) 1.27; 95% confidence interval [CI] [0.79 to 2.03];  $p = 0.327$ ); 4 of 150 (2.7%) versus 1 of 157 (0.6%) had died (adjusted OR 4.12; 95% CI [0.45 to 37.62];  $p = 0.210$ ); and 12 of 150 (8%) versus 23 of 157 (14.7%) had transferred out (adjusted OR 0.53; 95% CI [0.25 to 1.13];  $p = 0.099$ ). There were no significant differences between arms in other secondary outcomes. Twenty participants (11 in intervention and 9 in control) were lost to follow-up over the entire study period. The main limitation was that the data collectors in the control clusters were also young peers; however, they used a restricted version of the PEBApp to collect data and thus were not able to provide the PEBRA model.

**Conclusions:** Preference-based peer-coordinated care for young people living with HIV, compared to nurse-based care only, did not lead to conclusive evidence for an effect on viral suppression.

AIDS Behav. 2022 Sep 1.

doi: 10.1007/s10461-022-03838-8. Online ahead of print.

**[The Impact of an Economic Strengthening Intervention on Academic Achievement Among Adolescents Living with HIV: Findings from the Suubi + Adherence Cluster-Randomized Trial in Uganda \(2012-2018\)](#)**

[Samuel Kizito](#)<sup>1</sup>, [Josephine Nabayinda](#)<sup>1</sup>, [Joshua Kiyingi](#)<sup>1</sup>, [Torsten B Neilands](#)<sup>2</sup>, [Flavia Namuwonge](#)<sup>3</sup>, [Phionah Namatovu](#)<sup>1</sup>, [Proscovia Nabunya](#)<sup>1</sup>, [Ozge Sensoy Bahar](#)<sup>1</sup>, [Vicent Ssentumbwe](#)<sup>1</sup>, [Natasja Magorokosho](#)<sup>1</sup>, [Fred M Ssewamala](#)<sup>4</sup>

**Abstract**

We examined the impact of a family-based economic strengthening intervention on school dropout and repeating a class among ALWHIV in Uganda. In this cluster-randomized trial (2012-2018) conducted in 39 clinics, we recruited adolescents aged 10-16 years living with HIV. We included data from 613 adolescents. We plotted a Kaplan Meier survival curve and fitted Cox proportional hazards models to test the effect of the economic strengthening intervention on school dropout. The incidence of school dropout was 13.0% and 9.6% in the control and intervention groups, respectively. Also, economic empowerment reduced the risk of school dropout, aHR = 0.68 (95% CI 0.52-0.88),  $p$ -value 0.004. In other words, participants in the intervention group had 32% reduced hazards of dropping out of school. Also, increasing age aHR = 1.54 (95% CI 1.42-1.66),  $p$ -value < 0.001 and double orphanhood aHR = 0.67 (95% CI 0.47-0.96)  $p$ -value 0.030 increased the risks for dropping out of school. The intervention was not efficacious in reducing the rates of repeating a class. The intervention offered the ALWHIV an opportunity to live a productive adult life. More research is required on these kinds of interventions intended to keep ALWHIV and those impacted by HIV in school.

AIDS Behav. 2022 Oct;26(10):3337-3344.

doi: 10.1007/s10461-022-03637-1. Epub 2022 Apr 16.

**The Long-term (5-year) Impact of a Family Economic Empowerment Intervention on Adolescents Living with HIV in Uganda: Analysis of Longitudinal Data from a Cluster Randomized Controlled Trial from the Suubi+Adherence Study (2012-2018)**

[Rachel Brathwaite<sup>1</sup>](#), [Fred M Ssewamala<sup>2,3</sup>](#), [Massy Mutumba<sup>4</sup>](#), [Torsten B Neilands<sup>5</sup>](#), [William Byansi<sup>1</sup>](#), [Flavia Namuwonge<sup>6</sup>](#), [Christopher Damulira<sup>1</sup>](#), [Proscovia Nabunya<sup>1</sup>](#), [Gertrude Nakigozi<sup>7</sup>](#), [Fredrick Makumbi<sup>8</sup>](#), [Claude A Mellins<sup>9</sup>](#), [Mary M McKay<sup>10</sup>](#), [Suubi Adherence Field Team<sup>1</sup>](#)

**Abstract**

We examined the 5-year impact of an economic empowerment (EE) intervention on: adherence, viral suppression, sexual risk-taking intentions (primary); and physical health, educational and economic (secondary) outcomes among adolescents living with HIV in Uganda. The Suubi + Adherence study (2012-2018) randomized clinics to: (1) Control group, n = 19 clinics, n = 344 participants; (2) intervention group which received matched savings accounts, mentorship, financial management and, business development training, n = 20 clinics, n = 358 participants. Participants completed post-baseline assessments at 12-, 24-, 36-, and 48-months. No significant differences in viral load, sexual risk-intentions and physical health perception were observed. The intervention group had better adherence (at 24-months) (Contrast=-0.28; 95% CI: -0.55, -0.004), higher school enrolment (OR = 2.18; 95% CI:1.30, 3.66); reported savings OR = 2.03 (1.29, 3.18) and higher savings (Contrast = 0.40; 95% CI:0.10, 0.70) than controls at 48-months. The EE intervention was efficacious in improving adherence, school enrolment, and economic outcomes creating opportunities for improved overall health among adolescents living with HIV.

J Adolesc Health. 2023 May;72(5S):S41-S50.

doi: 10.1016/j.jadohealth.2022.12.012.

**A Structural Equation Model of the Impact of a Family-Based Economic Intervention on Antiretroviral Therapy Adherence Among Adolescents Living With HIV in Uganda**

[Samuel Kizito<sup>1</sup>](#), [Josephine Nabayinda<sup>1</sup>](#), [Torsten B Neilands<sup>2</sup>](#), [Joshua Kiyingi<sup>1</sup>](#), [Flavia Namuwonge<sup>3</sup>](#), [Christopher Damulira<sup>2</sup>](#), [Proscovia Nabunya<sup>1</sup>](#), [Jennifer Nattabi<sup>1</sup>](#), [Fred M Ssewamala<sup>4</sup>](#)

**Abstract**

**Purpose:** Antiretroviral therapy (ART) adherence among adolescents living with HIV (ALWHIV) is low, with poverty remaining a significant contributor. We examined the mediation pathways between an economic empowerment intervention and ART adherence among ALWHIV.

**Methods:** This cluster-randomized controlled trial (2012-2018) recruited 702 ALWHIV aged 10-16 in Uganda between January 2014 and December 2015. We randomized 39 clinics into the control (n = 344) or intervention group (n = 358). The intervention comprised a child development account, four microenterprise workshops, and 12 mentorship sessions. We used six self-reported items to measure adherence at 24 months, 36 months, and 48 months. We used structural equation modeling to assess the mediation effects through mental health and adherence self-efficacy, on adherence. We ran models corresponding to the 24, 36, and 48 months of follow-up.

**Results:** The mean age of the participants was 12 years, and 56% were female. At 36 (model 2) and 48 months (model 3), the intervention had a significant indirect effect on ART adherence [ $B = 0.069$ ,  $\beta = 0.039$  (95% confidence interval [CI]: 0.005-0.074)], and [ $B = 0.068$ ,  $\beta = 0.040$  (95% CI: 0.010-0.116)], respectively. In both models, there was a specific mediation effect through mental health [ $B = 0.070$ ,  $\beta = 0.040$  (95% CI: 0.007-0.063)], and [ $B = 0.039$ ,  $\beta = 0.040$  (95% CI: 0.020-0.117)]. Overall, 49.1%, 90.7%, and 36.8% of the total effects were mediated in models, 1, 2, and 3, respectively.

**Discussion:** EE interventions improve adherence, by improving mental health functioning. These findings warrant the need to incorporate components that address mental health challenges in programs targeting poverty to improve ART adherence in low-income settings.

J Int AIDS Soc. 2022 Sep;25(9):e25990.

doi: 10.1002/jia2.25990.

**[Monitoring adherence to antiretroviral therapy among adolescents in Southern Uganda: comparing Wisepill to Self-report in predicting viral suppression in a cluster-randomized trial](#)**

[Samuel Kizito](#)<sup>1</sup>, [Flavia Namuwonge](#)<sup>2</sup>, [Rachel Brathwaite](#)<sup>1</sup>, [Torsten B Neilands](#)<sup>3</sup>, [Proscovia Nabunya](#)<sup>1</sup>, [Ozge Sensoy Bahar](#)<sup>1</sup>, [Christopher Damulira](#)<sup>1</sup>, [Abel Mwebembezi](#)<sup>4</sup>, [Claude Mellins](#)<sup>5</sup>, [Mary M McKay](#)<sup>1</sup>, [Fred M Ssewamala](#)<sup>1</sup>

**Abstract**

**Introduction:** Optimal antiretroviral therapy (ART) adherence is crucial for improved patient outcomes; however, ART adherence among adolescents living with HIV (ALHIV) is low. Also, the performance of various adherence measures among ALHIV is under contention. We monitored ART adherence and compared Self-report (SR) and Wisepill electronic monitoring (EM) performance in measuring ART adherence and predicting HIV viral suppression among ALHIV.

**Methods:** Between January 2014 and December 2015, we recruited 702 ALHIV aged 10-16 years into our cluster-randomized controlled trial (2012-2018) in 39 clinics in Uganda. The intervention included a long-term savings child development account, four micro-enterprise workshops and 12 mentorship sessions. Using the entire sample, we performed multilevel logistic regression to predict monthly ART adherence trends for the first year of follow-up. Since it is possible that the intervention had different effects on SR and EM adherence, we used participants in the control arm only to compare adherence using SR and EM and to calculate their sensitivity and specificity in predicting viral suppression.

**Results:** There was a significant decline in adherence for each month throughout the entire follow-up period regardless of the group assigned. Good ART adherence was measured at 79.2% (75.2-82.6%) and 97.0% (95.4-98.1%) using EM and SR, respectively. Overall, 64.3% (60.6-67.9%) had suppressed viral loads. The specificities for EM and SR in predicting viral non-suppression were 80.4% (73.6-85.7%) and 96.7% (93.3-98.4%), while the sensitivities were 22.9% (15.0-33.3%) and 1.8% (0.4-6.9%), respectively. The area under the curve was low for both EM and SR, at 53.6% (45.7-61.5%) and 56.2% (53.2-59.3%), respectively. There was high agreement (78%) between SR and EM in monitoring adherence.

**Conclusions:** Our findings highlighted the need for strategies for sustained optimal adherence. SR and EM measure adherence with a considerable agreement; however, neither

is an accurate predictor of virological outcome. There is still a need for an acceptable, feasible and affordable method that predicts viral suppression among ALHIV.

BMJ Glob Health. 2022 Sep;7(9):e007206.

doi: 10.1136/bmjgh-2021-007206.

**[The impact of financial incentives on HIV incidence among adolescent girls and young women in Eswatini: Sitakhela Likusasa, a cluster randomised trial](#)**

[Marelize Gorgens](#)<sup>1</sup>, [Sosthenes Ketende](#)<sup>1</sup>, [Andrew F Longosz](#)<sup>1</sup>, [Mbuso Mabuza](#)<sup>2</sup>, [Muziwethu Nkambule](#)<sup>3</sup>, [Tengetile Dlamini](#)<sup>2</sup>, [Kelvin Sikwibele](#)<sup>4</sup>, [Vimbai Tsododo](#)<sup>4</sup>, [Tendai Chiopera](#)<sup>4</sup>, [Mxolisi Leroy Ndikandika](#)<sup>4</sup>, [Wendy Heard](#)<sup>1</sup>, [Gugu Maphalala](#)<sup>5</sup>, [Lindiwe Dlamini](#)<sup>6</sup>, [David Wilson](#)<sup>1</sup>, [Damien de Walque](#)<sup>7</sup>, [Khanya Mabuza](#)<sup>2</sup>

**Abstract**

**Introduction:** Incentives conditional on school attendance or on remaining free of sexually transmitted infections have produced mixed results in reducing HIV incidence.

**Methods:** HIV-negative adolescent girls and young women aged 15-22%-50% of whom were out of school-were recruited from 293 clusters in Eswatini from urban (30%) and rural areas (70%). Financial incentives conditional on education attendance were randomly allocated at the cluster level. All participants were further individually randomised into eligibility for a raffle incentive conditional on random selection into the raffle, on negative tests for syphilis and *Trichomonas vaginalis* and on being a raffle winner, creating four subarms in a 2x2 factorial design: no-intervention, raffle incentive, education incentive and raffle & education incentive. Randomisation was unblinded to participants. Logistic regressions were used in intention-to-treat analysis of HIV incidence over 3 years to estimate the impact of incentives conditional on school attendance and raffle incentives conditional on remaining sexually transmitted infection free.

**Results:** The study recruited 4389 HIV-negative participants, who were distributed into four subarms: no intervention (n=1068), raffle incentive (n=1162), education incentive (n=1088) and raffle and education incentive (n=1071). At endline, 272 participants from 3772 for whom endline data were collected, tested positive for HIV. HIV incidence among participants in education treatment arm was significantly lower than in the education control arm, 6.34% (119/1878) versus 8.08% (153/1894) (p=0.041); OR: 0.766 (0.598 to 0.981); adjusted OR (aOR): 0.754 (0.585 to 0.972). Compared with the no intervention subarm, HIV incidence in the raffle and education incentive subarm was significantly lower, 5.79% (54/878) versus 8.84% (80/905); OR: 0.634 (0.443 to 0.907); aOR: 0.622 (0.433 to 0.893), while it was not significantly lower in the raffle incentive subarm.

**Conclusion:** Financial incentives conditional on education participation significantly reduced HIV infection among adolescent girls and young women in Eswatini and appear to be a promising tool for prevention in high HIV prevalence settings.

JMIR Public Health Surveill. 2022 Sep 19;8(9):e30372.

doi: 10.2196/30372.

**[Effectiveness of Cash Transfer Delivered Along With Combination HIV Prevention Interventions in Reducing the Risky Sexual Behavior of Adolescent Girls and Young Women in Tanzania: Cluster Randomized Controlled Trial](#)**



[Evodius Kuringe<sup>1</sup>](#), [Alice Christensen<sup>2</sup>](#), [Jacqueline Materu<sup>1</sup>](#), [Mary Drake<sup>2</sup>](#), [Esther Majani<sup>2</sup>](#), [Caterina Casalini<sup>2</sup>](#), [Deusdedit Mjungu<sup>2</sup>](#), [Gaspar Mbita<sup>2</sup>](#), [Esther Kalage<sup>2</sup>](#), [Albert Komba<sup>2</sup>](#), [Daniel Nyato<sup>1</sup>](#), [Soori Nnko<sup>1</sup>](#), [Amani Shao<sup>1</sup>](#), [John Changalucha<sup>1</sup>](#), [Mwita Wambura<sup>1</sup>](#)

## Abstract

**Background:** Poverty and social inequality exacerbate HIV risk among adolescent girls and young women (AGYW) in sub-Saharan Africa. Cash transfers can influence the structural determinants of health, thereby reducing HIV risk.

**Objective:** This study assessed the effectiveness of cash transfer delivered along with combination HIV prevention (CHP) interventions in reducing the risky sexual behavior of AGYW in Tanzania. The incidence of herpes simplex virus type 2 (HSV-2) infection was used as a proxy for sexual risk behavior.

**Methods:** A cluster randomized controlled trial was conducted in 15 matched pairs of communities (1:1 intervention to control) across 3 strata (urban, rural high-risk, and rural low-risk populations) of the Shinyanga Region, Tanzania. The target population was out-of-school AGYW aged 15-23 years who had completed 10-hour sessions of social and behavior change communication. Eligible communities were randomly assigned to receive CHP along with cash transfer quarterly (intervention group) or solely CHP interventions (control group) with no masking. Study recruitment and baseline survey were conducted between October 30, 2017 and December 1, 2017. Participants completed an audio computer-assisted self-interview, HIV counselling and testing, and HSV-2 testing at baseline and during follow-up visits at 6, 12, and 18 months after the baseline survey. A Cox proportional hazards model with random effects specified at the level of clusters (shared frailty) adjusted for matching pairs and other baseline imbalances was fitted to assess the effects of cash transfer on the incidence of HSV-2 infection (primary outcome). Secondary outcomes included HIV prevalence at follow-up, self-reported intergenerational sex, and self-reported compensated sex. All secondary outcomes were measured at each study visit.

**Results:** Of the 3026 AGYW enrolled in the trial (1482 in the intervention and 1544 in the control), 2720 AGYW (1373 in the intervention and 1347 in the control) were included in the final analysis. Overall, HSV-2 incidence was not significantly different at all follow-up points between the study arms in the adjusted analysis (hazard ratio 0.96, 95% CI 0.67-1.38; P=.83). However, HSV-2 incidence was significantly lower in the rural low-risk populations who received the cash transfer intervention (hazard ratio 0.45, 95% CI 0.29-0.71; P=.001), adjusted for potential confounders.

**Conclusions:** Although this trial showed no significant impact of the cash transfer intervention on HSV-2 incidence among AGYW overall, the intervention significantly reduced HSV-2 incidence among AGYW in rural low-risk communities. Factors such as lesser poverty and more asset ownership in urban and rural high-risk communities may have undermined the impact of cash transfer.

## Adolescent substance use

Addict Behav. 2023 Feb;137:107522.

doi: 10.1016/j.addbeh.2022.107522. Epub 2022 Oct 10.

[Changes in alcohol beliefs mediate the effects of a school-based prevention program on alcohol use among Brazilian adolescents](#)

[Rodrigo Garcia-Cerde<sup>1</sup>](#), [Juliana Y Valente<sup>2</sup>](#), [Zila M Sanchez<sup>3</sup>](#)

## Abstract

**Objective:** To investigate the mechanisms of the #Tamojunto2.0 program that mediated the prevention of lifetime alcohol and drug use, including drug knowledge, behavioral beliefs, attitudes, decision-making skills, and refusal skills.

**Methods:** A cluster-randomized controlled trial was conducted in 73 public middle schools in three Brazilian cities. The sample included 5208 students (49.4 % girls;  $M_{age} = 13.2$  years). The intervention group attended twelve #Tamojunto2.0 lessons conducted by their previously trained teachers. The control group did not receive any intervention. Data were collected pre-intervention and at the 9-months follow-up. We performed multiple mediation models (for the whole sample, users, and non-users) with a post-estimation adjustment to standard errors to account for nesting. We analyzed all available mediators simultaneously according to each drug: alcohol, binge drinking, tobacco, marijuana, and inhalant lifetime use. To handle missing data, we used the "full-information maximum-likelihood" paradigm.

**Results:** Outcomes in the whole sample and among non-users showed that #Tamojunto2.0 indirectly prevented lifetime alcohol use and binge drinking by increasing negative and non-positive alcohol beliefs. Only the direct effect on decreasing lifetime alcohol consumption was statistically significant. However, an indirect increase in binge drinking was observed through knowledge about alcohol, but the direct effect was not statistically significant. No effects were reported for marijuana, tobacco, or inhalants. Among users, no statistically significant effects were found for alcohol or drug use.

**Conclusions:** The results suggest that the #Tamojunto2.0 program was only effective in delaying alcohol consumption via increasing negative and non-positive alcohol beliefs. It seems that mediating mechanisms vary depending on contextual characteristics, differences in socializing among adolescents, features of the educational systems, psychosocial conditions, or, fidelity issues of program implementation.

Int J Environ Res Public Health. 2023 Feb 20;20(4):3731.

doi: 10.3390/ijerph20043731.

## [The Effectiveness of an Empowerment Education Intervention for Substance Use Reduction among Inner-City Adolescents in Nigeria](#)

[Hassana Shuaibu Ojonuba<sup>1</sup>](#), [Haliza Abdul Rahman<sup>1,2</sup>](#), [Zeinab Zaremohzzabieh<sup>2</sup>](#), [Nor Afiah Mohd Zulkefli<sup>1</sup>](#)

## Abstract

(1) Background: Substance use among inner-city adolescents is at an alarming rate in Nigeria. Despite their high exposure to this risk, limited experimental tests have been conducted on prevention programs. (2) Methods: This study investigates the effectiveness of an empowerment education intervention in reducing the risk of substance use in Abuja's inner-city adolescents. Random selection placed adolescents into intervention and control conditions, and assessment was conducted at baseline, post-test, and 3-months follow-up intervention. After pre-test, the intervention group engaged in an empowerment education intervention of 11 sessions. (3) Results: In a post-test of three months, results show significant and positive changes among adolescents in substance use, including a notable reduction in positive attitudes toward drugs. In other words, the results showed adolescents reported less depression and substance use as well as higher peer support, parental support, social competence, and self-esteem at post-test and 3-month follow-ups as compared to the



pre-intervention period. In addition, at both post-test and the 3-month follow-up, the intervention group performed better than the control group on peer support, parental support, social competence, and self-esteem. (4) Conclusions: This study presents a new indication that the empowerment education intervention effectively reduces substance use among Nigeria's inner-city adolescents.

J Drug Educ. 2023 Jun 26;472379231185130.

doi: 10.1177/00472379231185130. Online ahead of print.

**[Effects of the Universal Prevention Curriculum for Schools on Substance Use Among Peruvian Adolescents: A Randomized Trial](#)**

[Mallie J Paschall](#)<sup>1</sup>, [Fernando Salazar Silva](#)<sup>2</sup>, [Zili Sloboda](#)<sup>3</sup>, [Christopher L Ringwalt](#)<sup>4</sup>, [Joel W Grube](#)<sup>1</sup>

**Abstract**

This group-randomized trial assessed the effects of a universal prevention training curriculum for school administrators and teachers that focused on effective strategies to prevent adolescent substance use and related problems. Twenty-eight schools in three regions of Peru were randomly assigned to either an intervention or control condition (14 schools per condition). Repeated cross-sectional samples of 11 to 19-year-old students participated in four surveys from May 2018 to November 2019 (N = 24,529). School administrators and teachers at intervention schools participated in a universal prevention training curriculum focusing on the development of a positive school climate as well as effective policies related to school substance use. All intervention and control schools were offered Unplugged, a classroom-based substance use prevention curriculum. Outcome measures included: lifetime drug use; past-year and past-month tobacco, alcohol, marijuana, and other drug use; awareness of school tobacco and alcohol use policies; perceived enforcement of school policies; school bonding; perceived friends' use of tobacco, alcohol, marijuana and other drugs; and personal problems in general and problems related to substance use. Multi-level analyses indicated significant reductions in past-year and past-month smoking, friends' substance use, and problems related to substance use and in general at intervention relative to control schools. Significant increases were found in intervention vs. control schools related to students' awareness of school substance use policies, perceived likelihood of getting caught for smoking, and school bonding. These findings suggest that the universal prevention training curriculum and the school policy and climate changes it promoted reduced substance use and related problems in the study population of Peruvian adolescents.

## **Anaemia and iron deficiency**

(See also Nutrition – micronutrients and food fortification)

Indian Pediatr. 2023 May 19;S097475591600539.

Online ahead of print.

## **Iron Preparations in the Management of Iron Deficiency Anemia in Infants and Children: A Systematic Review and Meta-analysis**

[Arulparithi Cuddalore Subramanian](#)<sup>1</sup>, [Arunbabu Thirunavukkarasu](#)<sup>2</sup>, [Manjani Sekar](#)<sup>3</sup>

### **Abstract**

**Background:** Various therapeutic iron preparations are available in the market, which differ in their pharmacokinetic and safety profiles. There is insufficient evidence regarding the superior safety or efficacy of one over the other.

**Objectives:** To study the effects of iron preparations on various parameters like hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and serum ferritin.

**Study design:** A systematic review and meta-analysis of randomized controlled trials (RCT) was conducted from inception till 3 June, 2022.

**Data sources and selection criteria:** Databases like MEDLINE and COCHRANE were searched for RCTs evaluating the effects and safety profile of various iron salts in the management of iron deficiency anemia in children and adolescents.

**Main results:** Eight studies with a total of 495 children were included the review. Pooled analysis showed ferrous sulphate to cause a significant increase in hemoglobin compared with other iron compounds [mean difference (95% CI) 0.53 (0.22 to 0.83; P <0.001)]. Also ferrous sulphate is superior to iron polymaltose complex (IPC) (P<0.001). However, there was a significant increase in gastrointestinal adverse effects with ferrous sulphate compared to IPC (P=0.03). Other iron compounds were more efficacious than IPC in raising hemoglobin levels (P<0.001). Among the few studies evaluating iron indices like MCV, MCH, and serum ferritin, there was no significant difference between the iron preparations (P>0.05).

**Conclusion:** A low quality evidence suggests that ferrous sulphate is more efficacious than other compounds (P<0.001), though, there is an increase in gastrointestinal side effects with ferrous sulphate.

Community Health Equity Res Policy. 2023 Apr;43(3):265-274.

doi: 10.1177/0272684X211022584. Epub 2021 Jun 6.

## **Risks of Anaemia Among Pre-School Children Following Maternal Nutrition Education and Counselling in Urban Informal Settlements of Nairobi, Kenya**

[Carolyn Kemunto Nyamasege](#)<sup>1,2</sup>, [Elizabeth W Kimani-Murage](#)<sup>2,3</sup>, [Jasper K Imungi](#)<sup>4</sup>, [Dasel W M Kaindi](#)<sup>4</sup>, [Yukiko Wagatsuma](#)<sup>5</sup>

### **Abstract**

Slum environment may pose risk to child health and nutrition. This study assessed the risks of anemia among under five-year-old children, five years after implementing a nutrition education and counseling intervention in two urban slums in Nairobi, Kenya. A cross-sectional study was conducted in May 2018 as a follow-up of a randomized controlled study carried out between 2012-2015. A trained nurse measured hemoglobin levels of 438 children from households which participated in the initial study. Multivariate logistic regression was conducted to identify risks of anemia. The mean (+SD) age of the children was 55.9 (5.3) months and mean (+SD) hemoglobin was 10.7 (1.5) g/dL. Anemia prevalence was 59.8%, 33.9% had mild, 24.7% moderate, and 1.2% severe anemia. Absence of home toilet (AOR = 3.31; 95% CI, 1.20-9.09), household which paid to use a toilet facility (AOR = 1.86; 95% CI, 1.12-3.08), child's frequency of eating colored fruits and vegetables (AOR = 0.28; 95% CI, 0.08-0.96), meat and meat products (AOR = 0.31; 95% CI, 0.23-6.01), number of meals a child aged

<15years ate a day preceding the study (AOR = 1.49; 95% CI, 1.14-1.98), and a mother who had a history of anemia (AOR = 2.89; 95% CI, 1.22-12.01), were factors significantly associated with child's anemia status. The environment of urban informal settings influences child anemia status. Further studies with interventions are therefore required in order to improve sanitation facilities and access to meats, fruits, and vegetables in urban slums through innovative kitchen gardens and small animal husbandry.

Lancet Glob Health. 2023 Jan;11(1):e105-e116.

doi: 10.1016/S2214-109X(22)00449-1.

**[Hepcidin-guided screen-and-treat interventions for young children with iron-deficiency anaemia in The Gambia: an individually randomised, three-arm, double-blind, controlled, proof-of-concept, non-inferiority trial](#)**

[Rita Wegmüller<sup>1</sup>](#), [Amat Bah<sup>2</sup>](#), [Lindsay Kendall<sup>3</sup>](#), [Morgan M Goheen<sup>4</sup>](#), [Saikou Sanyang<sup>3</sup>](#), [Ebrima Danso<sup>3</sup>](#), [Ebrima A Sise<sup>3</sup>](#), [Amadou Jallow<sup>3</sup>](#), [Hans Verhoef<sup>5</sup>](#), [Momodou W Jallow<sup>6</sup>](#), [Miriam Wathuo<sup>7</sup>](#), [Andrew E Armitage<sup>8</sup>](#), [Hal Drakesmith<sup>8</sup>](#), [Sant-Rayn Pasricha<sup>9</sup>](#), [James H Cross<sup>3</sup>](#), [Carla Cerami<sup>3</sup>](#), [Andrew M Prentice<sup>10</sup>](#)

**Abstract**

**Background:** Iron deficiency is the most prevalent nutritional disorder worldwide. Iron supplementation has modest efficacy, causes gastrointestinal side-effects that limit compliance, and has been associated with serious adverse outcomes in children across low-income settings. We aimed to compare two hepcidin-guided screen-and-treat regimens designed to reduce overall iron dosage by targeting its administration to periods when children were safe and ready to receive iron supplementation, with WHO's recommendation of universal iron supplementation.

**Methods:** We conducted an individually randomised, three-arm, double-blind, controlled, proof-of-concept, non-inferiority trial in 12 rural communities across The Gambia. Eligible participants were children aged 6-23 months with anaemia. Participants were randomly assigned (1:1:1) to either the WHO recommended regimen of one sachet of multiple micronutrient powder (MMP) daily containing 12.0 mg iron as encapsulated ferrous fumarate (control group); to MMP with 12.0 mg per day iron for the next 7 days if plasma hepcidin concentration was less than 5.5 µg/L, or to MMP without iron for the next 7 days if plasma hepcidin concentration was at least 5.5 µg/L (12 mg screen-and-treat group); or to MMP with 6.0 mg per day iron for the next 7 days if plasma hepcidin concentration was less than 5.5 µg/L, or to MMP without iron for the next 7 days if plasma hepcidin concentration was at least 5.5 µg/L (6 mg screen-and-treat group). Randomisation was done by use of a permuted block design (block size of 9), with stratification by haemoglobin and age, using computer-generated numbers. Participants and the research team (except for the data manager) were masked to group allocation. The primary outcome was haemoglobin concentration, with a non-inferiority margin of -5 g/L. A per-protocol analysis, including only children who had consumed at least 90% of the supplements (ie, supplement intake on  $\geq 75$  days during the study), was done to assess non-inferiority of the primary outcome at day 84 using a one-sided t test adjusted for multiple comparisons. Safety was assessed by use of ex-vivo growth tests of *Plasmodium falciparum* in erythrocytes and three species of sentinel bacteria in plasma samples from participants. This trial is registered with the ISRCTN registry, ISRCTN07210906.

**Findings:** Between April 23, 2014, and Aug 7, 2015, we prescreened 783 children, of whom 407 were enrolled into the study: 135 were randomly assigned to the control group, 136 to the 12 mg screen-and-treat group, and 136 to the 6 mg screen-and-treat group. 345 (85%) children were included in the per-protocol population: 115 in the control group, 116 in the 12 mg screen-and-treat group, and 114 in the 6 mg screen-and-treat group. Directly observed adherence was high across all groups (control group 94.8%, 12 mg screen-and-treat group 95.3%, and 6 mg screen-and-treat group 95.0%). 82 days of iron supplementation increased mean haemoglobin concentration by 7.7 g/L (95% CI 3.2 to 12.2) in the control group. Both screen-and-treat regimens were significantly less efficacious at improving haemoglobin (-5.6 g/L [98.3% CI -9.9 to -1.3] in the 12 mg screen-and-treat group and -7.8 g/L [98.3% CI -12.2 to -3.5] in the 6 mg screen-and-treat group) and neither regimen met the preset non-inferiority margin of -5 g/L. The 12 mg screen-and-treat regimen reduced iron dosage to 6.1 mg per day and the 6 mg screen-and-treat regimen reduced dosage to 3.0 mg per day. 580 adverse events were observed in 316 participants, of which eight were serious adverse events requiring hospitalisation mainly due to diarrhoeal disease (one [1%] participant in the control group, three [2%] in the 12 mg screen-and-treat group, and four [3%] in the 6 mg screen-and-treat group). The most common causes of non-serious adverse events (n=572) were diarrhoea (145 events [25%]), upper respiratory tract infections (194 [34%]), lower respiratory tract infections (62 [11%]), and skin infections (122 [21%]). No adverse events were deemed to be related to the study interventions.

**Interpretation:** The hepcidin-guided screen-and-treat strategy to target iron administration succeeded in reducing overall iron dosage, but was considerably less efficacious at increasing haemoglobin and combating iron deficiency and anaemia than was WHO's standard of care, and showed no differences in morbidity or safety outcomes.

BMC Pediatr. 2022 Dec 7;22(1):701.

doi: 10.1186/s12887-022-03766-5.

**[Spirulina as a daily nutritional supplement of young pre-school Cambodian children of deprived settings: a single-blinded, placebo-controlled, cross-over trial](#)**

[Hubert Barennes](#)<sup>1</sup>, [Laetitia Houdart](#)<sup>2</sup>, [Caroline de Courville](#)<sup>3</sup>, [Florent Barennes](#)<sup>3</sup>

**Abstract**

**Background:** Spirulina (SP) is widely used as a nutritional supplement to enhance child nutrition in low-income countries. We assessed Spirulina's efficacy of the current dose supplied by institutions in Cambodia on improving growth and anemia in a cross-over randomized controlled trial in preschool underprivileged children from similar settings.

**Methods:** Preschool children cared by a not-for-profit institution were randomly and blindly allocated (2 to 1) to spirulina or placebo: 100 g in total, given in 2 g per day. After 5 weeks of wash-out, participants were crossed-over to the other group. Anthropometric gain and selected hematological data (blood cell count, ferritin, and C-reactive protein) were assessed at each phase.

**Results:** A total of 179 children completed the trial, 149 (83.2%) completed all the anthropometrics, and 99 (55.3%) all hematological measures. Mean BMI was 14.18 (95%CI: 14.00-14.37) and 31(20.8%) children had thinness. Mean blood hemoglobin was 11.9 g/dL (95%CI: 11.8-12.1). The weight gain of the SP group showed a modest higher trend compared to placebo (0.63 kg; 95%CI: 0.54-0.72 and 0.46 kg; 95%CI: 0.33-0.58, respectively; p = 0.07).

Height increased similarly in both groups. The number of anemic children decreased by 6 (6.06%) and 11 (11.11%) on Placebo or SP, respectively ( $p = 0.004$ ). Tolerance was good.

**Conclusion:** SP may be recommended to improve childhood anemia. The analysis of the usual daily dose (2 g) provided by organizations in Cambodia shows a tendency to improve weight gain in the group supplemented with SP very close to significance, but no trend in height. Increased doses and longer supplementation should be evaluated further.

## Anaesthesia and intensive care

Paediatr Anaesth. 2023 Feb;33(2):129-133.

doi: 10.1111/pan.14577. Epub 2022 Oct 30.

### [Utilizing nasal-tragus length to estimate optimal endotracheal tube depth in neonates: A prospective randomized control study](#)

[Anjusha Thazhe Veettil](#)<sup>1</sup>, [Charu Bamba](#)<sup>1</sup>, [Vanya Chugh](#)<sup>2</sup>

#### Abstract

**Background:** Determination of the optimal depth of endotracheal tube insertion in neonates is challenging. Various formulae have been proposed and are being commonly used for this purpose. There is no single formula that is ideal or can be applied across different populations.

**Aim:** To compare weight and nasal-tragus length-based formulae as a guide to endotracheal tube insertion depth in term neonates undergoing surgery. The primary objective of the study was to determine the position of the endotracheal tube using either weight-based or nasal-tragus length-based formulae and the secondary objective was to determine the incidence of repositioning of the endotracheal tube.

**Methods:** A total of 120 full term neonates were divided into two groups with 60 neonates each (group N = NTL + 1 cm and group W = Weight + 6 cm). Endotracheal tube was inserted according to the pre-calculated value and fixed. A neonatal flexible fiberoptic bronchoscope was used to confirm the position of the endotracheal tube tip by measuring its distance from the carina. Repositioning was done if the distance from carina to endotracheal tube tip was less than 20 mm. Chi-squared and Mann-Whitney tests were used for the analysis.

**Results:** The mean distance measured from carina to endotracheal tube tip in group N was  $9.41 \pm 6.65$  mm and in group W was  $3.21 \pm 3.45$  mm ( $p$  value =  $<.001$ ). A higher incidence of optimal endotracheal tube placement was observed in group N which led to repositioning in 88.3% of neonates in group N and 100% in the group W (53/60 and 60/60, respectively,  $p$  value  $<.05$ ).

**Conclusion:** Based on the results from the studied sample, NTL +1 cm formula is a better predictor than Weight + 6 cm formula to determine endotracheal tube insertion depth in term Indian neonates.

Paediatr Anaesth. 2023 Jan;33(1):38-45.

doi: 10.1111/pan.14566. Epub 2022 Oct 8.

**[Supplemental intraoperative crystalloids for pediatric postoperative nausea and vomiting-A systematic review and meta-analysis](#)**

[Sunaakshi Puri](#)<sup>1</sup>, [Anjishnujit Bandyopadhyay](#)<sup>1</sup>, [Vighnesh Ashok](#)<sup>1</sup>

**Abstract**

**Background:** Postoperative nausea and/or vomiting is a relatively frequent occurrence after general anesthesia in pediatric patients. Supplemental perioperative crystalloid fluid administration has been shown to have a positive effect on the incidence of nausea and/or vomiting in adults undergoing surgery. The question arises whether supplemental intraoperative intravenous fluids in pediatric patients offers beneficial results with regards to pediatric postoperative nausea and/or vomiting.

**Methods:** Pubmed, EMBASE, Google Scholar, and Web of Science were searched up to March 2022 to perform a systematic review with meta-analysis of randomized controlled trials involving patients ≤18 years undergoing elective surgery under general anesthesia, with one group receiving conventional intraoperative fluids therapy and the other group receiving supplemental intraoperative fluid therapy, with intravenous crystalloids. The outcomes included incidence of postoperative vomiting, postoperative nausea and vomiting, the need for rescue anti-emetics, postoperative thirst, and adverse events attributed to supplemental intravenous fluid therapy. Relative risk (RR) with 95% confidence intervals (CIs) were reported for the outcomes using a random or fixed effects model.

**Results:** Seven randomized controlled trials (864 patients) were included in the final analysis. Supplemental intraoperative crystalloids reduce postoperative vomiting (RR 0.56, 95% CI 0.39-0.80;  $p = .001$ ), postoperative nausea and vomiting (RR 0.52, 95% CI 0.37-0.74;  $p = .0003$ ), postoperative thirst (RR 0.21, 95% CI 0.13,0.34;  $p < .01$ ), and the need for rescue anti-emetics postoperatively (RR 0.60, 95% CI 0.49-0.74;  $p = .00001$ ).

**Conclusion:** Supplemental intraoperative intravenous crystalloids significantly reduce several PONV outcomes in healthy children undergoing relatively simple and superficial surgeries under volatile agent-based general anesthesia.

Eur J Pediatr. 2023 Jan 20;1-7.

doi: 10.1007/s00431-022-04794-0. Online ahead of print.

**[Comparison of oral triclofos and intranasal midazolam and dexmedetomidine for sedation in children undergoing magnetic resonance imaging \(MRI\): an open-label, three-arm, randomized trial](#)**

[Shyam Chandrasekar](#)<sup>1</sup>, [Bhagirathi Dwibedi](#)<sup>2</sup>, [Rashmi Ranjan Das](#)<sup>1</sup>, [Biswa Mohan Padhy](#)<sup>3</sup>, [Bikram Kishore Behera](#)<sup>4</sup>

**Abstract**

The purpose of this study was to compare the efficacy of oral triclofos (TRI), intranasal midazolam (INM), and intranasal dexmedetomidine (IND) in achieving successful sedation in children undergoing MRI. This open-label, three-arm, randomized trial was conducted in a tertiary care teaching hospital over 18-month period. Children scheduled for MRI were enrolled. Rate of successful/adequate sedation was assessed using the Paediatric Sedation State Scale (PSSS). The primary outcome was the efficacy (successful sedation or sedation rate) of the three drugs. One-hundred and ninety-five children were included for the MRI procedure. IND was found to be superior in terms of achieving successful sedation. INM had a shorter onset and duration of sedation compared to IND and TRI, but with an increased failure rate (88.3%). Keeping INM as the reference group, it was found that the odds of



sedation increased 4.1 times on changing from INM to IND ( $p < 0.01$ ), and 2.26 times on changing from INM to TRI ( $p < 0.01$ ). Adverse events included nasal discomfort (18.3%) in INM group; and self-limited tachycardia (4.6%) and hypotension (10.8%) in the IND group.

**Conclusion:** IND was more efficacious than INM or TRI for procedural sedation in children undergoing MRI without any significant adverse events.

J Clin Anesth. 2023 Jan 3;85:111038.

doi: 10.1016/j.jclinane.2022.111038. Online ahead of print.

**[Long-axis in-plane combined with short-axis out-of-plane technique in ultrasound-guided arterial catheterization in infants: A randomized controlled trial](#)**

[Ziyi Wang](#)<sup>1</sup>, [Hongjie Guo](#)<sup>1</sup>, [Shujun Shi](#)<sup>1</sup>, [Ying Xu](#)<sup>2</sup>, [Mao Ye](#)<sup>2</sup>, [Lin Bai](#)<sup>2</sup>, [Yanzhe Tan](#)<sup>2</sup>, [Yihui Li](#)<sup>2</sup>, [LIFEI LIU](#)<sup>3</sup>

**Abstract**

**Study objective:** To determine whether the long-axis in-plane (LAX-IP) combined with short-axis out-of-plane (SAX-OOP) technique is more suitable than modified dynamic needle tip positioning (MDNTP) technique for ultrasound-guided radial artery catheterization in infants.

**Design:** A randomized controlled trial.

**Setting:** Department of Anesthesiology, Children's Hospital of Chongqing Medical University.

**Patients:** Overall, 72 patients, aged 1-12 months old, who were primarily undergoing thoracic or cardiac surgery in the Children's Hospital of Chongqing Medical University between July 1, 2021, and March 31, 2022, were selected. These patients were randomly divided into two groups: i) the MDNTP group and ii) the LAX-IP combined with SAX-OOP group.

**Interventions:** Radial artery cannulation in the two groups was performed using ultrasound-guided MDNTP or LAX-IP combined with SAX-OOP technique.

**Measurements:** The primary outcome was first-time success rate, and the secondary outcomes included total success rate, cannulation time, and incidence of complications.

**Main results:** In the LAX-IP combined with SAX-OOP group, the first-time success rate was 75.0% ( $n = 27$ ), total success rate was 97.2% ( $n = 35$ ), cannulation time was  $91.39 \pm 102.60$  s, puncture attempts was  $1.5 \pm 1.3$  times, and local hematoma was formed on the first day in one (2.8%) infant. In the MDNTP group, the first-time success rate was 36.1% ( $n = 13$ ) ( $P = 0.001$ ; RR, 2.08; 95% confidence interval, 1.29-3.34), total success rate was 91.7% ( $n = 33$ ) ( $P = 0.303$ ; RR, 1.06; 95% confidence interval, 0.95-1.19), cannulation time was  $181.00 \pm 146.72$  s ( $P = 0.047$ ; Median difference, -89.61; 95% confidence interval, -149.12 to -30.10), puncture attempts was  $2.3 \pm 1.6$  times ( $P = 0.133$ ; Median difference, -0.81), and local hematoma was formed on the first day in nine (25%) infants ( $P = 0.006$ ; RR, 0.11; 95% confidence interval, 0.01-0.83). No thrombosis occurred in any group.

**Conclusions:** The ultrasound-guided LAX-IP combined with SAX-OOP technique for radial arterial catheterization in infants, which was performed by anesthesia residents, exhibited an increased first-time success rate, reduced cannulation time, and lower incidence of complications than the MDNTP technique.

Paediatr Anaesth. 2023 Feb;33(2):123-128.

doi: 10.1111/pan.14581. Epub 2022 Oct 26.

### **Impact of intravenous dexamethasone on the initiation and recovery of atracurium in children: A double-blinded randomized controlled trial**

[Soumya Sarkar<sup>1</sup>](#), [Magesh Parthiban<sup>2</sup>](#), [Damarla Haritha<sup>3</sup>](#), [Bikash Ranjan Ray<sup>3</sup>](#), [Akhil Kant Singh<sup>3</sup>](#), [Shailendra Kumar<sup>3</sup>](#), [Puneet Khanna<sup>3</sup>](#), [Lokesh Kashyap<sup>3</sup>](#)

#### **Abstract**

**Background:** Chronic steroid intake has been associated with attenuation of neuromuscular block. Despite some promising animal and adult studies, the effect of a single dose of intravenous dexamethasone on neuromuscular blockers is not well established. Thus, the present study aimed to demonstrate the effect of dexamethasone given at the time of induction for the prevention of PONV on the action of neuromuscular blockers in children undergoing elective surgery.

**Method:** After obtaining approval from the Institute Ethics Committee and written informed parental consent, 100 ASA I and II children aged 4-15 years undergoing elective surgery randomized to receive either: 0.15 mg/kg (maximum of 5 mg) of dexamethasone diluted to a total volume of 2 ml with 0.9% saline (n = 50) or 2 ml of 0.9% saline (n = 50) at the time of induction. The time interval between application of atracurium and maximum T1 depression, 25% twitch height recovery of T1, amid 25% and 75% twitch height recovery of T1, amid the 25% twitch height recovery of T1 and recovery of the neuromuscular block to a TOF ratio of 0.9, and in between the initiation of atracurium injection till the recovery of the neuromuscular block to a TOF ratio of 0.9 was defined as onset time, clinical duration, recovery index, recovery time, and total recovery period, respectively, and recorded.

**Results:** The onset time and recovery index time were lower ( $1.96 \pm 0.39$ ,  $8.04 \pm 2.14$ , respectively) with dexamethasone in comparison with saline ( $2.01 \pm 0.51$ ,  $8.9 \pm 3.4$ , respectively) but not statistically significant. The clinical duration, recovery time, and total recovery period were similar.

**Conclusion:** Application of a single bolus dose (0.15 mg/kg) of dexamethasone during induction does not attenuate atracurium-induced neuromuscular blockade in children.

## **Intensive care**

Ann Card Anaesth. 2022 Oct-Dec;25(4):435-440.

doi: 10.4103/aca.aca\_81\_21.

### **Randomized control study of nebulized colistin as an adjunctive therapy in ventilator-associated pneumonia in pediatric postoperative cardiac surgical population**

[K S Bharathi<sup>1</sup>](#), [Ananda Bhat<sup>2</sup>](#), [Gegal Pruthi<sup>2</sup>](#), [Parimala P Simha<sup>2</sup>](#)

#### **Abstract**

**Background:** Ventilator-associated pneumonia (VAP) with multidrug-resistant (MDR) gram negative organisms is a common problem in intensive care unit (ICU). Aerosolized antibiotics enhance the efficacy of systemic antibiotics when added as adjuvants.

**Aim:** The primary objective of the study was to compare the clinical and bacteriological outcome of patients with VAP who were administered intravenous (IV) antibiotics alone with those patients who were treated with adjunctive nebulized colistin (NC) along with IV antibiotics. The secondary objective was to study the occurrence of any adverse events during colistin nebulization.



**Settings and design:** The study was a prospective, randomized, double-blinded controlled study conducted at a tertiary-care teaching institution.

**Materials and methods:** Ninety-eight children from surgical ICU aged less than 12 years who were diagnosed with VAP due to gram negative bacteria following cardiac surgery were chosen and divided randomly into two groups. The experimental group (NC group) was treated with systemic antibiotics along with NC, whereas the control group (NS group) was administered systemic antibiotics with nebulized normal saline (NS). Clinical and bacteriological outcomes were noted. Statistical analysis was done using SPSS Version 20.0 software. The patient characteristics were compared using independent Student's t test and Chi-square test.

**Results:** There was a statistically significant reduction in the duration of mechanical ventilation, postoperative ICU and hospital stay in the NC group compared with the NS group.

**Conclusion:** Aerosolized colistin may be considered as an adjunct to systemic IV antibiotics in pediatric patients with VAP due to gram negative bacteria susceptible to colistin.

Indian J Pediatr. 2023 May 25.

doi: 10.1007/s12098-023-04532-w. Online ahead of print.

### [Hypertonic Saline vs. Mannitol in Management of Elevated Intracranial Pressure in Children: A Meta-Analysis](#)

[Nihar Ranjan Mishra](#)<sup>1</sup>, [Amit Agrawal](#)<sup>2</sup>, [Rashmi Ranjan Das](#)<sup>3</sup>

#### **Abstract**

**Objective:** To compare the efficacy and safety of two hyperosmolar agents (hypertonic saline vs. mannitol) used for the reduction of elevated intracranial pressure (ICP) in children.

**Methods:** A meta-analysis of randomized controlled trials (RCTs) was conducted and GRADE system (Grading of Recommendations, Assessment, Development and Evaluation) of evidence was applied. Relevant databases were searched till 31<sup>st</sup> May 2022. Primary outcome was mortality rate.

**Results:** Of 720 citations retrieved, 4 RCTs were included in the meta-analysis (n = 365, male = 61%). Traumatic and non-traumatic cases of elevated ICP were included. There was no significant difference in the mortality rate between the two groups [relative risk (RR), 1.09; (95% confidence interval (CI), 0.74 to 1.6)]. No significant difference was found for any of the secondary outcomes, except serum osmolality (being significantly higher in mannitol group). Adverse events like shock and dehydration were significantly higher in the mannitol group, and hyponatremia in the hypertonic saline group. The evidence generated for primary outcome was of "low certainty", and for secondary outcomes, it varied from "very-low to moderate certainty".

**Conclusions:** There is no significant difference between hypertonic saline and mannitol used for the reduction of elevated ICP in children. The evidence generated for primary outcome (mortality rate) was of "low certainty", and for secondary outcomes, it varied from "very-low to moderate certainty". More data from high-quality RCTs are needed to guide any recommendation.

Indian Pediatr. 2023 Jun 15;60(6):385-388.

Epub 2023 Apr 20.

## [Hemodynamic Responses to Recorded Maternal Voice Among Sedated Children in the Pediatric Intensive Care Unit: An Open-Label Randomized Controlled Trial](#)

[Shreelata Mandal<sup>1</sup>](#), [Poonam Joshi<sup>1</sup>](#), [Lumchio Levis Murry<sup>2</sup>](#), [Rakesh Lodha<sup>3</sup>](#)

### **Abstract**

**Objective:** To assess the effect of maternal audiotaped voice on clinical parameters of sedated children.

**Methods:** A randomized controlled trial was conducted on 25 sedated critically ill children admitted to the pediatric intensive care unit. An audiotaped maternal voice was played to the children in the experimental group (n=13) via a headphone for 15 minutes, twice a day for 3 days. Children in the control group (n=12) received routine care without any additional auditory stimulation. Clinical and hemodynamic variables were recorded at 5 minutes interval three times.

**Results:** Significant changes were observed in the mean (SD) heart rate (per minute) at 10 minutes [129.83 (19.14) vs 124.29 (14.90), P=0.051], respiratory rate at 5 minutes [44.38 (17.79) vs 34.65 (7.64), P=<0.001] and 10 minutes [42.79 (13.89) vs 35.44 (7.65) P=<0.001], systolic blood pressure at 5 minutes [95.24 (15.01) vs 101.02 (19.83) P=0.045], and mean blood pressure at 15 minutes [68.66 (13.61) vs 73.61 (17.59) P=0.051] mmHg between the experimental and the control group, respectively.

**Conclusion:** Listening to recorded maternal voice had a positive effect on clinical parameters of sedated critically ill children.

## **Antibiotics**

Clin Microbiol Infect. 2022 Sep 6;S1198-743X(22)00461-X.

doi: 10.1016/j.cmi.2022.08.024. Online ahead of print.

### [Short-course antibiotics for common infections: what do we know and where do we go from here?](#)

[Rachael A Lee<sup>1</sup>](#), [Joshua T Stripling<sup>2</sup>](#), [Brad Spellberg<sup>3</sup>](#), [Robert M Centor<sup>4</sup>](#)

### **Abstract**

**Background:** Over the past 25 years, researchers have performed >120 randomized controlled trials (RCTs) illustrating short courses to be non-inferior to long courses of antibiotics for common bacterial infections.

**Objective:** We sought to determine whether clinical data from RCTs affirm the mantra of 'shorter is better' for antibiotic durations in 7 common infections: pneumonia, urinary tract infection, intra-abdominal infection, bacteraemia, skin and soft tissue infection, bone and joint infections, pharyngitis and sinusitis.

**Sources:** Published RCTs comparing short- versus long-course antibiotic durations were identified through searches of PubMed and clinical guideline documents.

**Content:** Short-course antibiotic durations consistently result in similar treatment success rates as longer antibiotic courses among patients with community-acquired pneumonia, complicated urinary tract infections in women, gram-negative bacteraemia, and skin and soft tissue infections when the diagnosis is confirmed, appropriate antimicrobials are used, and patients show clinical signs of improvement. For patients with osteomyelitis, 6 weeks of antibiotics is adequate for the treatment of osteomyelitis in the absence of implanted foreign

bodies and surgical debridement. Whether durations can be further shortened with debridement is unclear, although small studies are promising.

**Implications:** With few exceptions, short courses were non-inferior to long courses; future research should focus on appropriately defining the patient population, ensuring the correct choice and dose of antimicrobials, and developing meaningful outcomes relevant for frontline clinicians.

Am J Trop Med Hyg. 2022 Nov 7;tpmd220245.

doi: 10.4269/ajtmh.22-0245. Online ahead of print.

### **[Effect of Neonatal Azithromycin on All-Cause and Cause-Specific Infant Mortality: A Randomized Controlled Trial](#)**

[Ali Sié](#), [Mamadou Bountogo](#), [Alphonse Zakane](#), [Guillaume Compaoré](#), [Thierry Ouedraogo](#), [Elodie Lebas](#), [Fanice Nyatigo](#), [Huiyu Hu](#), [Jessica Brogdon](#), [Benjamin F Arnold](#), [Thomas M Lietman](#), [Catherine E Oldenburg](#), [NAITRE Study Team](#)

#### **Abstract**

Mass azithromycin distribution reduces all-cause childhood mortality in some high-mortality settings in sub-Saharan Africa. Although the greatest benefits have been shown in children 1 to 5 months old living in areas with high mortality rates, no evidence of a benefit was found of neonatal azithromycin in a low-mortality setting on mortality at 6 months. We conducted a 1:1 randomized, placebo-controlled trial evaluating the effect of a single oral 20-mg/kg dose of azithromycin or matching placebo administered during the neonatal period on all-cause and cause-specific infant mortality at 12 months of age in five regions of Burkina Faso. Neonates were eligible if they were between the ages of 8 and 27 days and weighed at least 2,500 g at enrollment. Cause of death was determined via the WHO 2016 verbal autopsy tool. We compared all-cause and cause-specific mortality using binomial regression. Of 21,832 infants enrolled in the study, 116 died by 12 months of age. There was no significant difference in all-cause mortality between the azithromycin and placebo groups (azithromycin: 52 deaths, 0.5%; placebo, 64 deaths, 0.7%; hazard ratio, 0.81; 95% CI, 0.56-1.17; P = 0.30). There was no evidence of a difference in the distribution of causes of death (P = 0.40) and no significant difference in any specific cause of death between groups. Mortality rates were low at 12 months of age, and there was no evidence of an effect of neonatal azithromycin on all-cause or cause-specific mortality.

Clin Infect Dis. 2022 Aug 31;75(3):515-518.

doi: 10.1093/cid/ciab1046.

### **[Impact of Biannual Mass Azithromycin Treatment on Enteropathogen Carriage in Children <5 Years Old in Niger](#)**

[James A Platts-Mills](#)<sup>1</sup>, [Elias G Ayoub](#)<sup>2</sup>, [Jixian Zhang](#)<sup>1</sup>, [Elizabeth T Rogawski McQuade](#)<sup>3</sup>, [Ahmed M Arzika](#)<sup>4</sup>, [Ramatou Maliki](#)<sup>4</sup>, [Amza Abdou](#)<sup>5</sup>, [Jeremy D Keenan](#)<sup>6</sup>, [Thomas M Lietman](#)<sup>6</sup>, [Jie Liu](#)<sup>1</sup>, [Eric R Houpt](#)<sup>1</sup>

#### **Abstract**

We analyzed samples obtained at baseline and 24 months in a mass azithromycin administration trial in Niger using quantitative polymerase chain reaction. In villages randomized to azithromycin, Shigella was the only pathogen reduced at 24 months

(prevalence ratio, 0.36 [95% confidence interval: .17-.79]; difference in log quantity, -.42 [-.75 to -.10]).

Int J Epidemiol. 2022 Dec 13;51(6):1775-1784.

doi: 10.1093/ije/dyab198.

**[Azithromycin distribution and childhood mortality in compliance-related subgroups in Niger: complier average causal effect and spillovers in a cluster-randomized, placebo-controlled trial](#)**

[Kieran S O'Brien](#)<sup>1,2</sup>, [Ahmed M Arzika](#)<sup>3</sup>, [Ramatou Maliki](#)<sup>3</sup>, [Abdou Amza](#)<sup>4</sup>, [Farouk Manzo](#)<sup>3</sup>, [Alio Karamba Mankara](#)<sup>3</sup>, [Elodie Lebas](#)<sup>1</sup>, [Catherine Cook](#)<sup>1</sup>, [Catherine E Oldenburg](#)<sup>1,5,6</sup>, [Travis C Porco](#)<sup>1,5,6,7</sup>, [Benjamin F Arnold](#)<sup>1,5</sup>, [Stefano Bertozzi](#)<sup>2,8,9</sup>, [Jeremy D Keenan](#)<sup>1,5</sup>, [Thomas M Lietman](#)<sup>1,5,6,7</sup>

**Abstract**

**Background:** Biannual azithromycin distribution to children 1-59 months old reduced all-cause mortality by 18% [incidence rate ratio (IRR) 0.82, 95% confidence interval (CI): 0.74, 0.90] in an intention-to-treat analysis of a randomized controlled trial in Niger. Estimation of the effect in compliance-related subgroups can support decision making around implementation of this intervention in programmatic settings.

**Methods:** The cluster-randomized, placebo-controlled design of the original trial enabled unbiased estimation of the effect of azithromycin on mortality rates in two subgroups: (i) treated children (complier average causal effect analysis); and (ii) untreated children (spillover effect analysis), using negative binomial regression.

**Results:** In Niger, 594 eligible communities were randomized to biannual azithromycin or placebo distribution and were followed from December 2014 to August 2017, with a mean treatment coverage of 90% [standard deviation (SD) 10%] in both arms. Subgroup analyses included 2581 deaths among treated children and 245 deaths among untreated children. Among treated children, the incidence rate ratio comparing mortality in azithromycin communities to placebo communities was 0.80 (95% CI: 0.72, 0.88), with mortality rates (deaths per 1000 person-years at risk) of 16.6 in azithromycin communities and 20.9 in placebo communities. Among untreated children, the incidence rate ratio was 0.91 (95% CI: 0.69, 1.21), with rates of 33.6 in azithromycin communities and 34.4 in placebo communities.

**Conclusions:** As expected, this analysis suggested similar efficacy among treated children compared with the intention-to-treat analysis. Though the results were consistent with a small spillover benefit to untreated children, this trial was underpowered to detect spillovers.

JAMA. 2023 Mar 7;329(9):716-724.

doi: 10.1001/jama.2022.24388.

**[Effect of Intrapartum Azithromycin vs Placebo on Neonatal Sepsis and Death: A Randomized Clinical Trial](#)**

[Anna Roca](#)<sup>1</sup>, [Bully Camara](#)<sup>1</sup>, [Joel D Bognini](#)<sup>2</sup>, [Usman N Nakakana](#)<sup>1</sup>, [Athasana M Somé](#)<sup>2</sup>, [Nathalie Beloum](#)<sup>1</sup>, [Toussaint Rouamba](#)<sup>2</sup>, [Fatoumata Sillah](#)<sup>1</sup>, [Madikoi Danso](#)<sup>1</sup>, [Joquina C Jones](#)<sup>1</sup>, [Shashu Graves](#)<sup>1</sup>, [Isatou Jagne](#)<sup>1</sup>, [Pauline Getanda](#)<sup>1</sup>, [Saffiatou Darboe](#)<sup>1</sup>, [Marc C](#)

[Tahita<sup>2</sup>](#), [Ebrahim Ndure<sup>1</sup>](#), [Hien S Franck<sup>2</sup>](#), [Sawadogo Y Edmond<sup>2</sup>](#), [Bai L Dondeh<sup>1</sup>](#), [Wilfried G J Nassa<sup>2</sup>](#), [Zakaria Garba<sup>2</sup>](#), [Abdoulie Bojang<sup>1</sup>](#), [Yusupha Njie<sup>1</sup>](#), [Christian Bottomley<sup>3</sup>](#), [Halidou Tinto<sup>2</sup>](#), [Umberto D'Alessandro<sup>1</sup>](#); [PregnAnZI-2 Working Group](#)

## Abstract

**Importance:** Neonatal sepsis is a leading cause of neonatal mortality. New interventions are needed to decrease neonatal sepsis and mortality in regions with highest burden.

**Objective:** To evaluate the efficacy of intrapartum azithromycin to reduce neonatal sepsis or mortality, as well as neonatal and maternal infections.

**Design, setting, and participants:** This double-blind, placebo-controlled, randomized clinical trial enrolled and followed up birthing parents and their infants at 10 health facilities in The Gambia and Burkina Faso, West Africa, between October 2017 and May 2021.

**Interventions:** Participants were assigned at random to receive oral azithromycin (2 g) or placebo (ratio 1:1) during labor.

**Main outcomes and measures:** The primary outcome was a composite of neonatal sepsis or mortality, with the former defined based on microbiologic or clinical criteria. Secondary outcomes were neonatal infections (skin, umbilical, eye and ear infections), malaria, and fever; postpartum infections (puerperal sepsis, mastitis), fever, and malaria; and use of antibiotics during 4-week follow-up.

**Results:** The trial randomized 11 983 persons in labor (median age, 29.9 years). Overall, 225 newborns (1.9% of 11 783 live births) met the primary end point. The incidence of neonatal mortality or sepsis was similar in the azithromycin and placebo groups (2.0% [115/5889] vs 1.9% [110/5894]; risk difference [RD], 0.09 [95% CI, -0.39 to 0.57]), as was the incidence of neonatal mortality (0.8% vs 0.8%; RD, 0.04 [95% CI, -0.27 to 0.35]) and neonatal sepsis (1.3% vs 1.3%; RD, 0.02 [95% CI, -0.38 to 0.43]). Newborns in the azithromycin group compared with the placebo group had lower incidence of skin infections (0.8% vs 1.7%; RD, -0.90 [95% CI, -1.30 to -0.49]) and need for antibiotics (6.2% vs 7.8%; RD, -1.58 [95% CI, -2.49 to -0.67]). Postpartum parents in the azithromycin group had lower incidence of mastitis (0.3% vs 0.5%; RD, -0.24 [95% CI, -0.47 to -0.01]) and puerperal fever (0.1% vs 0.3%; RD, -0.19 [95% CI, -0.36 to -0.01]).

**Conclusions and relevance:** Azithromycin administered orally during labor did not reduce neonatal sepsis or mortality. These results do not support routine introduction of oral intrapartum azithromycin for this purpose.

EBioMedicine. 2022 Sep;83:104227.

doi: 10.1016/j.ebiom.2022.104227. Epub 2022 Aug 19.

## [Effect of intra-partum azithromycin on the development of the infant nasopharyngeal microbiota: A post hoc analysis of a double-blind randomized trial](#)

[Bakary Sanyang<sup>1</sup>](#), [Thushan I de Silva<sup>2</sup>](#), [Abdoulie Kanteh<sup>3</sup>](#), [Abdoulie Bojang<sup>4</sup>](#), [Jarra Manneh<sup>3</sup>](#), [Wouter AA de Steenhuijsen Piters<sup>5</sup>](#), [Chikondi Peno<sup>6</sup>](#), [Debby Bogaert<sup>7</sup>](#), [Abdul Karim Sesay<sup>3</sup>](#), [Anna Roca<sup>8</sup>](#)

## Abstract

**Background:** Sepsis is a leading cause of neonatal death. Intrapartum azithromycin reduces neonatal nasopharyngeal carriage of potentially pathogenic bacteria, a prerequisite for sepsis. Early antibiotic exposure has been associated with microbiota perturbations with

varying effects. This study aims to understand the effect of intrapartum azithromycin intervention on the developing nasopharyngeal microbiota of the child.

**Methods:** Using 16S rRNA gene sequencing, we analysed the microbiota of 343 nasopharyngeal samples collected from birth to 12 months from 109 healthy infants selected from a double-blind randomized placebo-controlled clinical trial conducted in the Gambia (PregnAnZI-1). In the trial, 829 women were given 2g oral azithromycin or placebo (1:1) during labour with the objective of reducing bacterial carriage in mother and child during the neonatal period. The post-hoc analysis presented here assessed the effect of the intervention on the child nasopharyngeal microbiota development.

**Findings:** 55 children were from mothers given azithromycin and 54 from mothers given placebo. Comparing arms, we found an increase in alpha-diversity at day-6 ( $p = 0.018$ ), and a significant effect on overall microbiota composition at days 6 and 28 ( $R^2 = 4.4\%$ ,  $q = 0.007$  and  $R^2 = 2.3\%$ ,  $q = 0.018$  respectively). At genus level, we found lower representation of *Staphylococcus* at day-6 ( $q = 0.0303$ ) and higher representation of *Moraxella* at 12 months ( $q = 0.0443$ ). Unsupervised clustering of samples by microbial community similarity showed different community dynamics between the intervention and placebo arms during the neonatal period.

**Interpretation:** These results indicate that intrapartum azithromycin caused short-term alterations in the nasopharyngeal microbiota with modest overall effect at 12 months of age. Further exploration of the effects of these variations on microbiome function will give more insight on the potential risks and benefits, for the child, associated with this intervention.

BMJ Glob Health. 2022 Oct;7(10):e009801.

doi: 10.1136/bmjgh-2022-009801.

### [Simplified dosing of oral azithromycin for children 1-11 months old in child survival programmes: age-based and height-based dosing protocols](#)

[Huiyu Hu<sup>1</sup>](#), [Ahmed Mamane Arzika<sup>2</sup>](#), [Ali Sie<sup>3</sup>](#), [Amza Abdou<sup>4</sup>](#), [Ramatou Maliki<sup>2</sup>](#), [Alio Karamba Mankara<sup>2</sup>](#), [Mamadou Outtara<sup>3</sup>](#), [Mamadou Bountogo<sup>3</sup>](#), [Valentin Boudo<sup>3</sup>](#), [Fanny Yago-Wienne<sup>5</sup>](#), [Issouf Bamba<sup>5</sup>](#), [Charles Knirsch<sup>6</sup>](#), [Paul Emerson<sup>7</sup>](#), [P J Hooper<sup>7</sup>](#), [Elodie Lebas<sup>1</sup>](#), [Jessica Brogdon<sup>1</sup>](#), [Fanice Nyatigo<sup>1</sup>](#), [Catherine E Oldenburg<sup>1,8,9,10</sup>](#), [Thomas M Lietman<sup>1,8,9,10</sup>](#), [Kieran S O'Brien<sup>11,8,9,10</sup>](#)

#### **Abstract**

**Background:** To facilitate mass distribution of azithromycin, trachoma control programmes use height instead of weight to determine dose for children 6 months to 15 years old. WHO has recommended azithromycin distribution to children 1-11 months old to reduce mortality in high mortality settings under carefully monitored conditions. Weight was used to determine dose in children 1-5 months old in studies of azithromycin distribution for child survival, but a simplified approach using age or height for all aged 1-11 months old could increase programme efficiency in real-world settings.

**Methods:** This secondary analysis used data from two cluster randomised trials of azithromycin distribution for child mortality in Niger and Burkina Faso. An exhaustive search algorithm was developed to determine the optimal dose for different age groups, using tolerance limits of 10-20 mg/kg for children 1-2 months old and 15-30 mg/kg for children 3-11 months old. Height-based dosing was evaluated against the existing trachoma dosing pole and with a similar exhaustive search.



**Results:** The optimal two-tiered age-based approach suggested a dose of 80 mg (2 mL) for children 1-2 months old and 160 mg (4 mL) for children 3-11 months old. Under this schedule, 89%-93% of children would have received doses within tolerance limits in both study populations. Accuracy was 93%-94% with a three-tiered approach, which resulted in doses of 80 mg (2 mL), 120 mg (3 mL) and 160 mg (4 mL) for children 1-2, 3-4 and 5-11 months old, respectively. For children 1-5 months old, the existing height pole would result in 70% of doses within tolerance limits. The optimisation identified height-based dosing options with 95% accuracy, although this would require changes to the existing dosing pole as well as additional training to measure infants lying flat.

**Conclusions:** Overall, an age-based approach with two age tiers resulted in high accuracy while considering both concerns about overdosing in this young population and simplicity of field operations.

\*\*\* N Engl J Med. 2023 Feb 9.

doi: 10.1056/NEJMoa2212111. Online ahead of print.

### [Azithromycin to Prevent Sepsis or Death in Women Planning a Vaginal Birth](#)

[Alan T N Tita](#)<sup>1</sup>, [Waldemar A Carlo](#)<sup>1</sup>, [Elizabeth M McClure](#)<sup>1</sup>, [Musaku Mwenechanya](#)<sup>1</sup>, [Elwyn Chomba](#)<sup>1</sup>, [Jennifer J Hemingway-Foday](#)<sup>1</sup>, [Avinash Kavi](#)<sup>1</sup>, [Mrityunjay C Metgud](#)<sup>1</sup>, [Shivaprasad S Goudar](#)<sup>1</sup>, [Richard Derman](#)<sup>1</sup>, [Adrien Lokangaka](#)<sup>1</sup>, [Antoinette Tshetu](#)<sup>1</sup>, [Melissa Bauserman](#)<sup>1</sup>, [Carl Bose](#)<sup>1</sup>, [Poonam Shivkumar](#)<sup>1</sup>, [Manju Waikar](#)<sup>1</sup>, [Archana Patel](#)<sup>1</sup>, [Patricia L Hibberd](#)<sup>1</sup>, [Paul Nyongesa](#)<sup>1</sup>, [Fabian Esamai](#)<sup>1</sup>, [Osayame A Ekhuagere](#)<sup>1</sup>, [Sherri Bucher](#)<sup>1</sup>, [Saleem Jessani](#)<sup>1</sup>, [Shiyam S Tikmani](#)<sup>1</sup>, [Sarah Saleem](#)<sup>1</sup>, [Robert L Goldenberg](#)<sup>1</sup>, [Sk M Billah](#)<sup>1</sup>, [Ruth Lennox](#)<sup>1</sup>, [Rashidul Haque](#)<sup>1</sup>, [William Petri](#)<sup>1</sup>, [Lester Figueroa](#)<sup>1</sup>, [Manolo Mazariegos](#)<sup>1</sup>, [Nancy F Krebs](#)<sup>1</sup>, [Janet L Moore](#)<sup>1</sup>, [Tracy L Nolen](#)<sup>1</sup>, [Marion Koso-Thomas](#)<sup>1</sup>; [A-PLUS Trial Group](#)

#### **Abstract**

**Background:** The use of azithromycin reduces maternal infection in women during planned cesarean delivery, but its effect on those with planned vaginal delivery is unknown. Data are needed on whether an intrapartum oral dose of azithromycin would reduce maternal and offspring sepsis or death.

**Methods:** In this multicountry, placebo-controlled, randomized trial, we assigned women who were in labor at 28 weeks' gestation or more and who were planning a vaginal delivery to receive a single 2-g oral dose of azithromycin or placebo. The two primary outcomes were a composite of maternal sepsis or death and a composite of stillbirth or neonatal death or sepsis. During an interim analysis, the data and safety monitoring committee recommended stopping the trial for maternal benefit.

**Results:** A total of 29,278 women underwent randomization. The incidence of maternal sepsis or death was lower in the azithromycin group than in the placebo group (1.6% vs. 2.4%), with a relative risk of 0.67 (95% confidence interval [CI], 0.56 to 0.79; P<0.001), but the incidence of stillbirth or neonatal death or sepsis was similar (10.5% vs. 10.3%), with a relative risk of 1.02 (95% CI, 0.95 to 1.09; P = 0.56). The difference in the maternal primary outcome appeared to be driven mainly by the incidence of sepsis (1.5% in the azithromycin group and 2.3% in the placebo group), with a relative risk of 0.65 (95% CI, 0.55 to 0.77); the incidence of death from any cause was 0.1% in the two groups (relative risk, 1.23; 95% CI, 0.51 to 2.97). Neonatal sepsis occurred in 9.8% and 9.6% of the infants, respectively (relative risk, 1.03; 95% CI, 0.96 to 1.10). The incidence of stillbirth was 0.4% in the two groups (relative risk, 1.06; 95% CI, 0.74 to 1.53); neonatal death within 4 weeks after birth occurred in

Randomised trials in child health in developing countries July 2022 to June 2023

1.5% in both groups (relative risk, 1.03; 95% CI, 0.86 to 1.24). Azithromycin was not associated with a higher incidence in adverse events.

**Conclusions:** Among women planning a vaginal delivery, a single oral dose of azithromycin resulted in a significantly lower risk of maternal sepsis or death than placebo but had little effect on newborn sepsis or death.

World J Pediatr. 2023 Feb;19(2):129-138.

doi: 10.1007/s12519-022-00650-1. Epub 2022 Dec 23.

### [Safety and clinical efficacy of linezolid in children: a systematic review and meta-analysis](#)

[Yi Shi<sup>1,2</sup>](#), [Hai-Lan Wu<sup>3</sup>](#), [Yu-Hang Wu<sup>1</sup>](#), [Shuang Li<sup>1</sup>](#), [Li-Ya Zhang<sup>1</sup>](#), [Shan-Shan Xu<sup>1</sup>](#), [He-Yu Huang<sup>1</sup>](#), [Chun-Hong Zhang<sup>4</sup>](#), [Xu-Ben Yu<sup>4</sup>](#), [Kang Cai<sup>1</sup>](#), [Jing Zhang<sup>5</sup>](#), [Li-Su Huang<sup>6,7</sup>](#)

#### **Abstract**

**Background:** We aimed to evaluate the tolerability and efficacy of linezolid in children for treating suspected and diagnosed Gram-positive bacterial infections.

**Methods:** A systematic literature search was conducted up to April 23, 2021, using linezolid and its synonyms as search terms. Two reviewers independently identified and extracted relevant randomized controlled trials and prospective cohort studies. The extracted studies were included in a single-rate meta-analysis of adverse events and clinical outcomes using random-effects models.

**Results:** A total of 1082 articles were identified, and nine studies involving 758 children were included in the meta-analysis. The overall proportion of adverse events was 8.91% [95% confidence interval (CI) = 1.64%-36.52%], with diarrhea (2.24%), vomiting (2.05%), and rash (1.72%) being the most common. The incidences of thrombocytopenia and anemia were 0.68% and 0.16%, respectively. Some specific adverse events, including rash and gastrointestinal events, were more frequent in the oral administration subgroup. In terms of efficacy, the overall proportion of clinical improvement was 88.80% (95% CI = 81.31%-93.52%). Children with a history of specific bacteriological diagnosis or concomitant antibiotic therapy had a 1.13-fold higher clinical improvement than children without such histories. The proportion of microbial eradication was 92.68% (95% CI = 84.66%-96.68%). The proportion of all-cause mortality was 0.16% (95% CI = 0.00%-7.75%).

**Conclusions:** Linezolid was well-tolerated in pediatric patients and was associated with a low frequency of adverse events, such as anemia, thrombocytopenia, and neutropenia. Moreover, linezolid was effective in children with diagnosed and suspected Gram-positive infections.

## Antibiotic resistance and stewardship

BMC Pediatr. 2022 Sep 21;22(1):556.

doi: 10.1186/s12887-022-03608-4.

### [Impact of educational training and C-reactive protein point-of-care testing on antibiotic prescribing in rural and urban family physician practices in Latvia: a randomised controlled intervention study](#)

[Zane Likopa<sup>1,2</sup>](#), [Anda Kivite-Urtane<sup>3</sup>](#), [Vija Silina<sup>4</sup>](#), [Jana Pavare<sup>5,6</sup>](#)



## Abstract

**Background:** Although self-limiting viral infections are predominant, children with acute infections are often prescribed antibiotics by family physicians. The aim of the study is to evaluate the impact of two interventions, namely C-reactive protein point-of-care testing and educational training, on antibiotic prescribing by family physicians.

**Methods:** This randomised controlled intervention study included acutely ill children consulted by 80 family physicians from urban and rural practices in Latvia. The family physicians were divided into two groups of 40. The family physicians in the intervention group received both interventions, i.e. C-reactive protein point-of-care testing and educational training, whereas the family physicians in the control group continued to dispense their standard care. The primary outcome measure was the antibiotic prescribing at the index consultation (delayed or immediate prescription) in both study groups. The secondary outcome was CRP testing per study group. Patient- and family physician- related predictors of antibiotic prescribing were analysed as associated independent variables. Practice location effect on the outcomes was specially addressed, similar to other scientific literature.

**Results:** In total, 2039 children with acute infections were enrolled in the study. The most common infections observed were upper and lower respiratory tract infections. Overall, 29.8% (n = 607) of the study population received antibiotic prescription. Our binary logistic regression analysis did not find a statistically significant association between antibiotic prescriptions and the implemented interventions. In the control group of family physicians, a rural location was associated with more frequent antibiotic prescribing and minimal use of CRP testing of venous blood samples. However, in the intervention group of family physicians, a rural location was associated with a higher level of C-reactive protein point-of-care testing. Furthermore, in rural areas, a significant reduction in antibiotic prescribing was observed in the intervention group compared with the control group (29.0% (n = 118) and 37.8% (n = 128), respectively, p = 0.01).

**Conclusion:** Our results show that the availability of C-reactive protein point-of-care testing and educational training for family physicians did not reduce antibiotic prescribing. Nevertheless, our data indicate that regional variations in antibiotic-prescribing habits exist and the implemented interventions had an effect on family physicians practices in rural areas.

## Cash transfers and family economic support

J Glob Health. 2023 Apr 14;13:04026.

doi: 10.7189/jogh.13.04026.

### ["If you have light, your heart will be at peace": A qualitative study of household lighting and social integration in southwestern Uganda](#)

[Matthew Ponticiello<sup>1</sup>](#), [Edwin Nuwagira<sup>2</sup>](#), [Mellon Tayebwa<sup>2</sup>](#), [Joseph Mugerwa<sup>2</sup>](#), [Hellen Nahabwe<sup>2</sup>](#), [Catherine Nakasita<sup>2</sup>](#), [John Bosco Tumuhimbise<sup>2</sup>](#), [Nicholas L Lam<sup>3,4</sup>](#), [Matthew O Wiens<sup>5,6</sup>](#), [Jose Vallarino<sup>7</sup>](#), [Joseph G Allen<sup>7</sup>](#), [Daniel Muyanja<sup>2</sup>](#), [Alexander C Tsai<sup>8,9</sup>](#), [Radhika Sundararajan<sup>1,10</sup>](#), [Peggy S Laj<sup>7,8,9</sup>](#)

## Abstract

**Background:** Expanding electrification and access to other clean and affordable energy, such as solar energy, is a critical component of the Sustainable Development Goals, particularly in sub-Saharan Africa where 70% of people are energy insecure. Intervention trials related to access or less polluting household energy alternatives have typically focused on air quality and biological outcomes rather than on how an intervention affects the end user's lived experiences, a key determinant of uptake and adoption outside of a research setting. We explored perceptions of and experiences with a household solar lighting intervention in rural Uganda.

**Methods:** In 2019, we completed a one-year parallel group, randomized wait-list controlled trial of indoor solar lighting systems (ClinicalTrials.gov [NCT03351504](https://clinicaltrials.gov/ct2/show/study/NCT03351504)) in rural Uganda where participants are largely relying on kerosene and other fuel-based lighting received household indoor solar lighting systems. In this qualitative sub-study, we conducted one-on-one, in-depth qualitative interviews with all 80 female participants enrolled in the trial. Interviews explored how solar lighting and illumination impacted participants' lives. We applied a theoretical model linking social integration and health to analyse dynamic interactions across aspects of study participants' lived experiences. Sensors were used to measure daily lighting use before and after receipt of the intervention solar lighting system.

**Results:** Introduction of the solar lighting system increased daily household lighting use by 6.02 (95% confidence intervals (CI) = 4.05-8.00) hours a day. The solar lighting intervention had far-reaching social implications with improved social integration and, consequently, social health. Participants felt that lighting improved their social status, mitigated the stigma of poverty, and increased the duration and frequency of social interactions. Household relationships improved with access to lighting because of reduced conflicts over light rationing. Participants also described a communal benefit of lighting due to improved feelings of safety. At the individual-level, many reported improved self-esteem, sense of well-being, and reduced stress.

**Conclusion:** Improved access to lighting and illumination had far reaching implications for participants, including improved social integration. More empirical research, particularly in the light and household energy field, is needed that emphasizes the impacts of interventions on social health.

Econ Educ Rev. 2023 Aug;95:102429.

doi: 10.1016/j.econedurev.2023.102429. Epub 2023 Jun 14.

**[Effects of a single cash transfer on school re-enrollment during COVID-19 among vulnerable adolescent girls in Kenya: Randomized controlled trial](#)**

[John A Maluccio](#)<sup>1</sup>, [Erica Soler-Hampejsek](#)<sup>2</sup>, [Beth Kangwana](#)<sup>3</sup>, [Eva Muluve](#)<sup>3</sup>, [Faith Mbushi](#)<sup>3</sup>, [Karen Austrian](#)<sup>3</sup>

**Abstract**

COVID-19 related school closures in Kenya were among the longest in Africa, putting older adolescent girls nearing the end of secondary school at risk of permanent dropout. Using a randomized-controlled trial we evaluated a logistically simple cash transfer intervention in urban areas designed to promote their return to school. There were no required conditions for receiving the transfer and the intervention is interpreted as a labeled cash transfer. It had substantial significant effects on re-enrollment of adolescent girls, with greater effectiveness for older girls and even for some not enrolled earlier in the school year. The program effectiveness demonstrates feasibility of the approach and underscores the potential

importance of additional resources for schooling during the pandemic, when a large majority of households had suffered income losses.

## Community child health

\*\*\* BMJ Glob Health. 2022 Jul;7(7):e008909.

doi: 10.1136/bmjgh-2022-008909.

### [Effect of home-based childcare on childhood mortality in rural Maharashtra, India: a cluster randomised controlled trial](#)

[Ashish Rambhau Satav<sup>1,2</sup>](#), [Kavita Ashish Satav<sup>3</sup>](#), [Abhijeet Bharadwaj<sup>4</sup>](#), [Jayashree Pendharkar<sup>5</sup>](#), [Vibhawari Dani<sup>4</sup>](#), [Suresh Ughade<sup>6</sup>](#), [Dhananjay Raje<sup>7</sup>](#), [Eric A F Simões<sup>8</sup>](#)

#### Abstract

**Background:** Melghat, an impoverished rural area in Maharashtra state, India; has scarce hospital services and low health-seeking behaviour. At baseline (2004) the under-five mortality rate (U5MR) (number of deaths in children aged 0-5 years/1000 live births) was 147.21 and infant mortality rate (IMR) (number of deaths of infants aged under 1 year/1000 live births) was 106.6 per 1000 live births. We aimed at reducing mortality rates through home-based child care (HBCC) using village health workers (VHWs).

**Methods:** A cluster-randomised control trial was conducted in 34 randomly assigned clusters/villages of Melghat, Maharashtra state, between 2004 and 2009. Participants included all under-five children and their parents. Interventions delivered through VHWs were patient-public involvement, newborn care, disease management and behaviour change communications. Primary outcome indicators were U5MR and IMR. Secondary outcome indicators were neonatal mortality rate (NMR) (number of neonatal deaths aged 0-28 days/1000 live births) and perinatal mortality rate (PMR) (number of stillbirths and early neonatal deaths/1000 total births). Analysis was by intention-to-treat at the individual level. This trial was extended to a service phase (2010-2015) in both arms and a government replication phase (2016-2019) only for the intervention clusters/areas (IA).

**Findings:** There were 18 control areas/clusters (CA) allocated and analysed with 4426 individuals, and 16 of 18 allocated IA, analysed with 3230 individuals. The IMR and U5MR in IA were reduced from 106.60 and 147.21 to 32.75 and 50.38 (reduction by 69.28% and 65.78%, respectively) compared with increases in CA from 67.67 and 105.3 to 86.83 and 122.8, respectively, from baseline to end of intervention. NMR and PMR in IA showed reductions from 50.76 to 22.67 (by 55.34%) and from 75.06 to 24.94 (by 66.77%) respectively. These gains extended to villages in the service and replication phases.

**Interpretation:** This socio-culturally contextualised model for HBCC through VHWs backed up with institutional support is effective for significant reduction of U5MR, IMR and NMR in impoverished rural areas. This reduction was maintained in the study area during the service phase, indicating feasibility of implementation in large-scale public health programmes. Replicability of the model was demonstrated by a linear decline in all the mortality rates in 20 new villages during the government phase.

PLoS Med. 2023 Apr 14;20(4):e1004222.

doi: 10.1371/journal.pmed.1004222. Online ahead of print.

**Evaluation of a community health worker home visit intervention to improve child development in South Africa: A cluster-randomized controlled trial**

Peter C Rockers<sup>1</sup>, Jukka M Leppänen<sup>2</sup>, Amanda Tarullo<sup>3</sup>, Lezanie Coetzee<sup>4</sup>, Günther Fink<sup>5,6</sup>, Davidson H Hamer<sup>1,7</sup>, Aisha K Yousafzai<sup>8</sup>, Denise Evans<sup>4</sup>

**Abstract**

**Background:** Effective integration of home visit interventions focused on early childhood development into existing service platforms is important for expanding access in low- and middle-income countries (LMICs). We designed and evaluated a home visit intervention integrated into community health worker (CHW) operations in South Africa.

**Methods and findings:** We conducted a cluster-randomized controlled trial in Limpopo Province, South Africa. CHWs operating in ward-based outreach teams (WBOTs; clusters) and caregiver-child dyads they served were randomized to the intervention or control group. Group assignment was masked from all data collectors. Dyads were eligible if they resided within a participating CHW catchment area, the caregiver was at least 18 years old, and the child was born after December 15, 2017. Intervention CHWs were trained on a job aid that included content on child health, nutrition, developmental milestones, and encouragement to engage in developmentally appropriate play-based activities, for use during regular monthly home visits with caregivers of children under 2 years of age. Control CHWs provided the local standard of care. Household surveys were administered to the full study sample at baseline and endline. Data were collected on household demographics and assets; caregiver engagement; and child diet, anthropometry, and development scores. In a subsample of children, electroencephalography (EEG) and eye-tracking measures of neural function were assessed at a lab concurrent with endline and at 2 interim time points. Primary outcomes were as follows: height-for-age z-scores (HAZs) and stunting; child development scores measured using the Malawi Developmental Assessment Tool (MDAT); EEG absolute gamma and total power; relative EEG gamma power; and saccadic reaction time (SRT)-an eye-tracking measure of visual processing speed. In the main analysis, unadjusted and adjusted impacts were estimated using intention-to-treat analysis. Adjusted models included a set of demographic covariates measured at baseline. On September 1, 2017, we randomly assigned 51 clusters to intervention (26 clusters, 607 caregiver-child dyads) or control (25 clusters, 488 caregiver-child dyads). At endline (last assessment June 11, 2021), 432 dyads (71%) in 26 clusters remained in the intervention group, and 332 dyads (68%) in 25 clusters remained in the control group. In total, 316 dyads attended the first lab visit, 316 dyads the second lab visit, and 284 dyads the third lab visit. In adjusted models, the intervention had no significant impact on HAZ (adjusted mean difference (aMD) 0.11 [95% confidence interval (CI): -0.07, 0.30];  $p = 0.220$ ) or stunting (adjusted odds ratio (aOR) 0.63 [0.32, 1.25];  $p = 0.184$ ), nor did the intervention significantly impact gross motor skills (aMD 0.04 [-0.15, 0.24];  $p = 0.656$ ), fine motor skills (aMD -0.04 [-0.19, 0.11];  $p = 0.610$ ), language skills (aMD -0.02 [-0.18, 0.14];  $p = 0.820$ ), or social-emotional skills (aMD -0.02 [-0.20, 0.16];  $p = 0.816$ ). In the lab subsample, the intervention had a significant impact on SRT (aMD -7.13 [-12.69, -1.58];  $p = 0.012$ ), absolute EEG gamma power (aMD -0.14 [-0.24, -0.04];  $p = 0.005$ ), and total EEG power (aMD -0.15 [-0.23, -0.08];  $p < 0.001$ ), and no significant impact on relative gamma power (aMD 0.02 [-0.78, 0.83];  $p = 0.959$ ). While the effect on SRT was observed at the first 2 lab visits, it was no longer present at the third visit, which coincided with the overall endline assessment. At the end of the first year of the intervention period, 43% of CHWs adhered to monthly home visits. Due to

the COVID-19 pandemic, we were not able to assess outcomes until 1 year after the end of the intervention period.

**Conclusions:** While the home visit intervention did not significantly impact linear growth or skills, we found significant improvement in SRT. This study contributes to a growing literature documenting the positive effects of home visit interventions on child development in LMICs. This study also demonstrates the feasibility of collecting markers of neural function like EEG power and SRT in low-resource settings.

PLoS Med. 2023 Mar 2;20(3):e1004170.

doi: 10.1371/journal.pmed.1004170. eCollection 2023 Mar.

**[The effect of supervision on community health workers' effectiveness with households in rural South Africa: A cluster randomized controlled trial](#)**

[Mary Jane Rotheram-Borus](#)<sup>1</sup>, [Karl W le Roux](#)<sup>2,3,4,5</sup>, [Peter Norwood](#)<sup>1</sup>, [Linnea Stansert Katzen](#)<sup>2</sup>, [Andre Snyman](#)<sup>5</sup>, [Ingrid le Roux](#)<sup>6</sup>, [Elaine Dippenaar](#)<sup>5</sup>, [Mark Tomlinson](#)<sup>2,7</sup>

**Abstract**

**Background:** Community health workers (CHWs) can supplement professional medical providers, especially in rural settings where resources are particularly scarce. Yet, outcomes of studies evaluating CHWs effectiveness have been highly variable and lack impact when scaled nationally. This study examines if child and maternal outcomes are better when existing government CHWs, who are perinatal home visitors, receive ongoing enhanced supervision and monitoring, compared to standard care.

**Methods and findings:** A cluster randomized controlled effectiveness trial was conducted comparing outcomes over 2 years when different supervision and support are provided. Primary health clinics were randomized by clinic to receive monitoring and supervision from either (1) existing supervisors (Standard Care (SC); n = 4 clinics, 23 CHWs, 392 mothers); or (2) supervisors from a nongovernmental organization that provided enhanced monitoring and supervision (Accountable Care [AC]; n = 4 clinic areas, 20 CHWs, 423 mothers). Assessments were conducted during pregnancy and at 3, 6, 15, and 24 months post-birth with high retention rates (76% to 86%). The primary outcome was the number of statistically significant intervention effects among 13 outcomes of interest; this approach allowed us to evaluate the intervention holistically while accounting for correlation among the 13 outcomes and considering multiple comparisons. The observed benefits were not statistically significant and did not show the AC's efficacy over the SC. Only the antiretroviral (ARV) adherence effect met the significance threshold established a priori (SC mean 2.3, AC mean 2.9, p < 0.025; 95% CI = [0.157, 1.576]). However, for 11 of the 13 outcomes, we observed an improvement in the AC compared to the SC. While the observed outcomes were not statistically significant, benefits were observed for 4 outcomes: increasing breastfeeding for 6 months, reducing malnutrition, increasing ARV adherence, and improving developmental milestones. The major study limitation was utilizing existing CHWs and being limited to a sample of 8 clinics. There were no major study-related adverse events.

**Conclusions:** Supervision and monitoring were insufficient to improve CHWs' impact on maternal and child outcomes. Alternative strategies for staff recruitment and narrowing the intervention outcomes to the specific local community problems are needed for consistently high impact.



PLOS Digit Health. 2023 Jun 12;2(6):e0000217.

doi: 10.1371/journal.pdig.0000217. eCollection 2023 Jun.

**[Improving community health worker treatment for malaria, diarrhoea, and pneumonia in Uganda through inSCALE community and mHealth innovations: A cluster randomised controlled trial](#)**

[Karin Källander](#)<sup>1,2,3</sup>, [Seyi Soremekun](#)<sup>4</sup>, [Daniel LI Strachan](#)<sup>5,6</sup>, [Zelee Hill](#)<sup>5</sup>, [Frida Kasteng](#)<sup>2,7</sup>, [Edmound Kertho](#)<sup>8</sup>, [Agnes Nanyonjo](#)<sup>2,8</sup>, [Guus Ten Asbroek](#)<sup>9</sup>, [Maureen Nakirunda](#)<sup>8</sup>, [Patrick Lumumba](#)<sup>8</sup>, [Godfrey Ayebale](#)<sup>8</sup>, [Benson Bagorogoza](#)<sup>8</sup>, [Anna Vassall](#)<sup>7</sup>, [Sylvia Meek](#)<sup>1</sup>, [James Tibenderana](#)<sup>1</sup>, [Raghu Lingam](#)<sup>10,11</sup>, [Betty Kirkwood](#)<sup>10</sup>

**Abstract**

The inSCALE cluster randomised controlled trial in Uganda evaluated two interventions, mHealth and Village Health Clubs (VHCs) which aimed to improve Community Health Worker (CHW) treatment for malaria, diarrhoea, and pneumonia within the national Integrated Community Case Management (iCCM) programme. The interventions were compared with standard care in a control arm. In a cluster randomised trial, 39 sub-counties in Midwest Uganda, covering 3167 CHWs, were randomly allocated to mHealth; VHC or usual care (control) arms. Household surveys captured parent-reported child illness, care seeking and treatment practices. Intention-to-treat analysis estimated the proportion of appropriately treated children with malaria, diarrhoea, and pneumonia according to WHO informed national guidelines. The trial was registered at ClinicalTrials.gov ([NCT01972321](#)). Between April-June 2014, 7679 households were surveyed; 2806 children were found with malaria, diarrhoea, or pneumonia symptoms in the last one month. Appropriate treatment was 11% higher in the mHealth compared to the control arm (risk ratio [RR] 1.11, 95% CI 1.02, 1.21;  $p = 0.018$ ). The largest effect was on appropriate treatment for diarrhoea (RR 1.39; 95% CI 0.90, 2.15;  $p = 0.134$ ). The VHC intervention increased appropriate treatment by 9% (RR 1.09; 95% CI 1.01, 1.18;  $p = 0.059$ ), again with largest effect on treatment of diarrhoea (RR 1.56, 95% CI 1.04, 2.34,  $p = 0.030$ ). CHWs provided the highest levels of appropriate treatment compared to other providers. However, improvements in appropriate treatment were observed at health facilities and pharmacies, with CHW appropriate treatment the same across the arms. The rate of CHW attrition in both intervention arms was less than half that of the control arm; adjusted risk difference mHealth arm -4.42% (95% CI -8.54, -0.29,  $p = 0.037$ ) and VHC arm -4.75% (95% CI -8.74, -0.76,  $p = 0.021$ ). Appropriate treatment by CHWs was encouragingly high across arms. The inSCALE mHealth and VHC interventions have the potential to reduce CHW attrition and improve the care quality for sick children, but not through improved CHW management as we had hypothesised.

PLOS Digit Health. 2023 Jun 12;2(6):e0000235.

doi: 10.1371/journal.pdig.0000235. eCollection 2023 Jun.

**[Improving outcomes for children with malaria, diarrhoea and pneumonia in Mozambique: A cluster randomised controlled trial of the inSCALE technology innovation](#)**

[Seyi Soremekun](#)<sup>1</sup>, [Karin Källander](#)<sup>2,3,4</sup>, [Raghu Lingam](#)<sup>5</sup>, [Ana-Cristina Castel Branco](#)<sup>6</sup>, [Neha Batura](#)<sup>7</sup>, [Daniel LI Strachan](#)<sup>8</sup>, [Abel Muiambo](#)<sup>6</sup>, [Nelson Salomao](#)<sup>6</sup>, [Juliao Condoane](#)<sup>6</sup>, [Fenias Benhane](#)<sup>6</sup>, [Frida Kasteng](#)<sup>3</sup>, [Anna Vassall](#)<sup>9</sup>, [Zelee Hill](#)<sup>7</sup>, [Guus Ten Asbroek](#)<sup>10</sup>, [Sylvia Meek](#)<sup>2</sup>, [James Tibenderana](#)<sup>2</sup>, [Betty Kirkwood](#)<sup>11</sup>

## Abstract

**Background:** The majority of post-neonatal deaths in children under 5 are due to malaria, diarrhoea and pneumonia (MDP). The WHO recommends integrated community case management (iCCM) of these conditions using community-based health workers (CHW). However iCCM programmes have suffered from poor implementation and mixed outcomes. We designed and evaluated a technology-based (mHealth) intervention package 'inSCALE' (Innovations At Scale For Community Access and Lasting Effects) to support iCCM programmes and increase appropriate treatment coverage for children with MDP.

**Methods:** This superiority cluster randomised controlled trial allocated all 12 districts in Inhambane Province in Mozambique to receive iCCM only (control) or iCCM plus the inSCALE technology intervention. Population cross-sectional surveys were conducted at baseline and after 18 months of intervention implementation in approximately 500 eligible households in randomly selected communities in all districts including at least one child less than 60 months of age where the main caregiver was available to assess the impact of the intervention on the primary outcome, the coverage of appropriate treatment for malaria, diarrhoea and pneumonia in children 2-59 months of age. Secondary outcomes included the proportion of sick children who were taken to the CHW for treatment, validated tool-based CHW motivation and performance scores, prevalence of cases of illness, and a range of secondary household and health worker level outcomes. All statistical models accounted for the clustered study design and variables used to constrain the randomisation. A meta-analysis of the estimated pooled impact of the technology intervention was conducted including results from a sister trial (inSCALE-Uganda).

**Findings:** The study included 2740 eligible children in control arm districts and 2863 children in intervention districts. After 18 months of intervention implementation 68% (69/101) CHWs still had a working inSCALE smartphone and app and 45% (44/101) had uploaded at least one report to their supervising health facility in the last 4 weeks. Coverage of the appropriate treatment of cases of MDP increased by 26% in the intervention arm (adjusted RR 1.26 95% CI 1.12-1.42,  $p < 0.001$ ). The rate of care seeking to the iCCM-trained community health worker increased in the intervention arm (14.4% vs 15.9% in control and intervention arms respectively) but fell short of the significance threshold (adjusted RR 1.63, 95% CI 0.93-2.85,  $p = 0.085$ ). The prevalence of cases of MDP was 53.5% (1467) and 43.7% (1251) in the control and intervention arms respectively (risk ratio 0.82, 95% CI 0.78-0.87,  $p < 0.001$ ). CHW motivation and knowledge scores did not differ between intervention arms. Across two country trials, the estimated pooled effect of the inSCALE intervention on coverage of appropriate treatment for MDP was RR 1.15 (95% CI 1.08-1.24,  $p < 0.001$ ).

**Interpretation:** The inSCALE intervention led to an improvement in appropriate treatment of common childhood illnesses when delivered at scale in Mozambique. The programme will be rolled out by the ministry of health to the entire national CHW and primary care network in 2022-2023. This study highlights the potential value of a technology intervention aimed at strengthening iCCM systems to address the largest causes of childhood morbidity and mortality in sub-Saharan Africa

Glob Health Action. 2023 Dec 31;16(1):2203541.

doi: 10.1080/16549716.2023.2203541.

[Trial-based economic evaluation of the system-integrated activation of community health volunteers in rural Ghana](#)



[Yinseo Cho](#)<sup>1</sup>, [Koku Awoonor-Williams](#)<sup>2</sup>, [Damin Jun](#)<sup>3</sup>, [Chunghyeon Oh](#)<sup>4,5</sup>, [Seungman Cha](#)<sup>6,7</sup>

## Abstract

**Background:** Globally, steps to revitalise programmes deploying community health workers (CHWs) on a national scale have been growing, but few economic evaluations have been done on system-integrated CHW programmes. Ghana has dual cadres of CHWs: community health officers (CHOs) and community health volunteers (CHVs). CHO plays a major role in primary health services but has suffered from chronic staff shortages. We activated CHVs in communities to mitigate the negative impact due to CHO shortages. The CHVs conducted home visits and provided health education to prevent childhood diseases.

**Objective:** We evaluated the cost-effectiveness and cost-benefit of activating CHVs.

**Methods:** In a cluster-randomised trial with 40 communities in rural Ghana, the changes in disease incidence were inferred from a statistical model using a Bayesian generalised linear multilevel model. We evaluated the total incremental cost, benefit, and effectiveness for the intervention from an economic model. In cost-effectiveness analysis, disability-adjusted life years (DALYs) were estimated using a decision tree model. In the cost-benefit analysis, the cost-benefit ratio and net present value of benefit were estimated using a decision tree model, and a standardised sensitivity analysis was conducted. The decision tree model was a one-year cycle and run over 10-years. Costs, benefits, and effectiveness were discounted at a rate of 3% per year.

**Results:** According to the cost-effectiveness analysis, the programme was highly likely to exceed the WHO-CHOICE threshold (1-3 times GDP per capita), but it was unlikely to exceed the conservative threshold (10-50% of GDP per capita). In the cost-benefit analysis, the mean and median cost-benefit ratios were 6.4 and 4.8, respectively.

**Conclusion:** We found the potential economic strengths in the cost-benefit analysis. To integrate CHW programmes with national health systems, we need more research to find the most effective scope of work for CHWs.

## Child development and parenting programs

Lancet Child Adolesc Health. 2023 May;7(5):311-325.

doi: 10.1016/S2352-4642(23)00032-9. Epub 2023 Mar 31.

[\*\*Structured, multicomponent, community-based programme for women's health and infant health and development in rural Vietnam: a parallel-group cluster randomised controlled trial\*\*](#)

[Jane Fisher](#)<sup>1</sup>, [Thach Tran](#)<sup>2</sup>, [Ha Tran](#)<sup>3</sup>, [Stanley Luchters](#)<sup>4</sup>, [David B Hipgrave](#)<sup>5</sup>, [Hau Nguyen](#)<sup>2</sup>, [Thuy Tran](#)<sup>3</sup>, [Sarah Hanieh](#)<sup>6</sup>, [Julie Anne Simpson](#)<sup>6</sup>, [Beverley-Ann Biggs](#)<sup>7</sup>, [Tuan Tran](#)<sup>3</sup>

## Abstract

**Background:** Interventions to improve early childhood development have previously addressed only one or a few risk factors. Learning Clubs is a structured, facilitated, multicomponent programme designed to address eight potentially modifiable risk factors, and offered from mid-pregnancy to 12 months post partum; we aimed to establish whether this programme could improve the cognitive development of children at 2 years of age.

**Methods:** For this parallel-group cluster-randomised controlled trial, 84 of 116 communes (the clustering unit) in HaNam Province in rural Vietnam were randomly selected and randomly assigned to receive the Learning Clubs intervention (n=42) or usual care (n=42). Women aged at least 18 years who were pregnant (gestational age <20 weeks) were eligible for inclusion. Data sources were standardised, and study-specific questionnaires assessing risks and outcomes were completed in interviews in mid-pregnancy (baseline), late pregnancy (after 32 weeks of gestation), at 6-12 months post partum, and at the end of the study period when children were 2 years of age. Mixed-effects models were used to estimate trial effects, adjusting for clustering. The primary outcome was the cognitive development of children at 2 years of age, assessed by the Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III) cognitive score. This trial is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617000442303).

**Findings:** Between April 28, 2018, and May 30, 2018, 1380 women were screened and 1245 were randomly assigned (669 to the intervention group and 576 to the control group). Data collection was completed on Jan 17, 2021. Data at the end of the study period were contributed by 616 (92%) of 669 women and their children in the intervention group, and by 544 (94%) of 576 women and their children in the control group. Children aged 2 years in the intervention group had significantly higher mean Bayley-III cognitive scores than those in the control group (99.6 [SD 9.7] vs 95.6 [9.4]; mean difference 4.00 [95% CI 2.56-5.43]; p<0.0001). At 2 years of age, 19 (3%) children in the intervention group had Bayley-III scores less than 1 SD, compared with 32 (6%) children in the control group, but this difference was not significant (odds ratio 0.55 [95% CI 0.26-1.17]; p=0.12). There were no significant differences between groups in maternal, fetal, newborn, or child deaths.

**Interpretation:** A facilitated, structured, community-based, multicomponent group programme improved early childhood development to the standardised mean in rural Vietnam and could be implemented in other similarly resource-constrained settings.

BMC Public Health. 2022 Sep 10;22(1):1721.

doi: 10.1186/s12889-022-13776-8.

### [Feeding, caregiving practices, and developmental delay among children under five in lowland Nepal: a community-based cross-sectional survey](#)

[Sophiya Dulal](#)<sup>1</sup>, [Audrey Prost](#)<sup>2</sup>, [Surendra Karki](#)<sup>3,4</sup>, [Dafna Merom](#)<sup>5</sup>, [Bhim Prasad Shrestha](#)<sup>6</sup>, [Bishnu Bhandari](#)<sup>6</sup>, [Dharma S Manandhar](#)<sup>6</sup>, [David Osrin](#)<sup>2</sup>, [Anthony Costello](#)<sup>2</sup>, [Naomi M Saville](#)<sup>2</sup>

#### **Abstract**

**Background:** Nurturing care, including adequate nutrition, responsive caregiving and early learning, is critical to early childhood development. In Nepal, national surveys highlight inequity in feeding and caregiving practices for young children. Our objective was to describe infant and young child feeding (IYCF) and cognitive and socio-emotional caregiving practices among caregivers of children under five in Dhanusha district, Nepal, and to explore socio-demographic and economic factors associated with these practices.

**Methods:** We did a cross-sectional analysis of a subset of data from the MIRA Dhanusha cluster randomised controlled trial, including mother-child dyads (N = 1360), sampled when children were median age 46 days and a follow-up survey of the same mother-child dyads (N = 1352) when children were median age 38 months. We used World Health Organization IYCF

indicators and questions from the Multiple Indicator Cluster Survey-4 tool to obtain information on IYCF and cognitive and socio-emotional caregiving practices. Using multivariable logistic regression models, potential explanatory household, parental and child-level variables were tested to determine their independent associations with IYCF and caregiving indicators.

**Results:** The prevalence of feeding indicators varied. IYCF indicators, including ever breastfed (99%), exclusive breastfeeding (24-hour recall) (89%), and vegetable/fruit consumption (69%) were common. Problem areas were early initiation of breastfeeding (16%), colostrum feeding (67%), no pre-lacteal feeding (53%), timely introduction of complementary feeding (56%), minimum dietary diversity (49%) and animal-source food consumption (23%). Amongst caregiving indicators, access to 3+ children's books (7%), early stimulation and responsive caregiving (11%), and participation in early childhood education (27%) were of particular concern, while 64% had access to 2+ toys and 71% received adequate care. According to the Early Child Development Index score, only 38% of children were developmentally on track. Younger children from poor households, whose mothers were young, had not received antenatal visits and delivered at home were at higher risk of poor IYCF and caregiving practices.

**Conclusions:** Suboptimal caregiving practices, inappropriate early breastfeeding practices, delayed introduction of complementary foods, inadequate dietary diversity and low animal-source food consumption are challenges in lowland Nepal. We call for urgent integrated nutrition and caregiving interventions, especially as interventions for child development are lacking in Nepal.

J Dev Behav Pediatr. 2022 Dec 1;43(9):e590-e597.

doi: 10.1097/DBP.0000000000001118. Epub 2022 Sep 13.

**[Supporting Reading Aloud Beginning Prenatally and in Early Infancy: A Randomized Trial in Brazil](#)**

[Luciane R Piccolo<sup>1</sup>](#), [João Batista Araujo Oliveira<sup>2</sup>](#), [Guilherme Hirata<sup>3</sup>](#), [Walfrido Duarte Neto<sup>2</sup>](#), [Alan L Mendelsohn<sup>1</sup>](#)

**Abstract**

**Objective:** A previous study of a reading aloud intervention in Brazil, called Universidade do Bebê (UBB), demonstrated impacts on parenting and child outcomes for families with toddlers and preschoolers, even for parents with low literacy, and cognitive stimulation mediated effects on child outcomes. In a new study, we sought to determine whether similar results would be found when UBB was provided beginning in pregnancy through early toddlerhood, including (1) impacts on parenting and child development, (2) variation in impact on parenting and child outcomes by parent literacy level, and (3) indirect impacts on child outcomes through cognitive stimulation.

**Method:** Women with low income who were either pregnant or with children aged 0 to 24 months were randomized to UBB or control groups. UBB consisted of monthly workshops focused on reading aloud complemented by a book-lending library. Participants were evaluated at baseline and approximately 11 months later (M = 11.0, SD = 0.4; range 9.9-12.2 months) on parenting (cognitive stimulation, beliefs about early reading, screen time, and discipline) and child development.

**Results:** Four hundred families (n = 200 UBB) were randomized; 286 (71.5%; n = 150 UBB) received 11-month follow-up. UBB families showed increased cognitive stimulation (Cohen's  $d = 0.92$ ) and awareness about the importance of early reading ( $d = 0.90$ ) than controls, with no differences by parent literacy level. UBB was associated with reduced screen time and increased vocabulary, but only for families with low parent literacy. UBB effects on child outcomes were mediated by cognitive stimulation.

**Conclusion:** The findings support implementation of reading aloud programs beginning in pregnancy and early childhood.

Pediatrics. 2023 May 1;151(Suppl 2):e2023060221J.

doi: 10.1542/peds.2023-060221J.

### [Implementation Quality of an Early Childhood Parenting Program in Colombia and Child Development](#)

[Raquel Bernal<sup>1</sup>](#), [María Lucía Gómez<sup>2</sup>](#), [Santiago Pérez-Cardona<sup>1</sup>](#), [Helen Baker-Henningham<sup>2</sup>](#)

#### **Abstract**

**Objectives:** We conducted a cluster-randomized trial of an enhancement to an existing parenting program in rural Colombia (called the Family, Women, and Infancy Program [FAMI]), and found benefits to parenting practices and child development. In this study, we examine the effects of the enhancement on the quality of intervention implementation and examine associations between quality and child and maternal outcomes.

**Methods:** In Colombia, 340 FAMI mothers in 87 towns were randomly assigned to quality enhancement through the provision of structured curricula, play materials, and training and supervision from professional tutors, or to control (no enhancement). Children aged <12 months were enrolled (N = 1460). A subsample of 150 FAMI mothers (83 intervention, 67 control) in 29 towns (17 intervention, 12 control) participated in the assessment of the quality of group parenting sessions through independent observation. Child development and parenting practices were measured at endline (10.5 months after baseline).

**Results:** In intention-to-treat analyses, we found significant benefits of intervention for the observed quality of group sessions (1.67 SD [95% confidence interval, 1.23-2.11]). An SD increase in session quality predicted an increase in treatment mothers' attendance of 4.68 sessions (95% confidence interval, 1.37-7.98). Session quality partially mediated the effect of the intervention on parental practices and child development.

**Conclusions:** Enhancing an existing parenting program led to large benefits to the observed quality of intervention implementation. Quality was associated with increased maternal engagement, parenting practices, and child development. The observational measure of quality has potential to promote and maintain quality at scale.

Child Care Health Dev. 2023 Jul;49(4):750-759.

doi: 10.1111/cch.13089. Epub 2022 Dec 20.

### [Scaling-up an early childhood parenting intervention by integrating into government health care services in rural Bangladesh: A cluster-randomised controlled trial](#)

[Syeda Fardina Mehrin<sup>1</sup>](#), [Nur-E Salveen<sup>1</sup>](#), [Masuma Kawsir<sup>1</sup>](#), [Sally Grantham-McGregor<sup>2</sup>](#), [Jena D Hamadani<sup>1</sup>](#), [Helen Baker-Henningham<sup>3</sup>](#)

#### **Abstract**

**Aims:** We evaluated the feasibility and effectiveness of utilising government health supervisors to train and supervise primary health care workers (HWs) in community clinics to deliver parenting sessions as part of their usual duties.

**Methods:** We randomly allocated 16 unions in the Mymensing district of Bangladesh 1:1 to an intervention or control group. HWs in clinics in the eight intervention unions (n = 59 health workers, n = 24 clinics) were trained to deliver a group-based parenting intervention, with training and supervision provided by government supervisors. In each of the 24 intervention clinics, we recruited 24 mothers of children aged 6-24 months to participate in the parenting sessions (n = 576 mother/child dyads). Mother/child dyads attended fortnightly parenting sessions at the clinic in groups of four to five participants for 6 months (13 sessions). We collected data on supervisor and HW compliance in implementing the intervention, mothers' attendance and the observed quality of parenting sessions in all intervention clinics and HW burnout at endline in all clinics. We randomly selected 32 clinics (16 intervention, 16 control) and 384 mothers (192 intervention, 192 control) to participate in the evaluation on mother-reported home stimulation, measured at baseline and endline.

**Results:** Supervisors and HWs attended all training, 46/59 health workers (78%) conducted the majority of parenting sessions, (only two HWs [3.4%] refused) and mothers' attendance rate was 86%. However, supervision levels were low: only 32/57 (56.1%) of HWs received at least one supervisory visit. Intervention HWs delivered the parenting sessions with acceptable levels of quality on most items. The intervention significantly benefitted home stimulation (effect size = 0.53SD, 95% confidence interval: 0.50, 0.56, p < 0.001). HW burnout was low in both groups.

**Conclusion:** Integration into the primary health care service is a promising approach for scaling early childhood development programmes in Bangladesh, although further research is required to identify feasible methods for facilitator supervision.

Pediatrics. 2023 May 1;151(Suppl 2):e2023060221D.

doi: 10.1542/peds.2023-060221D.

### **[The Reach Up Parenting Program, Child Development, and Maternal Depression: A Meta-analysis](#)**

[Pamela Jervis](#)<sup>1,2</sup>, [Jacqueline Coore-Hall](#)<sup>3</sup>, [Helen O Pitchik](#)<sup>4</sup>, [Charles D Arnold](#)<sup>5</sup>, [Sally Grantham-McGregor](#)<sup>6</sup>, [Marta Rubio-Codina](#)<sup>7</sup>, [Helen Baker-Henningham](#)<sup>3,8</sup>, [Lia C H Fernald](#)<sup>4</sup>, [Jena Hamadani](#)<sup>9</sup>, [Joanne A Smith](#)<sup>3</sup>, [Julieta Trias](#)<sup>10</sup>, [Susan P Walker](#)<sup>3</sup>

#### **Abstract**

**Background and objectives:** Evidence is needed on effective approaches to build parents' ability to promote child development feasible in low- and middle-income countries. Our objective was to synthesize impact of the Reach Up early childhood parenting program in several low- and middle-income countries and examine moderation by family and implementation characteristics.

**Methods:** Systematic search using PubMed and Academic Search Elite/EBSCO Host. Randomized controlled trials of the Reach Up program from 1985 to February 2022 were selected. Data were extracted by 2 independent researchers. Primary outcomes were child cognitive, language, and motor development. Secondary outcomes were home stimulation and maternal depressive symptoms. We synthesized pooled effect sizes using random effect

inverse-variance weighting and effect modification by testing pooled subgroup effect estimates using the  $\chi^2$  test for heterogeneity.

**Results:** Average effect size across 18 studies ranged from 0.49 (95% confidence interval [CI] 0.32 to 0.66) for cognition, 0.38 (CI 0.24 to 0.51) for language, 0.27 (CI 0.13 to 0.40) for motor development, 0.37 (CI 0.21 to 0.54) for home stimulation, and -0.09 (CI -0.19 to 0.01) for maternal depressive symptoms. Impacts were larger in studies targeted to undernourished children, with mean enrollment older than age 12 months and intervention duration 6 to 12 months. Quality of evidence assessed with the Cochrane Assessment of Risk of Bias and GRADE system was moderate. Instruments used to assess child development varied. In moderator analyses, some subgroups included few studies.

**Conclusions:** Reach Up benefits child development and home stimulation and is adaptable across cultures and delivery methods. Child and implementation characteristics modified the effects, with implications for scaling.

Pediatrics. 2023 May 1;151(Suppl 2):e2023060221E.

doi: 10.1542/peds.2023-060221E.

### [Six-Year Follow-up of Childhood Stimulation on Development of Children With and Without Anemia](#)

[Sheikh Jamal Hossain<sup>1,2</sup>](#), [Fahmida Tofail<sup>3</sup>](#), [Syeda Fardina Mehrin<sup>1</sup>](#), [Jena D Hamadani<sup>1</sup>](#)

#### **Abstract**

**Background and objectives:** Previously, in 30 Bangladeshi villages, 2 groups of children with iron-deficiency anemia (IDA) and nonanemic (NA) iron sufficiency aged 6 to 24 months participated in 2 parallel cluster randomized controlled trials of the effect of psychosocial stimulation on neurodevelopment. The intervention was composed of weekly play sessions at home for 9 months. All children with anemia received iron treatment of 6 months. The intervention improved the mental development of NA but not IDA groups. Six years after end line when the children were aged 8 to 9 years, we aimed to determine if benefits were sustained in the NA group or late-onset benefits emerged in the IDA group.

**Methods:** We relocated 372 (90%) of the initial 412 children from all the clusters (villages), and assessed their IQ with the Wechsler Abbreviated Scale of Intelligence-II, motor development, and school achievement including math, spelling, and reading. Analyses were by intention-to-treat, adjusting for clustering.

**Results:** There was a significant interaction between anemia groups (IDA/NA) and intervention on IQ. The intervention benefitted the NA group's Full-Scale IQ (effect size, 0.43 [95% confidence interval, 0.08-0.79]) and Perceptual Reasoning Index (effect size, 0.48 [95% confidence interval, 0.08-0.89]) but did not affect the IDA group's outcomes. No other outcomes were significant.

**Conclusions:** The benefits from early childhood psychosocial stimulation on the NA group's IQ, 6 years after intervention ended, adds to the limited evidence on the sustainability of benefits in low- and middle-income countries. Reasons for lack of effect in children with anemia are unknown.

Pediatrics. 2023 May 1;151(Suppl 2):e2023060221H.



doi: 10.1542/peds.2023-060221H.

### **Early Stimulation and Enhanced Preschool: A Randomized Trial**

[Costas Meghir<sup>1,2</sup>](#), [Orazio Attanasio<sup>1,2</sup>](#), [Pamela Jervis<sup>2,3</sup>](#), [Monimalika Day<sup>4</sup>](#), [Prerna Makkar<sup>5</sup>](#), [Jere Behrman<sup>6</sup>](#), [Prachi Gupta<sup>4</sup>](#), [Rashim Pal<sup>4</sup>](#), [Angus Phimister<sup>2</sup>](#), [Nisha Vernekar<sup>2</sup>](#), [Sally Grantham-McGregor<sup>7</sup>](#)

#### **Abstract**

**Objectives:** To estimate the impacts of 2 interventions, early stimulation (ES) for children aged <3 years and enhanced preschool (EP) for children aged 3+ years, and their interactions.

**Methods:** In Odisha, India, 192 villages were randomly assigned to ES or to no ES. Within each village, about 8 mothers with children initially aged 7 to 16 months were enrolled, receiving ES or no ES accordingly (n = 1449). Subsequently, when children were aged ~3 years, the villages were rerandomized to either EP at Anganwadi centers or no EP. This yielded 4 groups: (1) ES and EP, (2) only ES, (3) only EP, and (4) no intervention. Trained Anganwadi workers ran the EP. Primary outcomes, measured at baseline and follow-up after ~1 year, were children's IQ (summarizing cognition, language, and executive functioning) and school readiness (SR). Secondary outcomes were home environments, caregivers' child-development knowledge and preschool quality.

**Results:** Fifteen months after ES ended, only ES had a sustained benefit on IQ (0.18 SD, P <.04) and on SR (0.13 SD, P <.08). Only EP improved IQ (0.17 SD, P <.04) and SR (0.24 SD, P <.01). Receiving both interventions improved IQ (0.24 SD, P <.01) and SR (0.21 SD, P <.01). No statistically significant interactions between the 2 interventions were observed.

**Conclusions:** Both ES and EP increased IQ and SR. Only ES impacts were sustained for 15 months. Only EP resulted in considerable catch-up for children who did not receive only ES. The absence of significant complementarities should be investigated further because of its profound policy implications.

Pediatrics. 2023 May 1;151(Suppl 2):e2023060221G.

doi: 10.1542/peds.2023-060221G.

### **An Integrated Mother-Child Intervention on Child Development and Maternal Mental Health**

[Fahmida Tofail<sup>1</sup>](#), [Munirul Islam<sup>1</sup>](#), [Fahmida Akter<sup>1</sup>](#), [Shekufeh Zonji<sup>2</sup>](#), [Bharati Roy<sup>1</sup>](#), [Sheikh Jamal Hossain<sup>3,4</sup>](#), [Abu Horaira<sup>1</sup>](#), [Shirina Akter<sup>1</sup>](#), [Dolly Goswami<sup>1</sup>](#), [Abdullah Brooks<sup>5</sup>](#), [Jena Hamadani<sup>3</sup>](#)

#### **Abstract**

**Objectives:** To evaluate an integrated, low-cost, facility-based group intervention designed to promote child care, boost maternal mental-wellbeing, reduce harsh discipline, and improve children's health, nutrition, and early development.

**Methods:** In Dhaka, 30 neighborhood clusters of a low-income urban community were randomized to intervention or control groups. Mothers with children between 6 and 24 months (n = 300) who self-reported negative discipline were identified and enrolled. A 1-year group intervention included integration of responsive caregiving, nutritional supplementation, caregivers' mental health, child protection, and health advice. Child outcomes were cognition (primary) and language, motor and behavioral development, growth, and hemoglobin and iron status (secondary). Maternal outcomes were depressive symptoms, self-esteem, negative discipline, and child care knowledge and practices.



**Results:** Overall, 222 (74%) mother-child dyads participated in the 1-year follow-up. Intervention and control groups differed on wealth, with no other significant differences. The intervention resulted in a 0.75 SD effect on cognition, 0.77 SD on language, 0.41 SD on motor, and 0.43 to 0.66 SDs on behavior during testing (emotion, cooperation, and vocalization) in the intervention arm. Mothers in the intervention group had fewer depressive symptoms (effect size: -0.72 SD), higher self-esteem (0.62 SD), better child care knowledge (2.02 SD), fewer harsh discipline practices (0.25 SD), and better home stimulation (0.73 SD). The intervention showed no effect on child growth or hemoglobin, but significantly improved serum iron status (-0.36 SD).

**Conclusions:** A comprehensive intervention, delivered through group sessions in health facilities, was effective in promoting child development and reducing maternal depressive symptoms among mothers who reported using negative or harsh discipline.

Child Care Health Dev. 2022 Dec 13.

doi: 10.1111/cch.13089. Online ahead of print.

**[Scaling-Up an Early childhood Parenting Intervention by Integrating into Government Health Care Services in Rural Bangladesh: A Cluster-Randomised Controlled Trial](#)**

[Syeda Fardina Mehrin](#)<sup>1</sup>, [Nur-E Salveen](#)<sup>1</sup>, [Masuma Kawsir](#)<sup>1</sup>, [Sally Grantham-McGregor](#)<sup>2</sup>, [Jena D Hamadani](#)<sup>1</sup>, [Helen Baker-Henningham](#)<sup>3</sup>

**Abstract**

**Aims:** We evaluated the feasibility and effectiveness of utilising government health supervisors to train and supervise primary health care workers (HWs) in community clinics to deliver parenting sessions as part of their usual duties.

**Methods:** We randomly allocated 16 unions in the Mymensing district of Bangladesh 1:1 to an intervention or control group. HWs in clinics in the eight intervention unions (n=59 health workers, n=24 clinics) were trained to deliver a group-based parenting intervention, with training and supervision provided by government supervisors. In each of the twenty-four intervention clinics, we recruited twenty-four mothers of children aged 6-24 months to participate in the parenting sessions (n=576 mother/child dyads). Mother/child dyads attended fortnightly parenting sessions at the clinic in groups of four-to-five participants for six months (13 sessions). We collected data on supervisor and HW compliance in implementing the intervention, mothers' attendance and the observed quality of parenting sessions in all intervention clinics and HW burnout at endline in all clinics. We randomly selected 32 clinics (16 intervention, 16 control), and 384 mothers (192 intervention, 192 control) to participate in the evaluation on mother-reported home stimulation, measured at baseline and endline.

**Results:** Supervisors and HWs attended all training, 46/59 health workers (78%) conducted the majority of parenting sessions, (only two HWs (3.4%) refused), and mothers' attendance rate was 86%. However, supervision levels were low: only 32/57 (56.1%) of HWs received at least one supervisory visit. Intervention HWs delivered the parenting sessions with acceptable levels of quality on most items. The intervention significantly benefitted home stimulation (effect size=0.53SD, 95% confidence interval: 0.50, 1.56, p<0.001). HW burnout was low in both groups.

**Conclusion:** Integration into the primary health care service is a promising approach for scaling early childhood development programmes in Bangladesh, although further research is required to identify feasible methods for facilitator supervision.

Cien Saude Colet. 2022 Dec;27(12):4341-4363.

doi: 10.1590/1413-812320222712.13472022. Epub 2022 Aug 26.

**Evaluation of the Happy Child Program: a randomized study in 30 Brazilian municipalities**

[Iná S Santos<sup>1</sup>](#), [Tiago N Munhoz<sup>1</sup>](#), [Raquel Siqueira Barcelos<sup>1</sup>](#), [Cauane Blumenberg<sup>1</sup>](#), [Caroline Cardozo Bortolotto<sup>1</sup>](#), [Alicia Matijasevich<sup>2</sup>](#), [Cristiane Salum<sup>3</sup>](#), [Hernane Guimarães Dos Santos Júnior<sup>4</sup>](#), [Letícia Marques<sup>5</sup>](#), [Luciano Correia<sup>6</sup>](#), [Marta Roverly de Souza<sup>7</sup>](#), [Pedro Israel Cabral de Lira<sup>8</sup>](#), [Vitor Pereira<sup>9</sup>](#), [Cesar G Victora<sup>1</sup>](#)

**Abstract**

The Happy Child Program (Programa Criança Feliz - PCF, in Portuguese) reaches 1.4 million Brazilian children under three years of age with home visits aimed at promoting neuropsychomotor development. Based on a conceptual model, PCF implementation and impact were evaluated in a randomized study in 30 municipalities. A total of 3,242 children were allocated to the intervention (IG) or control (CG) group, 80.0% of whom were prospectively followed up from late 2018 to late 2021. Development was assessed by the Ages and Stages Questionnaire (ASQ3). During the three-year study period, visits were replaced by virtual contacts for an average of 12 months due to COVID-19. At the endline survey, intent-to-treat analyses showed mean scores of 203.3 in the IG and 201.3 in the CG. Additional analyses using instrumental variables and propensity scores matching also showed no effect, since the number of contacts with the program was not associated with ASQ3 scores. No impact was observed on stimulation, responsive interactions or psychological attributes of children. The implementation study revealed low coverage in the IG, contamination of the CG, deficiencies in management and low quality of visits in many municipalities. The study did not demonstrate an impact of PCF implemented under routine conditions, but provides elements for its improvement.

BMC Pediatr. 2022 Oct 8;22(1):586.

doi: 10.1186/s12887-022-03579-6.

**Early child stimulation, linear growth and neurodevelopment in low birth weight infants**

[Ravi Prakash Upadhyay<sup>1,2</sup>](#), [Sunita Taneja<sup>3</sup>](#), [Tor A Strand<sup>4</sup>](#), [Halvor Sommerfelt<sup>5,6</sup>](#), [Mari Hysing<sup>7</sup>](#), [Sarmila Mazumder<sup>3</sup>](#), [Nita Bhandari<sup>3</sup>](#), [Jose Martinez<sup>5</sup>](#), [Tarun Dua<sup>8</sup>](#), [Patricia Kariger<sup>9</sup>](#), [Rajiv Bahl<sup>10</sup>](#)

**Abstract**

**Background:** Children with low birth weight (LBW) are at risk of linear growth faltering and developmental deficits. Evidence suggests that early child stimulation and care reflected as responsive caregiving and opportunities for learning can promote development. The current analysis aimed to measure the extent to which linear growth and early child stimulation modify each other's association with neurodevelopmental outcomes among LBW infants.

**Methods:** This is a secondary data analyses from a randomized controlled trial on the effect of community-initiated kangaroo mother care in LBW infants on their neurodevelopment at 12 months of corrected age. Bayley Scales of Infant and Toddler Development was used to assess cognitive, motor and language scores. Stimulation at home was assessed by the Pediatric Review of Children's Environmental Support and Stimulation (PROCESS) tool. PROCESS scores were categorized into three groups: < Mean-1SD (low stimulation); Mean  $\pm$  1 SD (moderate stimulation) and > mean + 1SD (high stimulation).

**Results:** A total of 516 infants were available for neurodevelopment assessments. Interactions were observed between length for age z-score (LAZ) and PROCESS score categories. In the low stimulation group, the adjusted regression coefficients for the association between LAZ and cognitive, motor and language scores were substantially higher than in the moderate and high stimulation group. Stimulation was positively associated with neurodevelopmental outcomes in both stunted and non-stunted infants; however, the association was twice as strong in stunted than in non-stunted.

**Conclusion:** Moderate to high quality stimulation may alleviate the risk of sub-optimal development in LBW infants with linear growth deficits.

J Glob Health. 2022 Oct 18;12:12005.

doi: 10.7189/jogh.12.12005.

[\*\*Effect of whole-body massage on growth and neurodevelopment in term healthy newborns: A systematic review\*\*](#)

[Mayank Priyadarshi<sup>1</sup>](#), [Vivek Kumar<sup>2</sup>](#), [Bharathi Balachander<sup>3</sup>](#), [Shuchita Gupta<sup>4</sup>](#), [Mari Jeeva Sankar<sup>2</sup>](#)

**Abstract**

**Background:** Infant massage is commonly practiced in many parts of the world. However, the effectiveness of this intervention has not been reviewed for term, healthy newborns.

**Methods:** This systematic review of randomized and quasi-randomized controlled trials assessed the effect of whole-body massage with or without oil, compared to no massage in term healthy newborns. Key outcomes were neonatal mortality, systemic infections, growth, behaviour (crying or fussing time, sleep duration), and neurodevelopment. We searched MEDLINE via PubMed, Cochrane CENTRAL, EMBASE, and CINAHL (updated till November 2021), and clinical trials databases and reference lists of retrieved articles. Two authors separately evaluated the risk of bias, extracted data, and synthesized effect estimates using mean difference (MD) and standardized mean difference (SMD). The GRADE approach was used to assess the certainty of evidence.

**Results:** We included 31 randomized and quasi-randomized trials involving 3860 participants. Infant massage was performed by different care providers starting in the neonatal period and continuing for 1-2 months in most studies. Thirteen studies reported the use of oil with body massage. No study reported neonatal mortality or systemic infections. Meta-analyses suggested that whole-body massage may increase infant length at the end of the intervention period (median assessment age 6 weeks; mean difference (MD) = 1.6 cm, 95% confidence interval (CI) = 1.4 to 1.7 cm; low certainty evidence), but the effect on weight (MD = 340 g, 95% CI = 240 to 441 g), head circumference (MD = 0.8 cm, 95% CI = 0.6 to 1.1 cm), sleep duration (MD = 0.62 hours/d, 95% CI = 0.12 to 1.12 hours/d) and bilirubin levels (MD = -31.8 mmol/L or -1.8 mg/dL, 95% CI = -23.5 to -40.0 mmol/L) was uncertain. The effect on

crying/fussing time at median 3 months of age, sleep duration at 6 months of age, weight, length, and head circumference at 6-12 months follow-up, and neurodevelopment outcomes, both at the end of the intervention period and follow-up was uncertain.

**Conclusions:** Whole-body massage may improve the infant length at the end of the intervention period (median age 6 weeks, range 1-6 months) but the effect on other short- or long-term outcomes is uncertain. There is a need for further well-designed trials in future.

Child Care Health Dev. 2022 Sep;48(5):736-743.

doi: 10.1111/cch.12981. Epub 2022 Feb 9.

**[Measuring the impact of a training intervention for early childhood centre staff on child development outcomes: Findings from a cluster randomized control field trial in rural Malawi](#)**

[Emma Jolley](#)<sup>1</sup>, [Stevens Bechange](#)<sup>2</sup>, [Mika Mankhwazi](#)<sup>3</sup>, [Jenipher Mbukwa Ngwira](#)<sup>4</sup>, [Rachel Murphy](#)<sup>1</sup>, [Elena Schmidt](#)<sup>5</sup>, [Paul Lynch](#)<sup>6</sup>

**Abstract**

**Background:** Evidence from low-income settings around early education interventions that can improve young children's development is sparse, particularly with regard to the most marginalized children. This study used a two-arm parallel cluster randomized control design to evaluate the impact of an adapted staff training programme on the developmental outcomes of children attending community-based early learning centres in Thyolo district, rural Malawi.

**Methods:** At baseline we randomly selected 48 centres, from each of which 20 children were randomly selected, although data from one centre was incomplete resulting in 932 children from 47 centres. Centres were randomly allocated to either the intervention or control arm. Twelve months later, follow-up data were collected from 44 centres. At baseline and endline, community-based childcare centre (CBCC) managers provided information about the centre, and parents/guardians provided information on the children, including the primary outcomes of age-standardized development scores in the language and social domains, measured using the Malawi Developmental Assessment Tool. Children in the bottom 2.5 percentile of either domain were considered to have a delay; a third outcome variable, Any Delay, was developed to indicate children with a delay in either or both domains. Centre-level mean scores were calculated, and linear regression models were constructed to assess differences between baseline and endline and between allocation groups.

**Results:** Analysis of the difference between baseline and endline measures in the allocation groups shows a non-significant reduction in delay associated with the study intervention across all domains. Adjustment for baseline characteristics within the CBCCs showed little impact on the magnitude of the observed effect, and the difference remained non-significant.

**Conclusions:** Despite no observed differences between allocation groups, the data did indicate a positive change in the intervention groups in both domains, particularly language. Community-based early learning in Malawi holds tremendous potential for promoting inclusive development and learning.

J Nutr. 2023 May;153(5):1597-1606.

doi: 10.1016/j.tjnut.2023.03.015. Epub 2023 Mar 15.

**[Long-Term Association Between Maternal Preconception Hemoglobin Concentration, Anemia, and Child Health and Development in Vietnam](#)**

[Melissa F Young](#)<sup>1</sup>, [Phuong Nguyen](#)<sup>2</sup>, [Lan Mai Tran](#)<sup>3</sup>, [Long Quynh Khuong](#)<sup>4</sup>, [Reynaldo Martorell](#)<sup>3</sup>, [Usha Ramakrishnan](#)<sup>3</sup>

**Abstract**

**Background:** The long-term association between preconception maternal hemoglobin (Hb) concentrations and child health and development is unclear.

**Objectives:** We examined associations between maternal preconception Hb concentrations and anemia with 1) birth outcomes (weight, length, preterm, gestational age, small for gestational age); 2) child Hb at 3 mo, 6 mo, 12 mo, and 24 mo; and 3) motor and mental development at 12 mo and 24 mo (Bayley scales for infant development) and cognitive functioning at 6-7 y (Wechsler Intelligence Scale for Children).

**Methods:** We used data from a randomized controlled trial (PRECONCEPT) conducted in Vietnam. Over 5000 women who were intending to conceive were recruited, and offspring were prospectively followed from birth (n = 1599) through 6-7 y (n = 1318). Multivariable linear and logistic regressions were used to assess the association between preconception Hb or anemia (Hb < 12g/dL) on child health and development outcomes, adjusted by supplementation group (tested for interactions) and confounding at maternal, child, and household levels.

**Results:** At preconception enrollment, 20% of the women were anemic. Maternal preconception Hb was positively associated with child Hb at 3 mo (0.06; 95% CI: 0.01, 0.12), 6 mo (0.08; 95% CI: 0.03, 0.13), 12 mo (0.10; 95% CI: 0.04, 0.15), and 24 mo (0.07; 95% CI: 0.02, 0.12). Likewise, maternal preconception Hb was associated with reduced risk of child anemia at 6 mo (0.89; 95% CI: 0.81, 0.98), 12 mo (0.81; 95% CI: 0.74, 0.89), and 24 mo (0.87; 95% CI: 0.79, 0.95). Maternal preconception anemia was negatively associated with cognition (-1.64; 95% CI: -3.09, -0.19) and language development (-1.61; 95% CI: -3.20, -0.03) at 24 mo. Preconception Hb was not associated with birth outcomes or cognitive outcomes at 6-7 y.

**Conclusions:** Maternal preconception Hb was associated with child Hb across the first 1000 d of life. However, preconception Hb was not a significant predictor of birth outcomes or cognitive outcomes at 6-7 y in this cohort from Vietnam.

## Child protection and family violence

Prev Sci. 2022 Nov;23(8):1457-1469.

doi: 10.1007/s11121-022-01433-w. Epub 2022 Sep 13.

**[The Families First Program to Prevent Child Abuse: Results of a Cluster Randomized Controlled Trial in West Java, Indonesia](#)**

[Mónica Ruiz-Casares](#)<sup>1,2</sup>, [Brett D Thombs](#)<sup>3,4</sup>, [Nancy E Mayo](#)<sup>5,6</sup>, [Michelle Andrina](#)<sup>7</sup>, [Susan C Scott](#)<sup>5</sup>, [Robert William Platt](#)<sup>5,8</sup>

**Abstract**

The Families First parenting program is a 10-week paraprofessional-administered adaptation of the Positive Discipline in Everyday Parenting program for West Java, Indonesia. It has not been tested in a randomized controlled trial. The objective was to evaluate the effects of Families First on physical and emotional punishment. We conducted a cluster randomized controlled trial and randomly assigned 20 rural and urban villages in West Java, Indonesia, to intervention or waitlist. Caregivers of children aged 0-7 years in intervention villages received Families First. Between 2017 and 2018, measurements were taken before randomization, immediately post-intervention, and 6 months post-intervention. Primary outcome was presence versus absence of caregiver-reported physical or emotional punishment immediately post-intervention. Intention-to-treat regression models accounted for clustering within villages and were run to compare between groups. Participants and study personnel could not be blinded. There were 374 caregivers in the 10 intervention villages and 362 in the 10 waitlist villages included in the trial and in outcome analyses. The intervention did not result in a lower proportion of intervention families using punishment immediately post-intervention (odds ratio [OR] for physical or emotional punishment immediately post intervention = 1.20 (95% CI 0.79-1.82). There were no significant differences for positive and involved parenting, setting limits, and opinion on discipline, but caregivers in the intervention group had significantly lower odds of using positive discipline (OR = 0.65 (95% CI 0.53-0.80). Families First did not prevent punishment in a setting with low levels of reported punishment but should be tested in a setting with higher levels or among people selected for risk or presence.

BMJ Open. 2023 Mar 6;13(3):e065759.

doi: 10.1136/bmjopen-2022-065759.

[\*\*Improving family functioning and reducing violence in the home in North Kivu, Democratic Republic of Congo: a pilot cluster-randomised controlled trial of Safe at Home\*\*](#)

[Kathryn L Falb<sup>1</sup>](#), [Khudejha Asghar<sup>2</sup>](#), [Alexandra Blackwell<sup>3</sup>](#), [Simon Baseme<sup>4</sup>](#), [Martin Nyanguba<sup>5</sup>](#), [Danielle Roth<sup>6</sup>](#), [Jean de Dieu Hategekimana<sup>4</sup>](#)

**Abstract**

**Objective:** To test the effectiveness of the Safe at Home programme which was developed to improve family well-being and prevent multiple forms of violence in the home.

**Design:** Waitlisted pilot cluster randomised controlled trial.

**Setting:** North Kivu, Democratic Republic of Congo.

**Participants:** 202 heterosexual couples.

**Intervention:** The Safe at Home programme.

**Primary and secondary outcome measures:** The primary outcome was family functioning, with secondary outcomes of past-3 month co-occurring violence, intimate partner violence (IPV) and harsh discipline. Pathway mechanisms assessed included attitudes related to acceptance of harsh discipline, gender equitable attitudes, positive parenting skills and power sharing within the couple.

**Results:** No significant improvements in family functioning were documented for women ( $\beta=1.49$ ; 95% CI: -2.75 to 5.74;  $p=0.49$ ) and men ( $\beta=1.09$ ; 95% CI: -3.13 to 4.74;  $p=0.69$ ).

However, women in Safe at Home reported a OR=0.15 ( $p=0.000$ ), OR=0.23 ( $p=0.001$ ) and OR=0.29 ( $p=0.013$ ) change in co-occurring IPV and harsh discipline;

physical/sexual/emotional IPV by their partner and use of physical and/or emotional harsh



discipline against their child, respectively, as compared with women in the waitlisted group. Men participating in Safe at Home reported a OR=0.23 (p=0.005) change in perpetration of co-occurring violence, OR=0.26 (p=0.003) change in any form of IPV perpetration and OR=0.56 (p=0.19) change in use of harsh discipline against their child as compared with the waitlist arm. Positive changes were also noted in pathway variables around attitudes, skills and behaviours within couples.

**Conclusion:** This pilot trial demonstrated the Safe at Home programme to be highly effective in preventing multiple forms of violence in the home and improving equitable attitudes and skills in couples. Future research should assess longitudinal impact and implementation at scale.

Pediatrics. 2023 May 1;151(Suppl 2):e2023060221L.

doi: 10.1542/peds.2023-060221L.

**[Family Violence Reduction Within a Parenting Intervention in Rwanda: A Mixed-Methods Study](#)**

[Sarah K G Jensen](#)<sup>1</sup>, [Shauna M Murray](#)<sup>2</sup>, [Matias Placencio-Castro](#)<sup>1,3</sup>, [Ursula Kajani](#)<sup>1</sup>, [Deborah Amponsah](#)<sup>1</sup>, [Vincent Sezibera](#)<sup>4</sup>, [Theresa S Betancourt](#)<sup>1</sup>

**Abstract**

**Background and objectives:** A mixed-methods study of mechanisms of change through which a home-visiting-based early childhood development intervention, Sugira Muryango ("strong family"), reduced violent discipline and intimate partner violence in Rwanda.

**Methods:** The cluster-randomized trial of Sugira Muryango enrolled socioeconomically vulnerable families with children aged 6 to 36 months in rural Rwanda. We interviewed 18 female caregivers early in the intervention, and 21 female caregivers and 11 male intimate partners were interviewed after the intervention. Coded interviews identify risk factors for violence and mechanisms of intervention-related change in violence. Quantitative analyses included 931 caregivers (52.6% female) who lived with an intimate partner to examine risk factors for violence, intervention effects, and mechanisms of violence reduction.

**Results:** The qualitative data identified daily hardships and alcohol problems as risk factors for violent discipline and intimate partner violence. Through Sugira Muryango, caregivers learned that strong relationships between partners and engagement of male caregivers in child care has positive impacts on children's development. Techniques taught by community lay workers improved communication, promoted positive parent-child interactions, and reduced intimate partner violence and violent discipline. Quantitative analyses also found that daily hardships predict violent discipline and intimate partner violence. Sugira Muryango reduced violent discipline, increased father engagement, and increased female caregiving warmth. Moreover, pre- to postintervention change in caregiving warmth was associated with reduced use of violent discipline among female caregivers and marginally associated with reduced female victimization.

**Conclusions:** Violence reduction can be integrated into early child development programs to reduce violent discipline and intimate partner violence.



doi: 10.1111/cch.13074. Epub 2022 Nov 9.

[\*\*A qualitative evaluation of the mechanisms of action in an early childhood parenting programme to prevent violence against children in Jamaica\*\*](#)

[Taja Francis<sup>1</sup>](#), [Dania Packer<sup>1</sup>](#), [Helen Baker-Henningham<sup>1,2</sup>](#)

**Abstract**

**Background:** Violence against children (VAC) is a global public health problem, and parenting programmes are a key strategy to reduce VAC at home. We developed and evaluated a preschool-based, early childhood, violence prevention, parenting programme (the Irie Homes Toolbox) in Jamaica and reported significant reductions in parents' use of VAC [Effect size (ES) = -0.29] and increases in parents' positive practices (ES = 0.30). This study presents qualitative findings on the mechanisms of action of the programme.

**Methods:** As part of a cluster randomized trial, 115 parents from nine preschools participated in the Irie Homes Toolbox parenting programme. The programme consisted of eight 90-min sessions with groups of six parents and focused on strengthening parent-child relationships, understanding children's behaviour, using appropriate discipline strategies and understanding and managing emotions. We conducted in-depth, semi-structured interviews with a stratified random sample of 28 parents (two to four parents per school) and with nine preschool teachers (one teacher per preschool). Topic guides were developed to explore participants' perspectives of the mechanisms of action of the programme. All interviews were audio-recorded and transcribed, and data were analysed using the framework approach.

**Results:** The most salient direct pathways to reduced VAC by both parent and teacher reports were through parents' use of alternative strategies to manage child misbehaviour and through improved parent well-being, especially parents' self-management skills. Other factors leading to reduced VAC by parents, reported by both parents and teachers, included self-identification as an 'Irie parent', use of proactive parenting strategies and improved child behaviour. Parents reported that the main factors leading to continued use of VAC were their inconsistency in using positive discipline strategies and poor emotional self-regulation.

**Conclusion:** Reports from participating parents and preschool teachers indicate that contents related to parental self-management and how to use positive discipline strategies to manage child misbehaviour were important factors on the pathway to reduced VAC.

## **Dengue**

(see Vaccines - dengue)

## **Diarrhoea**

(See also: Vaccines and immunization - Rotavirus vaccine, Hygiene and Environmental health, Malnutrition, Dengue, Nutrition - Environmental enteric dysfunction)

## **Treatment of diarrhoea**

PLoS One. 2022 Sep 19;17(9):e0274302.

doi: 10.1371/journal.pone.0274302. eCollection 2022.

**[Digestive tolerability and acceptability of Fibersol-2 in healthy and diarrheal children 1-3 years old at a rural facility, Bangladesh: Results from a four arm exploratory study](#)**

**[Abu Sadat Mohammad Sayeem Bin Shahid](#)<sup>1</sup>, **[Shahnawaz Ahmed](#)**<sup>2</sup>, **[Tanzina Tazul Renesa](#)**<sup>3</sup>, **[Anindita Tasnim Onni](#)**<sup>4</sup>, **[Sampa Dash](#)**<sup>5</sup>, **[Yuka Kishimoto](#)**<sup>6</sup>, **[Sumiko Kanahori](#)**<sup>6</sup>, **[Tahmeed Ahmed](#)**<sup>1</sup>, **[Abu Syed Golam Faruque](#)**<sup>1</sup>, **[Mohammad Jobayer Chisti](#)**<sup>1</sup>**

**Abstract**

**Background:** Fibersol-2 has some beneficial effects on human health. We aimed to evaluate the digestive tolerability and acceptability of Fibersol-2 in healthy and diarrheal children, as well as improvement in stool consistencies in young diarrheal children.

**Methods:** Sixty children of either sex, aged 1-3 years having four groups (healthy children/low dose, healthy children/high dose, children with diarrhea/low dose and children with diarrhea/high dose) were enrolled into this exploratory study between 1st August to 23rd October 2017. Two presumptive doses, low (2.5g) and high (5g), twice daily with 50 ml drinking water for seven days were the interventions. Outcomes were to observe the development of possible abdominal symptoms, such as pain, distension, rumbling, and bloating during the intervention and post-intervention periods in healthy and diarrheal children as well as improvement in stool consistencies in diarrheal children.

**Results:** Among the diarrheal children, the median (IQR) duration of resolution of diarrhea was 3.9 (2.9, 5.1) days vs. 3.5 (2.0, 8.0) days,  $p = 0.885$ ; in low dose and high dose groups, respectively. Significant difference was observed in terms of abdominal pain (27% vs. 7%,  $p = 0.038$ ) and distension (40% vs. 0%,  $p < 0.001$ ) in diarrheal children, compared to healthy children during the pre-intervention period. We also observed significant difference in respect of abdominal distension (23% vs. 0%,  $p = 0.011$ ), rumbling (27% vs. 0%,  $p = 0.005$ ) and bloating (43% vs. 3%,  $p = 0.001$ ) in diarrheal children, compared to healthy children during the intervention period. However, no significant difference was observed in relation to abdominal pain ( $p = 0.347$ ) and distension ( $p = 0.165$ ) during the pre-intervention period, compared to the intervention period in diarrheal children. Moreover, no significant difference was observed during the post-intervention period for the diarrheal and healthy children.

**Conclusion:** Fibersol-2 was found to be well tolerated in healthy and diarrheal children aged 1-3 years.

PLoS One. 2023 Jan 27;18(1):e0280934.

doi: 10.1371/journal.pone.0280934. eCollection 2023.

**[Is Fibersol-2 efficacious in reducing duration of watery diarrhea and stool output in children 1-3 years old? A randomized, parallel, double-blinded, placebo-controlled, two arm clinical trial](#)**

**[Abu Sadat Mohammad Sayeem Bin Shahid](#)**<sup>1</sup>, **[Shahnawaz Ahmed](#)**<sup>2</sup>, **[Sampa Dash](#)**<sup>3</sup>, **[Yuka Kishimoto](#)**<sup>4</sup>, **[Sumiko Kanahori](#)**<sup>4</sup>, **[Tahmeed Ahmed](#)**<sup>1</sup>, **[Abu Syed Golam Faruque](#)**<sup>1</sup>, **[Mohammad Jobayer Chisti](#)**<sup>1</sup>

**Abstract**

**Background:** Fibersol-2 has innumerable beneficial effects on human health. It is a fermentable, non-viscous, water-soluble, indigestible dextrin containing 90% dietary fiber produced from corn starch. We aimed to evaluate whether additional intake of Fibersol-2

along with oral rehydration solution treatment can reduce the duration of watery diarrhea and daily stool output in children 1-3 years as well as recovery of such children within 72 hours, compared to placebo.

**Methods:** This placebo-controlled double-blinded, randomized parallel two arm trial conducted in Kumudini Women's Medical College Hospital in rural Bangladesh between March and October, 2018 used 5 gm of either Fibersol-2 or placebo dissolved in 50-ml drinking water which was given orally to ninety-two children with watery diarrhea on enrollment twice daily for a period of 7 days. Randomization was done using a randomization table. We randomly allocated 45 (49%) and 47 (51%) children in Fibersol-2 and placebo groups, respectively. Outcome measures were duration of resolution of watery diarrhea, daily stool output and the proportion of children recovered within 72 hours. Primary and safety analyses were by intention to treat. This trial was registered at ClinicalTrials.gov, number [NCT03565393](https://clinicaltrials.gov/ct2/show/study/NCT03565393).

**Results:** There was no significant difference observed in terms of duration of resolution of diarrhea (adjusted mean difference 8.20, 95% CI -2.74 to 19.15,  $p = 0.14$ , adjusted effect size 0.03); the daily stool output (adjusted mean difference 73.57, 95% CI -94.17 to 241.32,  $p = 0.38$ , adjusted effect size 0.33) and the proportion of children recovered within 72 hours (adjusted odds ratio 0.49, 95% CI = 0.12 to 1.96,  $p = 0.31$ , adjusted risk difference -0.06 (95% CI -0.19 to -0.06), after regression analysis between Fibersol-2 and placebo.

**Conclusion:** No beneficial role of Fibersol-2 was observed in diarrheal children aged 1-3 years.

Comput Math Methods Med. 2022 Sep 20;2022:6234858.

doi: 10.1155/2022/6234858. eCollection 2022.

[\*\*Effectiveness and Safety of Saccharomyces Boulardii for the Treatment of Acute Gastroenteritis in the Pediatric Population: A Systematic Review and Meta-Analysis of Randomized Controlled Trials\*\*](#)

[Hongbo Fu<sup>1</sup>](#), [Jinrong Li<sup>2</sup>](#), [Xunhua Xu<sup>1</sup>](#), [Caihuai Xia<sup>1</sup>](#), [Yajuan Pan<sup>3</sup>](#)

**Abstract**

**Objective:** To explore the efficacy and safety of Saccharomyces boulardii for the treatment of acute gastroenteritis in children aged under 5.

**Methods:** Two independent researchers retrieved literature from PubMed, OVID, Embase, ScienceDirect, and other databases, followed by extracting indicators of the primary endpoints. Cochrane Q test and  $I^2$  statistics were used to evaluate interstudy heterogeneity. The relative risk (RR) and mean difference (MD) of related indicators were calculated and combined using the random- or fixed-effect model, as appropriate. Furthermore, the funnel plot and Egger's test were used to evaluate the publication bias. A two-sided  $P < 0.05$  denoted statistical significance.

**Results:** 10 articles were included in this meta-analysis, with a total of 1282 children having acute gastroenteritis. The use of Saccharomyces boulardii in children with acute gastroenteritis could effectively shorten diarrhea duration (MD = 19.70, 95% CI: -24.87, 14.52) and reduce the length of hospital stay (MD = -0.91, 95% CI: -1.28, -0.54). Compared with the control group, the RR of continued diarrhea was significantly lower in the treatment group after 1 day treatment (RR = -0.31, 95% CI: 0.59, 0.03) and 3 days treatment (RR = 0.52, 95% CI:

0.41, 0.66). In addition, treatment with *Saccharomyces boulardii* reduced the average number of diarrhea after 3 days of treatment by about 1.03 (MD = -1.03, 95% CI: -1.53, -0.53). There were no adverse drug reactions in both groups.

**Conclusion:** The use of probiotic *Saccharomyces boulardii* can significantly improve the symptoms of diarrhea in children with acute gastroenteritis and reduce the duration of diarrhea symptoms and the time of hospitalization. Meanwhile, the RR of continued diarrhea in children after 1 and 3 days of *Saccharomyces boulardii* treatment and the frequency of diarrhea after 3 days of *Saccharomyces boulardii* treatment were decreased. It is also safe and does not increase the incidence of adverse drug reactions.

Pak J Med Sci. 2022 Jul-Aug;38(6):1584-1588.

doi: 10.12669/pjms.38.6.5532.

**Comparison of Ondansetron versus Domperidone for treating vomiting in acute gastroenteritis in children at a resource limited setting of South Punjab, Pakistan**

Tauseef Ahmad<sup>1</sup>, Uzma Zarafshan<sup>2</sup>, Bushra Sahar<sup>3</sup>

**Abstract**

**Objectives:** To compare the efficacy of Ondansetron versus Domperidone for treating vomiting in acute gastroenteritis (AGE) in children at a resource limited emergency setting of South Punjab, Pakistan.

**Methods:** This open label randomized controlled trial was conducted at The Pediatric Emergency Department of Tehsil Headquarter Hospital, Liaquatpur, Pakistan, from July 2020 to June 2021. A total of 300 children of both genders aged below 12 years of age having 3 or more non-bilious, non-bloody vomiting episodes within 24 hours and with suggestive signs and symptoms of AGE were enrolled and randomized (150 in each group). Efficacy of both drugs was compared in terms of need of 2<sup>nd</sup> dose within 15 minutes, cessation of vomiting at 6-hour and 24-hour follow up.

**Results:** Out of a total of 300 children, 162 (54.0%) were male. Mean age was 4.7±2.3 years. Twenty seven (18.0%) children in Ondansetron group required 2<sup>nd</sup> dose within 15 minutes while 38 (25.3%) children in Domperidone group required the 2<sup>nd</sup> dose (p=0.1232). Cessation of vomiting at 6-hour interval was noted among 126 (84.0%) children in Ondansetron group in comparison to 118 (78.7%) in Domperidone group (p=0.2359). It was revealed that 127/142 (89.4%) children in Ondansetron group had cessation of vomiting at 24-hours follow up while this was noted to be among 108/134 (80.6%) children in Domperidone group (p=0.0390).

**Conclusion:** In comparison to Domperidone, Ondansetron was found to have better efficacy aiming cessation of AGE associated vomiting among children with mild to moderate dehydration.

## Diarrhoea prevention

(also see Hygiene and Environmental health; Water, Sanitation and Hygiene)

BMJ Open. 2022 Oct 31;12(10):e059878.

doi: 10.1136/bmjopen-2021-059878.

**Environmental and behavioural exposure pathways associated with diarrhoea and enteric pathogen detection in 5-month-old, periurban Kenyan infants: a cross-sectional study**

[Kelly K Baker<sup>1</sup>](#), [Jane Awiti Odhiambo Mumma<sup>2</sup>](#), [Sheillah Simiyu<sup>3</sup>](#), [Daniel Sewell<sup>4</sup>](#), [Kevin Tsai<sup>5</sup>](#), [John David Anderson<sup>6</sup>](#), [Amy MacDougall<sup>7</sup>](#), [Robert Dreibelbis<sup>7</sup>](#), [Oliver Cumming<sup>7</sup>](#)

**Abstract**

**Objectives:** The aim of this study was to test whether household environmental hygiene and behavioural conditions moderated associations between diarrhoea and enteric pathogen detection in infants 5 months of age in Kenya and pathogen sources, including latrine access, domestic animal co-habitation and public food sources.

**Design:** Cross-sectional study utilising enrolment survey data of households participating in the Safe Start cluster-randomised controlled trial.

**Setting:** Kisumu, Kenya.

**Participants:** A total of 898 caregivers with 5-month (22 week  $\pm$  1 week) aged infants were enrolled in the study and completed the enrolment survey.

**Primary and secondary outcome measures:** Outcomes were (1) caregiver-reported 7-day diarrhoea prevalence and (2) count of types of enteric viruses, bacteria and parasites in infant stool. Exposures and effect modifiers included water access and treatment, cohabitation with domestic animals, sanitation access, handwashing practices, supplemental feeding, access to refrigeration and flooring.

**Results:** Reported handwashing after handling animals (adjusted odds ratio (aOR)=0.20; 95% CI=0.06 to 0.50) and before eating (aOR=0.44; 95% CI=0.26 to 0.73) were strongly associated with lower risk of caregiver-reported diarrhoea, while cohabitation with animals (aOR=1.54; 95% CI=1.01 to 2.34) living in a household with vinyl-covered dirt floors (aOR=0.60; 95% CI=0.45 to 0.87) were strongly associated with pathogen codetection in infants. Caregiver handwashing after child ( $p=0.02$ ) or self-defecation ( $p=0.03$ ) moderated the relationship between shared sanitation access and infant exposure to pathogens, specifically private latrine access was protective against pathogen exposure of infants in households, where caregivers washed hands after defecation. In the absence of handwashing, access to private sanitation posed no benefits over shared latrines for protecting infants from exposure.

**Conclusion:** Our evidence highlights eliminating animal cohabitation and improving flooring, postdefecation and food-related handwashing, and safety and use of cow milk sources as interventions to prevent enteric pathogen exposure of young infants in Kenya.

Cochrane Database Syst Rev. 2023 Jan 25;1:CD013328.

doi: 10.1002/14651858.CD013328.pub2.

**Interventions to improve sanitation for preventing diarrhoea**

[Valerie Bauza<sup>1</sup>](#), [Wenlu Ye<sup>1,2</sup>](#), [Jiawen Liao<sup>1,3</sup>](#), [Fiona Majorin<sup>4</sup>](#), [Thomas Clasen<sup>1</sup>](#)

**Abstract**

**Background:** Diarrhoea is a major contributor to the global disease burden, particularly amongst children under five years in low- and middle-income countries (LMICs). As many of the infectious agents associated with diarrhoea are transmitted through faeces, sanitation interventions to safely contain and manage human faeces have the potential to reduce exposure and diarrhoeal disease.

**Objectives:** To assess the effectiveness of sanitation interventions for preventing diarrhoeal disease, alone or in combination with other WASH interventions.

**Search methods:** We searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL, MEDLINE, Embase, LILACS, and Chinese language databases available under the China National Knowledge Infrastructure (CNKI-CAJ). We also searched the metaRegister of Controlled Trials (mRCT) and conference proceedings, contacted researchers, and searched references of included studies. The last search date was 16 February 2022.

**Selection criteria:** We included randomized controlled trials (RCTs), quasi-RCTs, non-randomized controlled trials (NRCTs), controlled before-and-after studies (CBAs), and matched cohort studies of interventions aimed at introducing or expanding the coverage and/or use of sanitation facilities in children and adults in any country or population. Our primary outcome of interest was diarrhoea and secondary outcomes included dysentery (bloody diarrhoea), persistent diarrhoea, hospital or clinical visits for diarrhoea, mortality, and adverse events. We included sanitation interventions whether they were conducted independently or in combination with other interventions.

**Data collection and analysis:** Two review authors independently assessed eligible studies, extracted relevant data, assessed risk of bias, and assessed the certainty of evidence using the GRADE approach. We used meta-analyses to estimate pooled measures of effect, described results narratively, and investigated potential sources of heterogeneity using subgroup analyses.

**Main results:** Fifty-one studies met our inclusion criteria, with a total of 238,535 participants. Of these, 50 studies had sufficient information to be included in quantitative meta-analysis, including 17 cluster-RCTs and 33 studies with non-randomized study designs (20 NRCTs, one CBA, and 12 matched cohort studies). Most were conducted in LMICs and 86% were conducted in whole or part in rural areas. Studies covered three broad types of interventions: (1) providing access to any sanitation facility to participants without existing access practising open defecation, (2) improving participants' existing sanitation facility, or (3) behaviour change messaging to improve sanitation access or practices without providing hardware or subsidy, although many studies overlapped multiple categories. There was substantial heterogeneity amongst individual study results for all types of interventions. Providing access to any sanitation facility Providing access to sanitation facilities was evaluated in seven cluster-RCTs, and may reduce diarrhoea prevalence in all age groups (risk ratio (RR) 0.89, 95% confidence interval (CI) 0.73 to 1.08; 7 trials, 40,129 participants, low-certainty evidence). In children under five years, access may have little or no effect on diarrhoea prevalence (RR 0.98, 95% CI 0.83 to 1.16, 4 trials, 16,215 participants, low-certainty evidence). Additional analysis in non-randomized studies was generally consistent with these findings. Pooled estimates across randomized and non-randomized studies provided similar protective estimates (all ages: RR 0.79, 95% CI 0.66 to 0.94; 15 studies, 73,511 participants; children < 5 years: RR 0.83, 95% CI 0.68 to 1.02; 11 studies, 25,614 participants). Sanitation facility improvement Interventions designed to improve existing sanitation facilities were evaluated in three cluster-RCTs in children under five and may reduce diarrhoea prevalence (RR 0.85, 95% CI 0.69 to 1.06; 3 trials, 14,900 participants, low-certainty evidence). However, some of these interventions, such as sewerage connection, are not easily randomized. Non-randomized studies across participants of all ages provided estimates that improving sanitation facilities may reduce diarrhoea, but may be subject to confounding (RR 0.61, 95% CI 0.50 to 0.74; 23 studies, 117,639 participants, low-certainty evidence). Pooled estimates across randomized and non-randomized studies provided similar protective estimates (all ages: RR 0.65, 95% CI 0.55 to 0.78; 26 studies, 132,539 participants; children < 5 years: RR 0.70, 95% CI 0.54 to 0.91, 12 studies, 23,353 participants).



Behaviour change messaging only (no hardware or subsidy provided) Strategies to promote behaviour change to construct, upgrade, or use sanitation facilities were evaluated in seven cluster-RCTs in children under five, and probably reduce diarrhoea prevalence (RR 0.82, 95% CI 0.69 to 0.98; 7 studies, 28,909 participants, moderate-certainty evidence). Additional analysis from two non-randomized studies found no effect, though with very high uncertainty. Pooled estimates across randomized and non-randomized studies provided similar protective estimates (RR 0.85, 95% CI 0.73 to 1.01; 9 studies, 31,080 participants). No studies measured the effects of this type of intervention in older populations. Any sanitation intervention A pooled analysis of cluster-RCTs across all sanitation interventions demonstrated that the interventions may reduce diarrhoea prevalence in all ages (RR 0.85, 95% CI 0.76 to 0.95, 17 trials, 83,938 participants, low-certainty evidence) and children under five (RR 0.87, 95% CI 0.77 to 0.97; 14 trials, 60,024 participants, low-certainty evidence). Non-randomized comparisons also demonstrated a protective effect, but may be subject to confounding. Pooled estimates across randomized and non-randomized studies provided similar protective estimates (all ages: RR 0.74, 95% CI 0.67 to 0.82; 50 studies, 237,130 participants; children < 5 years: RR 0.80, 95% CI 0.71 to 0.89; 32 studies, 80,047 participants). In subgroup analysis, there was some evidence of larger effects in studies with increased coverage amongst all participants (75% or higher coverage levels) and also some evidence that the effect decreased over longer follow-up times for children under five years. There was limited evidence on other outcomes. However, there was some evidence that any sanitation intervention was protective against dysentery (RR 0.74, 95% CI 0.54 to 1.00; 5 studies, 34,025 participants) and persistent diarrhoea (RR 0.57, 95% CI 0.43 to 0.75; 2 studies, 2665 participants), but not against clinic visits for diarrhoea (RR 0.86, 95% CI 0.44 to 1.67; 2 studies, 3720 participants) or all-cause mortality (RR 0.99, 95% CI 0.89 to 1.09; 7 studies, 46,123 participants).

**Authors' conclusions:** There is evidence that sanitation interventions are effective at preventing diarrhoea, both for young children and all age populations. The actual level of effectiveness, however, varies by type of intervention and setting. There is a need for research to better understand the factors that influence effectiveness.

Int J Environ Res Public Health. 2022 Oct 8;19(19):12905.

doi: 10.3390/ijerph191912905.

**[Randomized Controlled Trial of the Cholera-Hospital-Based-Intervention-for-7-Days \(CHoBI7\) Cholera Rapid Response Program to Reduce Diarrheal Diseases in Bangladesh](#)**

[Christine Marie George](#)<sup>1</sup>, [Tahmina Parvin](#)<sup>2,3</sup>, [Md Sazzadul Islam Bhuyian](#)<sup>2,3</sup>, [Ismat Minhaj Uddin](#)<sup>2,3</sup>, [Fatema Zohura](#)<sup>2,3</sup>, [Jahed Masud](#)<sup>2,3</sup>, [Shirajum Monira](#)<sup>3</sup>, [David A Sack](#)<sup>1</sup>, [Jamie Perin](#)<sup>1</sup>, [Munirul Alam](#)<sup>3</sup>, [A S G Faruque](#)<sup>3</sup>

**Abstract**

(a) Objective: To build an evidence base on effective water, sanitation, and hygiene interventions to reduce diarrheal diseases in cholera hotspots, we developed the CHoBI7 Cholera Rapid Response Program. (b) Methods: Once a cholera patient (confirmed by bacterial culture) is identified at a health facility, a health promoter delivers a targeted WASH intervention to the cholera hotspot (households within 20 m of a cholera patient) through both in-person visits during the first week and bi-weekly WASH mobile messages for the 3-



month program period. A randomized controlled trial of the CHoBI7 Cholera Rapid Response Program was conducted with 284 participants in 15 cholera hotspots around cholera patients in urban Dhaka, Bangladesh. This program was compared to the standard message in Bangladesh on the use of oral rehydration solution for dehydration. Five-hour structured observation of handwashing with soap and diarrhea surveillance was conducted monthly. (c) Findings: Handwashing with soap at food- and stool-related events was significantly higher in the CHoBI7 Cholera Rapid Response Program arm compared to the standard message arm at all timepoints (overall 54% in the CHoBI7 arm vs. 23% in the standard arm,  $p < 0.05$ ). Furthermore, there was a significant reduction in diarrheal prevalence for all participants (adults and children) (Prevalence Ratio (PR) 0.35, 95% CI: 0.14-0.85) and for children under 5 years of age (PR: 0.27, 95% CI: 0.085-0.87) during the 3-month program. (d) Conclusions: These findings demonstrate that the CHoBI7 Cholera Rapid Response Program is effective in lowering diarrhea prevalence and increasing handwashing with soap for a population at high risk of cholera.

Trop Med Int Health. 2022 Aug;27(8):669-677.  
doi: 10.1111/tmi.13793. Epub 2022 Jun 30.

**Impact of integrated water, sanitation, hygiene, health and nutritional interventions on diarrhoea disease epidemiology and microbial quality of water in a resource-constrained setting in Kenya: A controlled intervention study**

[Ernest Apondi Wandera](#)<sup>1,2</sup>, [Betty Muriithi](#)<sup>1</sup>, [Cyrus Kathiiko](#)<sup>1</sup>, [Felix Mutunga](#)<sup>1</sup>, [Mary Wachira](#)<sup>1</sup>, [Maurine Mumo](#)<sup>1</sup>, [Anne Mwangi](#)<sup>3</sup>, [Joseph Tinkoi](#)<sup>3</sup>, [Mirasine Meiguran](#)<sup>3</sup>, [Pius Akumu](#)<sup>3</sup>, [Valeria Ndege](#)<sup>3</sup>, [Fredrick Kasiku](#)<sup>3</sup>, [James Ang'awa](#)<sup>3</sup>, [Ryoichiro Mochizuki](#)<sup>4</sup>, [Satoshi Kaneko](#)<sup>1</sup>, [Kouichi Morita](#)<sup>1</sup>, [Collins Ouma](#)<sup>5</sup>, [Yoshio Ichinose](#)<sup>1</sup>

**Abstract**

**Objectives:** We assessed the impact of water, hygiene and sanitation (WASH), maternal, new-born and child health (MNCH), nutrition and early childhood development (ECD) on diarrhoea and microbial quality of water in a resource-constrained rural setting in Kenya.

**Methods:** Through a controlled intervention study, we tested faecal and water samples collected from both the intervention and control sites before and after the interventions using microbiological, immunological and molecular assays to determine the prevalence of diarrhoeagenic agents and microbial quality of water. Data from the hospital registers were used to estimate all-cause diarrhoea prevalence.

**Results:** After the interventions, we observed a 58.2% (95% CI: 39.4-75.3) decline in all-cause diarrhoea in the intervention site versus a 22.2% (95% CI: 5.9-49.4) reduction of the same in the control site. Besides rotavirus and pathogenic *Escherichia coli*, the rate of isolation of other diarrhoea-causing bacteria declined substantially in the intervention site. The microbial quality of community and household water improved considerably in both the intervention (81.9%; 95% CI: 74.5%-87.8%) and control (72.5%; 95% CI: 64.2%-80.5%) sites with the relative improvements in the intervention site being slightly larger.

**Conclusions:** The integrated WASH, MNCH, nutrition and ECD interventions resulted in notable decline in all-cause diarrhoea and improvements in water quality in the rural resource-limited population in Kenya. This indicates a direct public health impact of the interventions and provides early evidence for public health policy makers to support the sustained implementation of these interventions.

BMJ Open. 2022 Sep 21;12(9):e060858.

doi: 10.1136/bmjopen-2022-060858.

**[Are better existing WASH practices in urban slums associated with a lower long-term risk of severe cholera? A prospective cohort study with 4 years of follow-up in Mirpur, Bangladesh](#)**

[Sophie Kang](#)<sup>#1</sup>, [Fahima Chowdhury](#)<sup>#2,3</sup>, [Juyeon Park](#)<sup>4</sup>, [Tasnuva Ahmed](#)<sup>2</sup>, [Birkneh Tilahun Tadesse](#)<sup>4</sup>, [Md Taufiqul Islam](#)<sup>2</sup>, [Deok Ryun Kim](#)<sup>4</sup>, [Justin Im](#)<sup>4</sup>, [Asma Binte Aziz](#)<sup>4</sup>, [Masuma Hoque](#)<sup>2</sup>, [Gideok Pak](#)<sup>4</sup>, [Farhana Khanam](#)<sup>2</sup>, [Faisal Ahmmed](#)<sup>2</sup>, [Xinxue Liu](#)<sup>5</sup>, [K Zaman](#)<sup>2</sup>, [Ashraful Islam Khan](#)<sup>2</sup>, [Jerome H Kim](#)<sup>6</sup>, [Florian Marks](#)<sup>4,7</sup>, [Firdausi Qadri](#)<sup>2</sup>, [John D Clemens](#)<sup>2,6,8</sup>

**Abstract**

**Objective:** To investigate the association between existing household water quality, sanitation and hygiene (WASH) practices and severe cholera risk in a dense urban slum where cholera is highly endemic.

**Design, setting and participants:** We assembled a large prospective cohort within a cluster randomised trial evaluating the effectiveness of oral cholera vaccine. Our dynamic cohort population (n=193 576) comprised individuals living in the 'non-intervention' clusters of the trial, and were followed over 4 years. This study was conducted in a dense urban slum community of Dhaka, Bangladesh and cholera surveillance was undertaken in 12 hospitals serving the study area.

**Primary outcome measure:** First severe cholera episode detected during follow-up period.

**Methods:** We applied a machine learning algorithm on a training subpopulation (n=96 943) to develop a binary ('better', 'not better') composite WASH variable predictive of severe cholera. The WASH rule was evaluated for performance in a separate validation subpopulation (n=96 633). Afterwards, we used Cox regression models to evaluate the association between 'better' WASH households and severe cholera risk over 4 years in the entire study population.

**Results:** The 'better' WASH rule found that water quality and access were the most significant factors associated with severe cholera risk. Members of 'better' WASH households, constituting one-third of the population, had a 47% reduced risk of severe cholera (95% CI: 29 to 69; p<0.001), after adjusting for covariates. The protective association between living in a 'better' WASH household and severe cholera persisted in all age groups.

**Conclusions:** Salutary existing household WASH practices were associated with a significantly reduced long-term risk of severe cholera in an urban slum of Dhaka. These findings suggest that WASH adaptations already practised in the community may be important for developing and implementing effective and sustainable cholera control programmes in similar settings.

Matern Child Health J. 2022 Jul;26(7):1507-1515.

doi: 10.1007/s10995-022-03408-3. Epub 2022 Mar 15.

**[Effects of Educational Interventions on Maternal Self-efficacy and Childhood Diarrhea: A Randomized Clinical Trial](#)**

[Jardeliny Corrêa da Penha<sup>1</sup>](#), [Ludmila Alves do Nascimento<sup>2</sup>](#), [Leidiane Minervina Moraes de Sabino<sup>3</sup>](#), [Elizamar Regina da Rocha Mendes<sup>4</sup>](#), [Silvana Santiago da Rocha<sup>5</sup>](#), [Emilia Soares Chaves Roubert<sup>3</sup>](#), [Francisca Elisângela Teixeira Lima<sup>4</sup>](#), [Regina Cláudia de Oliveira Melo<sup>4</sup>](#), [Paulo César de Almeida<sup>6</sup>](#), [Emanuella Silva Joventino Melo<sup>3</sup>](#), [Lorena Pinheiro Barbosa<sup>4</sup>](#)

### Abstract

**Objective:** Diarrhea still causes high morbidity and mortality in children under five, requiring constant interventions. Thus, the study aims to evaluate the effects of educational technologies on maternal self-efficacy to prevent childhood diarrhea.

**Methods:** Randomized clinical trial carried out in Fortaleza, Ceará, Brazil, with four randomized groups of mothers of children under 5 years of age, as follows: control group (n = 61), group A (booklet, n = 60), group B (video, n = 60), and group AB (booklet and video, n = 60). From June to October 2015, data collection was carried out in three moments (the first in person and the others by telephone monitoring).

**Results:** All groups improved their self-efficacy after the intervention, with higher scores in the group AB (booklet and video). A statistically significant association was found between the occurrence of diarrhea and maternal self-efficacy in groups A (booklet) ( $p = 0.023$ ) and AB (booklet and video) ( $p = 0.042$ ) at the second moment of data collection. From the second moment to the third moment, the risk of diarrhea decreased in group A, from 12.8 to 1.3, and in group AB, from 8.5 to 1.1.

**Conclusion:** The technologies used, isolated or combined, were effective in improving maternal self-efficacy and decreasing the occurrence of childhood diarrhea; therefore, they can be used by nurses as health education tools.

Lancet. 2022 Jul 2;400(10345):48-59.

doi: 10.1016/S0140-6736(22)00937-0.

### [Effectiveness of interventions to improve drinking water, sanitation, and handwashing with soap on risk of diarrhoeal disease in children in low-income and middle-income settings: a systematic review and meta-analysis](#)

[Jennyfer Wolf<sup>1</sup>](#), [Sydney Hubbard<sup>2</sup>](#), [Michael Brauer<sup>3</sup>](#), [Argaw Ambelu<sup>4</sup>](#), [Benjamin F Arnold<sup>5</sup>](#), [Robert Bain<sup>6</sup>](#), [Valerie Bauza<sup>2</sup>](#), [Joe Brown<sup>7</sup>](#), [Bethany A Caruso<sup>8</sup>](#), [Thomas Clasen<sup>2</sup>](#), [John M Colford Jr<sup>5</sup>](#), [Matthew C Freeman<sup>2</sup>](#), [Bruce Gordon<sup>9</sup>](#), [Richard B Johnston<sup>9</sup>](#), [Andrew Mertens<sup>5</sup>](#), [Annette Prüss-Ustün<sup>9</sup>](#), [Ian Ross<sup>10</sup>](#), [Jeffrey Stanaway<sup>11</sup>](#), [Jeff T Zhao<sup>11</sup>](#), [Oliver Cumming<sup>10</sup>](#), [Sophie Boisson<sup>9</sup>](#)

### Abstract

**Background:** Estimates of the effectiveness of water, sanitation, and hygiene (WASH) interventions that provide high levels of service on childhood diarrhoea are scarce. We aimed to provide up-to-date estimates on the burden of disease attributable to WASH and on the effects of different types of WASH interventions on childhood diarrhoea in low-income and middle-income countries (LMICs).

**Methods:** In this systematic review and meta-analysis, we updated previous reviews following their search strategy by searching MEDLINE, Embase, Scopus, Cochrane Library, and BIOSIS Citation Index for studies of basic WASH interventions and of WASH interventions providing a high level of service, published between Jan 1, 2016, and May 25, 2021. We included randomised and non-randomised controlled trials conducted at household or community level that matched exposure categories of the so-called service ladder approach

of the Sustainable Development Goal (SDG) for WASH. Two reviewers independently extracted study-level data and assessed risk of bias using a modified Newcastle-Ottawa Scale and certainty of evidence using a modified Grading of Recommendations, Assessment, Development, and Evaluation approach. We analysed extracted relative risks (RRs) and 95% CIs using random-effects meta-analyses and meta-regression models. This study is registered with PROSPERO, CRD42016043164.

**Findings:** 19 837 records were identified from the search, of which 124 studies were included, providing 83 water (62 616 children), 20 sanitation (40 799 children), and 41 hygiene (98 416 children) comparisons. Compared with untreated water from an unimproved source, risk of diarrhoea was reduced by up to 50% with water treated at point of use (POU): filtration (n=23 studies; RR 0.50 [95% CI 0.41-0.60]), solar treatment (n=13; 0.63 [0.50-0.80]), and chlorination (n=25; 0.66 [0.56-0.77]). Compared with an unimproved source, provision of an improved drinking water supply on premises with higher water quality reduced diarrhoea risk by 52% (n=2; 0.48 [0.26-0.87]). Overall, sanitation interventions reduced diarrhoea risk by 24% (0.76 [0.61-0.94]). Compared with unimproved sanitation, providing sewer connection reduced diarrhoea risk by 47% (n=5; 0.53 [0.30-0.93]). Promotion of handwashing with soap reduced diarrhoea risk by 30% (0.70 [0.64-0.76]).

**Interpretation:** WASH interventions reduced risk of diarrhoea in children in LMICs. Interventions supplying either water filtered at POU, higher water quality from an improved source on premises, or basic sanitation services with sewer connection were associated with increased reductions. Our results support higher service levels called for under SDG 6. Notably, no studies evaluated interventions that delivered access to safely managed WASH services, the level of service to which universal coverage by 2030 is committed under the SDG.

## Ear disease and hearing loss

Am J Otolaryngol. 2022 Sep-Oct;43(5):103573.

doi: 10.1016/j.amjoto.2022.103573. Epub 2022 Aug 5.

### [Pharmacokinetics of ciprofloxacin and fluocinolone acetonide otic solution in pediatric patients](#)

[Zorik Spektor](#)<sup>1</sup>, [Iftikhar Hussain](#)<sup>2</sup>, [Richard Neil Van Leeuwen](#)<sup>3</sup>, [Steven Goudy](#)<sup>4</sup>, [Kenneth Esterhuizen](#)<sup>5</sup>, [Ryan Meyer](#)<sup>6</sup>, [James Hedrick](#)<sup>7</sup>

#### Abstract

**Purpose:** To describe the pharmacokinetics (PK) of ciprofloxacin 0.3 % and fluocinolone acetonide 0.025 % otic solution (CIPRO+FLUO), ciprofloxacin 0.3 % otic solution alone (CIPRO), and fluocinolone acetonide 0.025 % otic solution alone (FLUO) administered into the middle ears of pediatric patients with Acute Otitis Media with Tympanostomy Tubes (AOMT).

**Materials and methods:** We performed a PK analysis of patients who participated in two multicenter, randomized, double-blind AOMT clinical trials (SALVAT studies CIFLOTIII/10IA02 and CIFLOTIII/10IA04). Each patient received 0.25 mL of CIPRO+FLUO, CIPRO, or FLUO twice a day instilled into the ear canal(s) for 7 days to treat AOMT. Blood samples of patients with unilateral AOMT were collected before the administration of the first dose of study medication at Visit 1 (day 1) and within 1-2 h after the last dose on day 7. Blood samples were

analyzed to detect ciprofloxacin and fluocinolone acetonide concentrations using two validated liquid chromatography-tandem mass spectrometry (LC-MS-MS) methods, with the lower limit of quantification for ciprofloxacin and fluocinolone acetonide in plasma samples being 1 ng/mL. Thirty randomly selected patients between 10 months and 10 years of age (mean age, 4.4 years) were included in the study. Although all available samples were analyzed, only PK data of the 22 patients with both samples and unilateral disease were considered for study purposes.

**Results:** No detectable concentrations of ciprofloxacin or fluocinolone acetonide in plasma were observed (<1 ng/mL).

**Conclusions:** These results demonstrated negligible systemic exposure to ciprofloxacin and fluocinolone acetonide following topical otic administration in pediatric patients with AOMT.

## **Ebola and viral haemorrhagic fever**

## **Endocrine disorders and bone health**

### **Diabetes**

### **Bone health**

## **Epilepsy and acute seizures**

Seizure. 2022 Nov;102:74-82.

doi: 10.1016/j.seizure.2022.09.017. Epub 2022 Sep 26.

[Treatment of benzodiazepine-resistant status epilepticus: Systematic review and network meta-analyses](#)

[Puneet Jain<sup>1</sup>, Satinder Aneja<sup>2</sup>, Jessie Cunningham<sup>3</sup>, Ravindra Arya<sup>4</sup>, Suvasini Sharma<sup>5</sup>](#)

### **Abstract**

**Purpose:** Multiple interventions have been studied for benzodiazepine-resistant status epilepticus (SE) in children and adults. This review aimed to summarize the available evidence and provide estimates of comparative effectiveness and ranking of treatment effects.

**Methods:** All randomized controlled trials studying patients (>1 month of age) with benzodiazepine-resistant SE were included. Outcomes including seizure cessation within 60 min, seizure freedom for 24 h, death, respiratory depression warranting intubation and cardiovascular instability were studied. Conventional and network meta-analyses (NMA) were done.

**Results:** Seventeen studies were included (16 in NMA). Phenobarbital and high-dose levetiracetam were significantly superior to phenytoin with respect to seizure cessation within 60 min. Network ranking demonstrated that phenobarbital had the highest probability of being the best among the studied interventions followed by high-dose

levetiracetam and high-dose valproate. Network meta-analysis was limited by predominant indirect evidence and high heterogeneity. On pairwise comparisons, phenobarbital was found to be associated with a higher risk of need for intubation and cardiovascular instability. Levetiracetam had a better safety profile than fosphenytoin.

**Conclusions:** Based on low quality evidence, phenobarbital appears to be the most effective agent for seizure cessation within 60 min of administration in patients with benzodiazepine resistant status epilepticus. High-dose levetiracetam, high-dose valproate and fosphenytoin are probably equally effective. Choice of medication may be guided by effectiveness, safety concerns, availability, cost and systemic co-morbidities.

Epilepsy Res. 2022 Oct 20;188:107037.

doi: 10.1016/j.eplepsyres.2022.107037. Online ahead of print.

**[The IN-MIDAZ study - Intranasal midazolam in aborting seizures - An epilepsy monitoring unit based randomized controlled trial for efficacy](#)**

[Raja Gulfam Shaikh<sup>1</sup>](#), [Bhargavi Ramanujan<sup>2</sup>](#), [Rajesh Kumar Singh<sup>2</sup>](#), [Deepti Vibha<sup>2</sup>](#), [Santosh Mehta<sup>3</sup>](#), [Renjith Appukuttan<sup>3</sup>](#), [Manjari Tripathi<sup>4</sup>](#)

**Abstract**

**Objective:** To compare efficacy and safety of Intranasal and Intramuscular routes of midazolam administration in terminating seizures.

**Method:** This was an open label Randomized controlled trial (RCT). People with drug resistant epilepsy (DRE) undergoing Video Electroencephalogram (VEEG) monitoring, were randomized in a 1:1 ratio to receive either Intranasal (IN) or Intramuscular (IM) midazolam, for prolonged seizures: longer than 5 min for focal, and longer than 2 min for focal to bilateral tonic-clonic. Outcome assessor was blinded to the allocation arm. Primary outcome was time to electrographic seizure termination after administration of midazolam. All adverse events in both the groups were noted.

**Result:** A total of 1108 seizures were recorded in 130 subjects, of which 110 (65 seizures in 23 subjects in IN group; 45 seizures in 18 subjects in IM group) seizures required midazolam administration and were included in final analysis. Mean time to electrographic seizure termination after midazolam administration was  $45.1 \pm 23.8$  s in the IM group and  $90.4 \pm 59.0$  s in the IN group ( $p = 0.0014$ ); mean time to clinical seizure termination was  $53.9 \pm 25.8$  s in IM group and  $104.3 \pm 66.4$  s in the IN group ( $p = 0.002$ ). Local side effects were more in IN group; hypotension as serious adverse event was noted in the IM group.

**Significance:** Though mean time to electrographic and clinical seizure termination was significantly lesser in Intramuscular group for both adults and pediatric population, it was still under 2 min in the Intranasal midazolam group. IN midazolam is a useful option for terminating seizures.

Indian J Pediatr. 2023 May;90(5):433-437.

doi: 10.1007/s12098-022-04178-0. Epub 2022 Jun 15.

**[Efficacy of Oral vs. Intravenous Calcium Supplementation for Continuation Therapy in Hypocalcemic Seizures: A Randomized, Controlled Trial](#)**



[Himanshu Dhir<sup>1</sup>](#), [Deepak Kumar<sup>1</sup>](#), [Dheeraj Shah<sup>1</sup>](#), [Prerna Batra<sup>1</sup>](#), [Rafat S Ahmed<sup>2</sup>](#), [Piyush Gupta<sup>3</sup>](#)

### Abstract

**Objective:** To evaluate efficacy of oral vs. intravenous calcium supplementation for continuation therapy in hypocalcemic seizures.

**Methods:** Sixty children between 1 mo and 5 y presenting with hypocalcemic seizures without any other underlying febrile, chronic systemic disease, or acute neurological illness were included. Participants were randomized to receive either intravenous (IV) 10% calcium gluconate (n = 30) or oral elemental calcium (n = 30) for 48 h following initial seizure control with intravenous calcium.

**Results:** Seizures recurred in 3 (10%) children in IV group as compared to 4 (13.3%) in oral calcium group (p = 0.278) within 48 h. Serum calcium levels achieved in the two treatment groups at 24 h [7.96 (1.32) vs. 8.23 (1.58) mg/dL; p = 0.476] and 48 h [8.5 (1.01) vs. 8.63 (1.39) mg/dL; p = 0.681] were comparable.

**Conclusion:** Oral calcium may be as efficacious as intravenous calcium during continuation phase of treating hypocalcemic seizures; however, further studies are needed for definite recommendations.

Indian J Pediatr. 2023 May;90(5):450-456.

doi: 10.1007/s12098-022-04225-w. Epub 2022 Jun 28.

### [Effect of Daily Vitamin D Supplementation on Serum Vitamin D Levels in Children with Epilepsy Receiving Sodium Valproate Monotherapy: A Randomized, Controlled Trial](#)

[Sruti Mishra<sup>1</sup>](#), [Devendra Mishra<sup>2</sup>](#), [Bhawna Mahajan<sup>3</sup>](#), [Mukta Mantan<sup>2</sup>](#), [Amir Maroof Khan<sup>4</sup>](#)

### Abstract

**Objectives:** To compare the change in serum vitamin D levels and to compare the changes in serum levels of calcium, phosphate, alkaline phosphatase and parathyroid hormone in vitamin D supplemented and unsupplemented groups after 3 mo.

**Methods:** In this randomized, parallel group, nonblinded, controlled trial, 40 children, 2-12 y of age with newly diagnosed epilepsy, and vitamin D sufficient status, and started on valproate monotherapy, were randomized into the intervention group (n = 20), which was given daily oral 600 IU vitamin D supplementation, and the control group (n = 20), which was not given any supplementation. Changes in the biochemical parameters was measured in the two groups after 3 mo.

**Results:** There was a significant reduction in the median (IQR) vitamin D levels in the control group as compared to an increase seen in the intervention group [-6.64 (-8.4, -2.65) vs. 5.66 (1.81, 7.12); p < 0.001]. In the control group, 37.5% children developed vitamin D insufficiency and 12.5% developed deficiency whereas only 5% of the intervention group developed vitamin D insufficiency (p = 0.005). There was a significant decrease in ionized calcium (p = 0.02), increase in serum phosphate (p = 0.02), and alkaline phosphatase level (p = 0.003) in the unsupplemented group as compared to the supplemented group.

**Conclusion:** Vitamin D supplementation can reduce the valproate-associated decline in vitamin D levels and the negative impact on other markers of bone mineral metabolism.



Dev Med Child Neurol. 2022 Nov;64(11):1330-1343.

doi: 10.1111/dmcn.15330. Epub 2022 Jun 29.

**Treatment of children with infantile spasms: A network meta-analysis**

[Puneet Jain<sup>1</sup>](#), [Jitendra K Sahu<sup>2</sup>](#), [Paul S Horn<sup>3,4</sup>](#), [Vann Chau<sup>5</sup>](#), [Cristina Go<sup>1</sup>](#), [Quenby Mahood<sup>6</sup>](#), [Ravindra Arya<sup>3,4</sup>](#)

**Abstract**

**Aim:** We performed a systematic review and network meta-analysis (NMA) to obtain comparative effectiveness estimates and rankings of non-surgical interventions used to treat infantile spasms.

**Method:** All randomized controlled trials (RCTs) including children 2 months to 3 years of age with infantile spasms (with hypsarrhythmia or hypsarrhythmia variants on electroencephalography) receiving appropriate first-line medical treatment were included. Electroclinical and clinical remissions within 1 month of starting treatment were analyzed.

**Results:** Twenty-two RCTs comparing first-line treatments for infantile spasms were reviewed; of these, 17 were included in the NMA. Both frequentist and Bayesian network rankings for electroclinical remission showed that high dose adrenocorticotrophic hormone (ACTH), methylprednisolone, low dose ACTH and magnesium sulfate (MgSO<sub>4</sub>) combination, low dose ACTH, and high dose prednisolone were most likely to be the 'best' interventions, although these were not significantly different from each other. For clinical remission, low dose ACTH/MgSO<sub>4</sub> combination, high dose ACTH (with/without vitamin B<sub>6</sub>), high dose prednisolone, and low dose ACTH were 'best'.

**Interpretation:** Treatments including ACTH and high dose prednisolone are more effective in achieving electroclinical and clinical remissions for infantile spasms.

**What this paper adds:** Adrenocorticotrophic hormone and high dose prednisolone are more effective than other medications for infantile spasms. Symptomatic etiology decreases the likelihood of remission even after adjusting for treatment lag.

Indian J Pediatr. 2023 May 26.

doi: 10.1007/s12098-023-04527-7. Online ahead of print.

**Modified Atkins Diet vs. Ketogenic Diet in the Management of Children with Epileptic Spasms Refractory to First Line Treatment: An Open Labelled, Randomized Controlled Trial**

[Shobhna Sharma<sup>1</sup>](#), [Surekha Dabla<sup>2</sup>](#), [Jaya Shankar Kaushik<sup>3</sup>](#)

**Abstract**

**Objective:** To compare the efficacy and tolerability of modified Atkins diet (mAD) and ketogenic diet (KD) among children aged 9 mo to 3 y with epileptic spasms refractory to the first line treatment.

**Methods:** An open labelled, randomized controlled trial with parallel group assignment was conducted among children aged 9 mo to 3 y with epileptic spasms refractory to the first line treatment. They were randomized to either receive the mAD along with conventional anti-seizure medications (n = 20) or KD with conventional anti-seizure medications (n = 20). Primary outcome measure was proportion of children who achieved "spasm freedom" at 4 wk and 12 wk. Secondary outcome measures were proportion of children who achieved >50% and >90% reduction in spasms at 4 wk and 12 wk, nature and proportion of the adverse effects as per parental reports.

**Results:** Proportion of children achieving spasm freedom [mAD {4 (20%)} vs. KD {3 (15%)}: OR (95% CI) 1.42 (0.27-7.34); P = 0.67], >50% spasm reduction [mAD {3 (15%)} vs. KD {5 (25%)}: OR (95% CI) 0.53 (0.11-2.59); P = 0.63] and >90% spasm reduction [mAD {4 (20%)} vs. KD {2 (10%)}: OR (95% CI) 2.25 (0.36-13.97); P = 0.41] was comparable between the two groups at 12 wk. The diet was well tolerated in both the groups with vomiting and constipation being the most common reported adverse effect.

**Conclusions:** mAD is an effective alternative to KD in the management of children with epileptic spasms refractory to first line treatment. However, further studies with adequately powered sample size and longer follow-up are required.

J Neurol Neurosurg Psychiatry. 2022 Dec;93(12):1299-1305.  
doi: 10.1136/jnnp-2022-329027. Epub 2022 Sep 1.

### **Efficacy of pulse intravenous methylprednisolone in epileptic encephalopathy: a randomised controlled trial**

[Anush Rangarajan<sup>1</sup>](#), [Ravindranadh Chowdary Mundlamuri<sup>1</sup>](#), [Raghavendra Kenchaiah<sup>1</sup>](#), [Parthipulli Vasuki Prathyusha<sup>2</sup>](#), [Lakshminarayanapuram Gopal Viswanathan<sup>1</sup>](#), [Ajay Asranna<sup>1</sup>](#), [Aparajita Chatterjee<sup>1</sup>](#), [Madhu Nagappa<sup>1</sup>](#), [Doniparthi Venkata Seshagiri<sup>1</sup>](#), [Karthik Kulanthaivelu<sup>3</sup>](#), [Rose Dawn Bharath<sup>3</sup>](#), [Saini Jitender<sup>3</sup>](#), [Kandavel Thennarasu<sup>2</sup>](#), [Sanjib Sinha<sup>4</sup>](#)

#### **Abstract**

**Background:** High-level evidence for using steroids in epileptic encephalopathy (EE), other than West syndrome (WS), is lacking. This study investigated the efficacy and safety of pulse intravenous methylprednisolone (IVMP) in EE other than WS.

**Methods:** This is an open-label evaluator-blinded randomised controlled study. Children aged 6 months or more with EE other than WS were included. Eighty children were randomised into intervention and non-intervention groups with 40 in each group. At the first visit (T1) seizure frequency, electroencephalographic (EEG) and Vineland Social Maturity Scale (VSMS) were obtained, and antiseizure medication (ASM) were optimised. After 1 month (T2), subjects were randomised to intervention (ASM+3 months IVMP pulse) or non-intervention group (only ASM) with 40 subjects in each group. They were followed up for 4 months (T3) and assessed.

**Results:** After 4 months of follow-up, 75% of patients receiving IVMP had >50% seizure reduction versus 15.4% in control group ( $\chi^2=28.29$ ,  $p<0.001$ ) (RR 4.88, 95% CI 2.29 to 10.40), median percentage change in seizure frequency (91.41% vs 10%,  $p<0.001$ ), improvement in EEG (45.5% vs 9.4%,  $\chi^2=10.866$ ,  $p=0.001$ ) and social age domain of VSMS scores ( $Z=-3.62$ ,  $p<0.001$ ) compared with baseline. None of the patients in the intervention group had any serious side-effects.

**Discussion:** Three-month pulse IVMP therapy showed significant improvement in seizure frequency, EEG parameters and VSMS scores, with no steroid-related serious adverse effects. It can be considered as a safe and effective add on treatment in children with EE other than WS.

Epilepsia Open. 2022 Dec;7(4):781-791.  
doi: 10.1002/epi4.12659. Epub 2022 Oct 26.

## [\*\*A cluster-randomized trial comparing home-based primary health care and usual clinic care for epilepsy in a resource-limited country\*\*](#)

[Gagandeep Singh<sup>1,2,3</sup>](#), [Suman Sharma<sup>1</sup>](#), [Namita Bansal<sup>1</sup>](#), [Meenakshi Sharma<sup>4</sup>](#), [Anurag Chowdhury<sup>5</sup>](#), [Sarit Sharma<sup>5</sup>](#), [Rajinder K Bansal<sup>2</sup>](#), [Jatinder S Goraya<sup>6</sup>](#), [Raj K Setia<sup>7</sup>](#), [Birinder S Paul<sup>2</sup>](#), [Josemir W Sander<sup>3,8,9,10</sup>](#)

### **Abstract**

**Objective:** To ascertain whether home-based care with community and primary healthcare workers' support improves adherence to antiseizure medications, seizure control, and quality of life over routine clinic-based care in community samples of people with epilepsy in a resource-poor country.

**Methods:** Participants included consenting individuals with active epilepsy identified in a population survey in impoverished communities. The intervention included antiseizure medication provision, adherence reinforcement and epilepsy self- and stigma management guidance provided by a primary health care-equivalent worker. We compared the intervention group to a routine clinic-based care group in a cluster-randomized trial lasting 24 months. The primary outcome was antiseizure medication adherence, appraised from monthly pill counts. Seizure outcomes were assessed by monthly seizure aggregates and time to first seizure and impact by the Personal Impact of Epilepsy scale.

**Results:** Enrolment began on September 25, 2017 and was complete by July 24, 2018. Twenty-four clusters, each comprising ten people with epilepsy, were randomized to either home- or clinic-care. Home-care recipients were more likely to have used up their monthly-dispensed epilepsy medicine stock (regression coefficient: 0.585; 95% confidence intervals, 0.289-0.881; P = 0.001) and had fewer seizures (regression coefficient: -2.060; 95%CI, -3.335 to -0.785; P = 0.002). More people from clinic-care (n = 44; 37%) than home-care (n = 23; 19%) exited the trial (P = 0.003). The time to first seizure, adverse effects and the personal impact of epilepsy were similar in the two arms.

**Significance:** Home care for epilepsy compared to clinic care in resource-limited communities improves medication adherence and seizure outcomes and reduces the secondary epilepsy treatment gap.

## **Fever**

## **Fluid management**

Pediatr Emerg Care. 2022 Sep 1;38(9):436-441.

doi: 10.1097/PEC.0000000000002621. Epub 2022 Jan 26.

### [\*\*0.45% Versus 0.9% Saline in 5% Dextrose as Maintenance Fluids in Children Admitted With Acute Illness: A Randomized Control Trial\*\*](#)

[Kumar Ratnjeet<sup>1</sup>](#), [Pallavi Pallavi](#), [Urmila Jhamb](#), [Romit Saxena](#)

**Background:** The safety of giving intravenous (IV) maintenance fluids according to Holliday and Segar's recommendations of 1957 has recently been questioned after reports of complications caused by iatrogenic hyponatremia in children receiving hypotonic fluids.

However, the current practice of choice of maintenance IV fluids for hospitalized children varies worldwide. This study was planned to compare 0.45% and 0.9% saline in 5% dextrose at standard maintenance rates in hospitalized children aged 3 months to 12 years.

**Objective:** Primary objective was to study change in serum sodium level at 24 hours in children receiving total IV fluid maintenance therapy as 0.45% or 0.9% normal saline in 5% dextrose. Secondary objectives of this study were to estimate change in serum sodium levels from the baseline to 48 or 72 hours, if IV fluids were continued, and to find incidence of hyponatremia and hypernatremia after administering these 2 types of maintenance fluids.

**Methods:** This study was an open-label, randomized control trial conducted at the Department of Pediatrics of a tertiary care hospital from July 22, 2019, to October 28, 2019. Two hundred children aged 3 months to 12 years admitted in pediatric emergency and requiring IV maintenance fluid were randomized into 2 groups (group A received 0.45% saline in 5% dextrose, group B received 0.9% normal saline in 5% dextrose) with 100 in each group.

**Results:** Both groups were comparable for baseline characteristics. Fall in mean serum sodium from baseline was more with increasing duration of IV fluids until 24 hours in 0.45% saline group as compared with 0.9% saline group, which was statistically significant ( $P < 0.001$ ). The incidence of mild and moderate hyponatremia was significantly more in hypotonic group at 12 hours ( $P < 0.001$ ) and 24 hours ( $P < 0.001$ ). However, there was no significant difference at 48 hours.

**Conclusions:** The fall in serum sodium values was significant, and there was significant risk of hyponatremia with the use of hypotonic fluids at 12 and 24 hours. Hence, the use of isotonic fluids seems to be more appropriate among the hospitalized children.

Cochrane Database Syst Rev. 2023 May 17;5(5):CD013640.

doi: 10.1002/14651858.CD013640.pub2.

### [Balanced crystalloid solutions versus 0.9% saline for treating acute diarrhoea and severe dehydration in children](#)

[Ivan D Florez](#)<sup>1,2,3</sup>, [Javier Sierra](#)<sup>1,4</sup>, [Giordano Pérez-Gaxiola](#)<sup>5</sup>

#### **Abstract**

**Background:** Although acute diarrhoea is a self-limiting disease, dehydration may occur in some children. Dehydration is the consequence of an increased loss of water and electrolytes (sodium, chloride, potassium, and bicarbonate) in liquid stools. When these losses are high and not replaced adequately, severe dehydration appears. Severe dehydration is corrected with intravenous solutions. The most frequently used solution for this purpose is 0.9% saline. Balanced solutions (e.g. Ringer's lactate) are alternatives to 0.9% saline and have been associated with fewer days of hospitalization and better biochemical outcomes. Available guidelines provide conflicting recommendations. It is unclear whether 0.9% saline or balanced intravenous fluids are most effective for rehydrating children with severe dehydration due to diarrhoea.

**Objectives:** To evaluate the benefits and harms of balanced solutions for the rapid rehydration of children with severe dehydration due to acute diarrhoea, in terms of time in hospital and mortality compared to 0.9% saline.

**Search methods:** We used standard, extensive Cochrane search methods. The latest search date was 4 May 2022.

**Selection criteria:** We included randomized controlled trials in children with severe dehydration due to acute diarrhoea comparing balanced solutions, such as Ringer's lactate or Plasma-Lyte with 0.9% saline solution, for rapid rehydration.

**Data collection and analysis:** We used standard Cochrane methods. Our primary outcomes were 1. time in hospital and 2.

**Mortality:** Our secondary outcomes were 3. need for additional fluids, 4. total amount of fluids received, 5. time to resolution of metabolic acidosis, 6. change in and the final values of biochemical measures (pH, bicarbonate, sodium, chloride, potassium, and creatinine), 7. incidence of acute kidney injury, and 8.

**Adverse events:** We used GRADE to assess the certainty of the evidence.

**Main results:** Characteristics of the included studies We included five studies with 465 children. Data for meta-analysis were available from 441 children. Four studies were conducted in low- and middle-income countries and one study in two high-income countries. Four studies evaluated Ringer's lactate, and one study evaluated Plasma-Lyte. Two studies reported the time in hospital, and only one study reported mortality as an outcome. Four studies reported final pH and five studies reported bicarbonate levels. Adverse events reported were hyponatremia and hypokalaemia in two studies each. Risk of bias All studies had at least one domain at high or unclear risk of bias. The risk of bias assessment informed the GRADE assessments. Primary outcomes Compared to 0.9% saline, the balanced solutions likely result in a slight reduction of the time in hospital (mean difference (MD) -0.35 days, 95% confidence interval (CI) -0.60 to -0.10; 2 studies; moderate-certainty evidence). However, the evidence is very uncertain about the effect of the balanced solutions on mortality during hospitalization in severely dehydrated children (risk ratio (RR) 0.33, 95% CI 0.02 to 7.39; 1 study, 22 children; very low-certainty evidence). Secondary outcomes Balanced solutions probably produce a higher increase in blood pH (MD 0.06, 95% CI 0.03 to 0.09; 4 studies, 366 children; low-certainty evidence) and bicarbonate levels (MD 2.44 mEq/L, 95% CI 0.92 to 3.97; 443 children, four studies; low-certainty evidence). Furthermore, balanced solutions likely reduces the risk of hypokalaemia after the intravenous correction (RR 0.54, 95% CI 0.31 to 0.96; 2 studies, 147 children; moderate-certainty evidence). Nonetheless, the evidence suggests that balanced solutions may result in no difference in the need for additional intravenous fluids after the initial correction; in the amount of fluids administered; or in the mean change of sodium, chloride, potassium, and creatinine levels.

**Authors' conclusions:** The evidence is very uncertain about the effect of balanced solutions on mortality during hospitalization in severely dehydrated children. However, balanced solutions likely result in a slight reduction of the time in the hospital compared to 0.9% saline. Also, balanced solutions likely reduce the risk of hypokalaemia after intravenous correction. Furthermore, the evidence suggests that balanced solutions compared to 0.9% saline probably produce no changes in the need for additional intravenous fluids or in other biochemical measures such as sodium, chloride, potassium, and creatinine levels. Last, there may be no difference between balanced solutions and 0.9% saline in the incidence of hyponatraemia.

**[Comparison of isotonic versus hypotonic intravenous fluid for maintenance fluid therapy in neonates more than or equal to 34 weeks of gestational age - a randomized clinical trial](#)**

[Krishna Dathan](#)<sup>1</sup>, [Mangalabharathi Sundaram](#)<sup>2</sup>

**Abstract**

**Background and objectives:** The use of hypotonic fluids as maintenance therapy in the neonatal population has been in practice for a long time, but there is a lack of evidence for the choice of this fluid in neonates. This study compared isotonic (sodium chloride, 0.9%, and dextrose, 5%) versus hypotonic (sodium chloride, 0.15%, and dextrose, 5%) intravenous fluid for maintenance fluid therapy in neonates more than or equal to 34 weeks of gestational age.

**Methods:** In this triple-blind randomized clinical trial, we recruited 60 neonates admitted to a neonatal intensive care unit of a tertiary care children's hospital from June 2017 through May 2018 with normal baseline serum sodium levels, anticipated to require intravenous maintenance fluids for 24 hours or longer (intention-to-treat analyses). Patients were randomized to receive isotonic or hypotonic intravenous fluid at maintenance rates for 72 hours. The primary outcome was the incidence of hyponatremia (defined as serum sodium <135mEq/L) at 24 hours in both groups. The secondary outcomes were incidence of hypernatremia at 24 hours (defined as serum sodium >145 mEq/L), the incidence of hypo and hypernatremia at 48 and 72 hours, mean serum sodium at 24, 48, and 72 hours, rate of change of serum sodium during the study period, mean serum osmolality at the end of the study period, the absolute difference in osmolality during the study period, the absolute difference in weight during the study period and edema during the study period.

**Results:** Of 60 enrolled neonates, 31 received isotonic fluids and 29 received hypotonic fluids. Three patients in the hypotonic group developed hyponatremia and none in isotonic group at 24 h (RR = 0.13; 95% CI = 0.007 - 2.485;  $p = .106$ ). Fourteen neonates developed hypernatremia in the isotonic group and one in hypotonic group at 24 h (RR = 13.09; 95% CI = 1.83 - 93.4;  $p = .0001$ ).

**Conclusions:** Our study results do not support the hypothesis that isotonic fluid is superior to hypotonic fluid in reducing the proportion of neonates developing hyponatremia after 24 hours of intravenous fluid therapy. The proportion of neonates developing hypernatremia is significantly higher after using isotonic fluid for maintenance therapy.

J Pediatr Surg. 2023 Apr;58(4):735-740.

doi: 10.1016/j.jpedsurg.2022.11.015. Epub 2022 Dec 16.

**[Goal-directed fluid therapy guided by Plethysmographic Variability Index \(PVI\) versus conventional liberal fluid administration in children during elective abdominal surgery: A randomized controlled trial](#)**

[Preethy J Mathew](#)<sup>1</sup>, [Sanjay Sharma](#)<sup>1</sup>, [Neerja Bhardwaj](#)<sup>1</sup>, [Vighnesh Ashok](#)<sup>2</sup>, [Muneer A Malik](#)<sup>3</sup>

**Abstract**

**Background:** PVI has been shown to be an accurate predictor of fluid responsiveness in paediatric patients. Evidence regarding the role of PVI to guide intraoperative fluid therapy in paediatric abdominal surgery is lacking. We aimed to assess the effect of PVI-guided fluid therapy on the volume of intraoperative fluids administered and post-operative biochemical and recovery profile in children undergoing elective abdominal surgery.



**Methods:** 42 children, 6 months-3 years scheduled for elective open bowel surgery were randomised to receive either 'conventional liberal intraoperative fluids' (liberal group) or 'goal-directed intraoperative fluids' (GDT group). PVI <13 was targeted in the GDT group. The primary outcome was the volume of intraoperative fluids administered. Postoperative serum lactate, base excess, hematocrit, recovery of bowel function and duration of postoperative hospital stay were the secondary outcomes.

**Results:** The mean fluid administered intra-operatively was significantly lower in the GDT group as compared to the liberal group ( $24.1 \pm 9.6$  mL/kg vs  $37.0 \pm 8.9$  mL/kg,  $p < 0.001$ ). The postoperative hemoglobin concentration (g%) was significantly lower in the liberal group as compared to the GDT group ( $8.1 \pm 1.3$  vs  $9.2 \pm 1.4$ ,  $p = 0.008$ ). Recovery of bowel function (hours) was significantly delayed in the liberal group as compared to the GDT group ( $58.2 \pm 17.9$  vs  $36.5 \pm 14.1$ ,  $p < 0.001$ ).

**Conclusion:** Intraoperative PVI-guided fluid therapy significantly reduces the volume of intravenous crystalloids administered to children undergoing open bowel surgery. These children also had faster recovery of bowel function and less hemodilution in the immediate postoperative period, compared to those who received liberal intraoperative fluid therapy.

## Fungal infections

## Gastrointestinal problems

J Ethnopharmacol. 2022 Nov 15;298:115582.

doi: 10.1016/j.jep.2022.115582. Epub 2022 Aug 10.

### [Rosa damascena together with brown sugar mitigate functional constipation in children over 12 months old: A double-blind randomized controlled trial](#)

[Mohammad Hadi Imanieh<sup>1</sup>](#), [Naser Honar<sup>1</sup>](#), [Abdolali Mohagheghzadeh<sup>2</sup>](#), [Mahmood Haghighat<sup>1</sup>](#), [Seyed Mohsen Dehghani<sup>1</sup>](#), [Ghazaleh Mosleh<sup>3</sup>](#), [Maryam Ataollahi<sup>1</sup>](#), [Heidar Safarpour<sup>4</sup>](#), [Behnaz Darban<sup>5</sup>](#), [Fereshteh Karbasian<sup>5</sup>](#), [Ali Reza Safarpour<sup>1</sup>](#), [Amir Hossein Hassani<sup>6</sup>](#), [Abbas Avazpour<sup>7</sup>](#)

#### Abstract

**Ethnopharmacological relevance:** *Rosa × damascena* Herrm., known as damask rose, is a bushy shrub that is found abundantly in Fars province, Iran. This species has been used in Iranian traditional practices for the treatment of abdominal pain and constipation, as gastrointestinal diseases. Brown sugar (*Saccharum officinarum* L.) has also shown laxative effects in pediatric patients with functional constipation.

**Aim of study:** This study aimed to compare the effects of Polyethylene Glycol (PEG) and a syrup made of *R. damascena* and brown sugar on the treatment of functional constipation in children aged above 12 months.

**Materials and methods:** This double-blind randomized clinical trial was performed on 100 patients. One group received PEG and the other received an herbal syrup containing the decocted extract of 0.1 g *R. damascena* petals mixed with 0.85 g brown sugar per 1 mL. The patients were followed up for two and four weeks and their progresses were recorded.

**Results:** The cure rate was 100% in the R. damascena group and 91.7% in the control group. R. damascena and brown sugar syrup had an odds ratio of 1.09 in the treatment of functional constipation compared to PEG, but the difference was not statistically significant. The only adverse effect detected in the R. damascena group after four weeks was the bad taste of the medication that was too sweet. Nonetheless, this could be solved during the pharmaceutical processes.

**Conclusion:** The R. damascena extract and brown sugar syrup can be used as an effective, safe, and inexpensive agent in the treatment of functional constipation.

J Pediatr Gastroenterol Nutr. 2023 Jan 1;76(1):14-19.

doi: 10.1097/MPG.0000000000003622. Epub 2022 Sep 22.

### **Efficacy of Oral Psyllium in Pediatric Irritable Bowel Syndrome: A Double-Blind Randomized Control Trial**

[Jagadeesh Menon<sup>1</sup>](#), [Babu Ram Thapa<sup>1</sup>](#), [Rajni Kumari<sup>2</sup>](#), [Srikanth Puttaiah Kadyada<sup>1</sup>](#), [Satyavati Rana<sup>3</sup>](#), [Sadhna B Lal<sup>1</sup>](#)

#### **Abstract**

**Objective:** Pediatric irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder with variable response to various therapeutic agents. Psyllium has been proven to be effective in adults; however, there is no study in children. The objective of this study is to evaluate the efficacy of psyllium husk as compared to placebo in pediatric IBS patients.

**Methods:** In this double-blind randomized controlled trial, 43 children were assigned to psyllium arm (Group A) and 38 into placebo arm (Group B). Severity is assessed at baseline and after 4 weeks of treatment using IBS severity scoring scale (IBS-SSS) and classified into mild, moderate, and severe categories. Categorical data was compared with chi-square test and paired categorical variable was compared with McNemer test.

**Results:** Mean ages ( $\pm$ SD; in years) of Groups A and B were 9.87 (2.7) and 9.82 (3.17), respectively, with median duration of illness of 12 months. At baseline, type, severity, and parameters (IBS-SSS) of IBS were equally distributed in 2 groups. There was a significant reduction in median interquartile range (IQR) of total IBS-SSS in psyllium versus placebo [75 (42.5-140) vs 225 (185-270);  $P < 0.001$ ] at 4 weeks. Similarly 43.9% in Group A versus 9.7% in Group B attained remission [IBS-SSS  $< 75$  ( $P < 0.0001$ )]. The mean difference in IBS-SSS between Group A and Group B was -122.85 with risk ratio of 0.64 (95% CI; 0.42-0.83;  $P = 0.001$ ) and absolute risk reduction of 32% (NNT = 3).

**Conclusions:** Psyllium husk is effective for the therapy of pediatric IBS when compared with placebo in short term.

## **Hygiene, sanitation and environmental health**

### **Indoor air pollution**

Environ Res

. 2023 Apr 29;231(Pt 1):115991.

doi: 10.1016/j.envres.2023.115991. Online ahead of print.

**[Who benefits most from a prenatal HEPA filter air cleaner intervention on childhood cognitive development? The UGAAR randomized controlled trial](#)**

[Battsetseg Ulziikhuu](#)<sup>1</sup>, [Enkhjargal Gombojav](#)<sup>2</sup>, [Chimeglkham Banzrai](#)<sup>2</sup>, [Sarangerel Batsukh](#)<sup>2</sup>, [Enkhtuul Enkhtuya](#)<sup>2</sup>, [Buyantushig Boldbaatar](#)<sup>2</sup>, [David C Bellinger](#)<sup>3</sup>, [Bruce P Lanphear](#)<sup>4</sup>, [Lawrence C McCandless](#)<sup>4</sup>, [Pablo Nepomnaschy](#)<sup>4</sup>, [Katrina Salvante](#)<sup>4</sup>, [Joanne Weinberg](#)<sup>5</sup>, [Ryan W Allen](#)<sup>6</sup>

**Abstract**

**Background:** Air pollution exposure during pregnancy affects children's brain function. Maternal stress and nutrition, socioeconomic status, and the child's sex may modify this relationship.

**Objective:** To identify characteristics of children with the largest increases in full-scale IQ (FSIQ) after their mothers used HEPA filter air cleaners during pregnancy.

**Methods:** In this randomized controlled trial we randomly assigned women to receive 1-2 air cleaners or no air cleaners during pregnancy. We analyzed maternal hair samples for cortisol and dehydroepiandrosterone (DHEA). When the children were 48 months old, we measured FSIQ with the Wechsler Preschool and Primary Scale of Intelligence. We evaluated ten potential modifiers of the intervention-FSIQ relationship using interaction terms in separate regression models. To account for correlations between modifiers, we also used a single regression model containing main effects and intervention x modifier terms for all potential modifiers.

**Results:** Among 242 mother-child dyads with complete data, the intervention was associated with a 2.3-point increase (95% CI: -1.5, 6.0 points) in mean FSIQ. The intervention improved mean FSIQ among children of mothers in the bottom (5.4 points; 95% CI: -0.8, 11.5) and top (6.1 points; 95% CI: 0.5, 11.8) cortisol tertiles, but not among those whose mothers were in the middle tertile. The largest between-group difference in the intervention's effect was a 7.5-point (95% CI: -0.7, 15.7) larger increase in mean FSIQ among children whose mothers did not take vitamins than among children whose mothers did take vitamins (interaction p-value = 0.07). We also observed larger benefits among children whose mothers did not complete university, and those with lower hair DHEA concentrations, hair cortisol concentrations outside the middle tertile, or more perceived stress.

**Conclusion:** The benefits of reducing air pollution during pregnancy on brain development may be greatest for children whose mothers who do not take vitamins, experience more stress, or have less education.

Environ Int. 2022 Jul 25;168:107432.

doi: 10.1016/j.envint.2022.107432. Online ahead of print.

**[Portable HEPA filter air cleaner use during pregnancy and children's autistic behaviors at four years of age: The UGAAR randomized controlled trial](#)**

[Undarmaa Enkhbat](#)<sup>1</sup>, [Enkhjargal Gombojav](#)<sup>2</sup>, [Chimeglkham Banzrai](#)<sup>3</sup>, [Sarangerel Batsukh](#)<sup>4</sup>, [Buyantushig Boldbaatar](#)<sup>5</sup>, [Enkhtuul Enkhtuya](#)<sup>6</sup>, [David C Bellinger](#)<sup>7</sup>, [Bruce P Lanphear](#)<sup>8</sup>, [Lawrence C McCandless](#)<sup>9</sup>, [Ryan W Allen](#)<sup>10</sup>

**Abstract**

**Background:** Developmental exposure to airborne particulate matter (PM) may increase children's risk of developing autism spectrum disorder. We quantified the impact of reducing PM exposure during pregnancy on the development of autistic traits in children. We also

assessed associations between indoor fine PM (PM<sub>2.5</sub>) concentrations during pregnancy and autistic traits.

**Methods:** In this parallel-group randomized controlled trial, we randomized 540 non-smoking pregnant women to receive HEPA filter air cleaners or to a control group, which did not receive air cleaners. We administered the Social Responsiveness Scale (SRS-2) to caregivers when children were a median of 48 months (range: 48 to 51 months). Our primary outcome was the SRS-2 total T-score. We imputed missing data using multiple imputation with chained equations and our primary analysis was by intention to treat. In secondary analyses, we estimated associations between full pregnancy and trimester-specific indoor PM<sub>2.5</sub> concentrations and T-scores.

**Results:** We enrolled participants at a median of 11 weeks' gestation. Our analysis included 478 children (233 control, 245 intervention). The intervention reduced average indoor PM<sub>2.5</sub> concentrations by 29% (95% CI: 21, 37%). The mean SRS-2 total T-score was 0.5 units lower (95% CI: -2.5, 1.5) among intervention participants, with evidence of larger benefits for children at the high end of the T-score distribution. An interquartile range (9.6 µg/m<sup>3</sup>) increase in indoor PM<sub>2.5</sub> during pregnancy was associated with 1.8-unit (95% CI: 0.3, 3.2) increase in mean SRS-2 total T-score. Effect estimates for PM<sub>2.5</sub> concentrations by trimester were smaller and confidence intervals spanned no effect.

**Conclusion:** Reducing indoor PM during pregnancy had little impact on mean autism-related behavior scores in children. However, indoor PM<sub>2.5</sub> concentrations during pregnancy were associated with higher scores. Exposure to particulate matter during pregnancy may influence the development of autistic traits in childhood.

N Engl J Med. 2022 Nov 10;387(19):1735-1746.

doi: 10.1056/NEJMoa2206734. Epub 2022 Oct 10.

### [Liquefied Petroleum Gas or Biomass for Cooking and Effects on Birth Weight](#)

[Thomas F Clasen](#)<sup>1</sup>, [Howard H Chang](#)<sup>1</sup>, [Lisa M Thompson](#)<sup>1</sup>, [Miles A Kirby](#)<sup>1</sup>, [Kalpana Balakrishnan](#)<sup>1</sup>, [Anaité Díaz-Artiga](#)<sup>1</sup>, [John P McCracken](#)<sup>1</sup>, [Ghislaine Rosa](#)<sup>1</sup>, [Kyle Steenland](#)<sup>1</sup>, [Ashley Younger](#)<sup>1</sup>, [Vigneswari Aravindalochanan](#)<sup>1</sup>, [Dana B Barr](#)<sup>1</sup>, [Adly Castañaza](#)<sup>1</sup>, [Yunyun Chen](#)<sup>1</sup>, [Marilú Chiang](#)<sup>1</sup>, [Maggie L Clark](#)<sup>1</sup>, [Sarada Garg](#)<sup>1</sup>, [Stella Hartinger](#)<sup>1</sup>, [Shirin Jabbarzadeh](#)<sup>1</sup>, [Michael A Johnson](#)<sup>1</sup>, [Dong-Yun Kim](#)<sup>1</sup>, [Amy E Lovvorn](#)<sup>1</sup>, [Eric D McCollum](#)<sup>1</sup>, [Libny Monroy](#)<sup>1</sup>, [Lawrence H Moulton](#)<sup>1</sup>, [Alexie Mukeshimana](#)<sup>1</sup>, [Krishnendu Mukhopadhyay](#)<sup>1</sup>, [Luke P Naeher](#)<sup>1</sup>, [Florien Ndagijimana](#)<sup>1</sup>, [Aris Papageorghiou](#)<sup>1</sup>, [Ricardo Piedrahita](#)<sup>1</sup>, [Ajay Pillariseti](#)<sup>1</sup>, [Naveen Puttaswamy](#)<sup>1</sup>, [Ashlinn Quinn](#)<sup>1</sup>, [Usha Ramakrishnan](#)<sup>1</sup>, [Sankar Sambandam](#)<sup>1</sup>, [Sheela S Sinharoy](#)<sup>1</sup>, [Gurusamy Thangavel](#)<sup>1</sup>, [Lindsay J Underhill](#)<sup>1</sup>, [Lance A Waller](#)<sup>1</sup>, [Jiantong Wang](#)<sup>1</sup>, [Kendra N Williams](#)<sup>1</sup>, [Joshua P Rosenthal](#)<sup>1</sup>, [William Checkley](#)<sup>1</sup>, [Jennifer L Peel](#)<sup>1</sup>, [HAPIN Investigators](#)

### **Abstract**

**Background:** Exposure during pregnancy to household air pollution caused by the burning of solid biomass fuel is associated with adverse health outcomes, including low birth weight. Whether the replacement of a biomass cookstove with a liquefied petroleum gas (LPG) cookstove would result in an increase in birth weight is unclear.

**Methods:** We performed a randomized, controlled trial involving pregnant women (18 to <35 years of age and at 9 to <20 weeks' gestation as confirmed on ultrasonography) in Guatemala, India, Peru, and Rwanda. The women were assigned in a 1:1 ratio to use a free

LPG cookstove and fuel (intervention group) or to continue using a biomass cookstove (control group). Birth weight, one of four prespecified primary outcomes, was the primary outcome for this report; data for the other three outcomes are not yet available. Birth weight was measured within 24 hours after birth. In addition, 24-hour personal exposures to fine particulate matter (particles with a diameter of  $\leq 2.5 \mu\text{m}$  [ $\text{PM}_{2.5}$ ]), black carbon, and carbon monoxide were measured at baseline and twice during pregnancy.

**Results:** A total of 3200 women underwent randomization; 1593 were assigned to the intervention group, and 1607 to the control group. Uptake of the intervention was nearly complete, with traditional biomass cookstoves being used at a median rate of less than 1 day per month. After randomization, the median 24-hour personal exposure to fine particulate matter was  $23.9 \mu\text{g}$  per cubic meter in the intervention group and  $70.7 \mu\text{g}$  per cubic meter in the control group. Among 3061 live births, a valid birth weight was available for 94.9% of the infants born to women in the intervention group and for 92.7% of infants born to those in the control group. The mean ( $\pm\text{SD}$ ) birth weight was  $2921\pm 474.3 \text{ g}$  in the intervention group and  $2898\pm 467.9 \text{ g}$  in the control group, for an adjusted mean difference of  $19.6 \text{ g}$  (95% confidence interval,  $-10.1$  to  $49.2$ ).

**Conclusions:** The birth weight of infants did not differ significantly between those born to women who used LPG cookstoves and those born to women who used biomass cookstoves.

PLoS One. 2022 Jul 28;17(7):e0272053.

doi: 10.1371/journal.pone.0272053. eCollection 2022.

**[Impact of prenatal maternal psychological distress on fetal biometric parameters in household air pollution-exposed Nigerian women](#)**

[Oluwafunmilade Deji-Abiodun](#)<sup>1</sup>, [Babatunde Adedokun](#)<sup>1</sup>, [Donee Alexander](#)<sup>1</sup>, [Anindita Dutta](#)<sup>1</sup>, [Tope Ibigbami](#)<sup>2</sup>, [John Olamijulo](#)<sup>2</sup>, [Dayo Adepoju](#)<sup>2</sup>, [Samuel Adekunle](#)<sup>2</sup>, [Oladosu Ojengbede](#)<sup>3</sup>, [Christopher O Olopade](#)<sup>1</sup>

**Abstract**

**Rationale:** Studies identify prenatal household air pollution (HAP) exposure and maternal psychological distress (PMPD) as independent factors contributing to gestational ill-health and adverse birth outcomes.

**Objective:** We investigated the impact of PMPD on fetal biometric parameters (FBP) in HAP-exposed pregnant Nigerian women.

**Methods:** The randomized controlled trial (RCT; ClinicalTrials.gov [NCT02394574](#)) investigated effects of HAP exposure in pregnant Nigerian women ( $n = 324$ ), who customarily cooked with polluting fuels (firewood or kerosene). Half of the women (intervention group) were given CleanCook ethanol stoves to use for 156 days during the study. Once a month, all women were administered an abridged version of the SF-12v2TM health-related quality of life questionnaire to assess psychological distress. Using mixed effects linear regression models, adjusted for relevant covariates, we analyzed associations between the women's exposure to  $\text{PM}_{2.5}$  (particulate matter with an aerodynamic diameter  $< 2.5$  microns) from HAP, their PMPD scores, and FBP (ultrasound estimated fetal weight [UEFW], head circumference [HC], abdominal circumference [AC], femur length [FL], biparietal diameter [BPD], estimated gestational age [GA] and intrauterine growth restriction [IUGR]), and birth anthropometric measures (birth weight [BW] and birth length [BL]).

**Results:** PMPD negatively impacted UEFW, HC, FL, BPD and BL ( $p < 0.05$ ). Controls (kerosene/firewood users) experienced significantly higher PMPD compared with ethanol-stove users ( $p < 0.05$ ). The mediation analysis revealed that the proportion of the outcome (fetal biometrics, birth anthropometrics, IUGR and GA), which can be explained via PMPD by groups (intervention vs. control) after adjusting for confounding variables was 6.2% (0.062). No significant correlation was observed between levels of PM<sub>2.5</sub> exposure and PMPD scores. **Conclusions:** PMPD was an independent mediator of adverse fetal biometric parameters in pregnant women, who were exposed to HAP from burning of firewood/kerosene. Formulating preventative measures to alleviate maternal distress during pregnancy and reducing exposure to HAP is important from public health perspectives.

## Water, Sanitation and Hygiene

(see also Diarrhoea – prevention)

BMC Public Health. 2022 Nov 7;22(1):2034.

doi: 10.1186/s12889-022-14398-w.

### [School water, sanitation, and hygiene \(WaSH\) intervention to improve malnutrition, dehydration, health literacy, and handwashing: a cluster-randomised controlled trial in Metro Manila, Philippines](#)

[Stephanie O Sangalang<sup>1</sup>](#), [Allen Lemuel G Lemence<sup>2</sup>](#), [Zheina J Ottong<sup>3,4</sup>](#), [John Cedrick Valencia<sup>5</sup>](#), [Mikaela Olaguera<sup>6</sup>](#), [Rovin James F Canja<sup>5</sup>](#), [Shyrill Mae F Mariano<sup>7</sup>](#), [Nelissa O Prado<sup>8,9</sup>](#), [Roazel Mari Z Ocaña<sup>10</sup>](#), [Patricia Andrea A Singson<sup>11</sup>](#), [Maria Lourdes Cumagun<sup>12</sup>](#), [Janine Liao<sup>13</sup>](#), [Maria Vianca Jasmin C Anglo<sup>14</sup>](#), [Christian Borgemeister<sup>15</sup>](#), [Thomas Kistemann<sup>15,16</sup>](#)

#### Abstract

**Background:** The impacts of multicomponent school water, sanitation, and hygiene (WaSH) interventions on children's health are unclear. We conducted a cluster-randomized controlled trial to test the effects of a school WaSH intervention on children's malnutrition, dehydration, health literacy (HL), and handwashing (HW) in Metro Manila, Philippines.

**Methods:** The trial lasted from June 2017 to March 2018 and included children, in grades 5, 6, 7, and 10, from 15 schools. At baseline 756 children were enrolled. Seventy-eight children in two clusters were purposively assigned to the control group (CG); 13 clusters were randomly assigned to one of three intervention groups: low-intensity health education (LIHE; two schools,  $n = 116$  children), medium-intensity health education (MIHE; seven schools,  $n = 356$  children), and high-intensity health education (HIHE; four schools,  $n = 206$  children). The intervention consisted of health education (HE), WaSH policy workshops, provision of hygiene supplies, and WaSH facilities repairs. Outcomes were: height-for-age and body mass index-for-age Z scores (HAZ, BAZ); stunting, undernutrition, overnutrition, dehydration prevalence; HL and HW scores. We used anthropometry to measure children's physical growth, urine test strips to measure dehydration, questionnaires to measure HL, and observation to measure HW practice. The same measurements were used during baseline and endline. We used multilevel mixed-effects logistic and linear regression models to assess intervention effects.



**Results:** None of the interventions reduced undernutrition prevalence or improved HAZ, BAZ, or overall HL scores. Low-intensity HE reduced stunting (adjusted odds ratio [aOR] 0.95; 95% CI 0.93 to 0.96), while low- (aOR 0.57; 95% CI 0.34 to 0.96) and high-intensity HE (aOR 0.63; 95% CI 0.42 to 0.93) reduced overnutrition. Medium- (adjusted incidence rate ratio [aIRR] 0.02; 95% CI 0.01 to 0.04) and high-intensity HE (aIRR 0.01; 95% CI 0.00 to 0.16) reduced severe dehydration. Medium- (aOR 3.18; 95% CI 1.34 to 7.55) and high-intensity HE (aOR 3.89; 95% CI 3.74 to 4.05) increased observed HW after using the toilet/urinal.

**Conclusion:** Increasing the intensity of HE reduced prevalence of stunting, overnutrition, and severe dehydration and increased prevalence of observed HW. Data may be relevant for school WaSH interventions in the Global South. Interventions may have been more effective if adherence was higher, exposure to interventions longer, parents/caregivers were more involved, or household WaSH was addressed.

Vaccine. 2023 Mar 31;41(14):2368-2375.

doi: 10.1016/j.vaccine.2023.02.054. Epub 2023 Mar 8.

**[The interplay between WASH practices and vaccination with oral cholera vaccines in protecting against cholera in urban Bangladesh: Reanalysis of a cluster-randomized trial](#)**

[Fahima Chowdhury](#)<sup>1</sup>, [Asma Binte Aziz](#)<sup>2</sup>, [Faisal Ahmmed](#)<sup>3</sup>, [Tasnuva Ahmed](#)<sup>3</sup>, [Sophie Sy Kang](#)<sup>2</sup>, [Justin Im](#)<sup>2</sup>, [Juyeon Park](#)<sup>4</sup>, [Birkneh Tilahun Tadesse](#)<sup>2</sup>, [Md Taufiqul Islam](#)<sup>3</sup>, [Deok Ryun Kim](#)<sup>2</sup>, [Masuma Hoque](#)<sup>3</sup>, [Gideok Pak](#)<sup>2</sup>, [Farhana Khanam](#)<sup>3</sup>, [Nigel A J McMillan](#)<sup>5</sup>, [Xinxue Liu](#)<sup>6</sup>, [Khalequ Zaman](#)<sup>3</sup>, [Ashraful Islam Khan](#)<sup>3</sup>, [Jerome H Kim](#)<sup>2</sup>, [Florian Marks](#)<sup>7</sup>, [Firdausi Qadri](#)<sup>3</sup>, [John D Clemens](#)<sup>8</sup>

**Abstract**

The current global initiative to end Cholera by 2030 emphasizes the use of oral cholera vaccine (OCV) combined with feasible household Water-Sanitation-Hygiene (WASH) interventions. However, little is known about how improved WASH practices and behaviors and OCV interact to reduce the risk of cholera. We reanalyzed two arms of a cluster-randomized trial in urban Bangladesh, to evaluate the effectiveness of OCV given as a 2-dose regimen. One arm (30 clusters, n = 94,675) was randomized to vaccination of persons aged one year and older with OCV, and the other arm (30 clusters, n = 80,056) to no intervention. We evaluated the prevention of cholera by household WASH, classified at baseline using a previously validated rule, and OCV over 2 years of follow-up. When analyzed by assignment to OCV clusters rather than receipt of OCV, in comparison to persons living in "Not Better WASH" households in the control clusters, reduction of severe cholera (the primary outcome) was similar for persons in "Not Better WASH" households in vaccine clusters (46%, 95% CI:24,62), for persons in "Better WASH" households in the control clusters (48%, 95% CI:25,64), and for persons in "Better WASH" households in the vaccine clusters (48%, 95% CI:16,67). In contrast, when analyzed by actual receipt of a complete OCV regimen, in comparison to persons in "Not Better WASH" households in the control clusters, protection against severe cholera increased steadily from 39% (95% CI:13,58) in residents of "Better WASH" households in the control clusters to 57% (95% CI:35,72) in vaccinated persons in "Not Better WASH" households to 63% (95% CI:21,83) in vaccinated persons in "Better WASH" households. This analysis suggests that improved household WASH and OCV received may interact to provide greater protection against cholera. However, the divergence

between findings related to intent to vaccinate versus those pertaining to actual receipt of OCV underscores the need for further research on this topic.

Public Health Nutr. 2022 Nov;25(11):3195-3203.  
doi: 10.1017/S1368980022001744. Epub 2022 Aug 19.

**[How providing a low-cost water filter pitcher led Latino parents to reduce sugar-sweetened beverages and increase their water intake: explanatory qualitative results from the Water Up!@Home intervention trial](#)**

[Claudia Santillán-Vázquez](#)<sup>1</sup>, [Lucero Hernández](#)<sup>2</sup>, [Amanda C Reese](#)<sup>2</sup>, [Rosalina Burgos-Gil](#)<sup>3</sup>, [Sean D Cleary](#)<sup>2</sup>, [Ivonne M Rivera](#)<sup>4</sup>, [Joel Gittelsohn](#)<sup>5</sup>, [Mark C Edberg](#)<sup>2</sup>, [Rafael Monge-Rojas](#)<sup>6</sup>, [Uriyoán Colón-Ramos](#)<sup>2</sup>

**Abstract**

**Objective:** This study sought to explain results of the Water Up!@Home randomised controlled trial where low-income parents were randomised to receive an educational intervention +a low-cost water filter pitcher or only the filter. Parents in both groups had reported statistically significant reductions in sugar-sweetened beverages (SSB) and increases in water intake post-intervention.

**Design:** Qualitative explanatory in-depth interviews analysed thematically and deductively.

**Setting:** Washington, DC metropolitan area, USA.

**Participants:** Low-income Latino parents of infants/toddlers who had participated in the Water Up! @Home randomised controlled trial.

**Results:** The filter-stimulated water consumption in both groups by (1) increasing parents' perception of water safety; (2) acting as a cue to action to drink water; (3) improving the flavour of water (which was linked to perceptions of safety) and (4) increasing the perception that this option was more economical than purchasing bottled water. Safe and palatable drinking water was more accessible and freely available in their homes; participants felt they did not need to ration their water consumption as before. Only intervention participants were able to describe a reduction in SSB intake and described strategies, skills and knowledge gained to reduce SSB intake. Among the comparison group, there was no thematic consensus about changes in SSB or any strategies or skills to reduce SSB intake.

**Conclusions:** A low-cost water filter facilitated water consumption, which actively (or passively for comparison group) displaced SSB consumption. The findings have implications for understanding and addressing the role of water security on SSB consumption.

BMJ. 2022 Oct 26;379:e072046.  
doi: 10.1136/bmj-2022-072046.

**[Impact of a package of health, nutrition, psychosocial support, and WaSH interventions delivered during preconception, pregnancy, and early childhood periods on birth outcomes and on linear growth at 24 months of age: factorial, individually randomised controlled trial](#)**

[Sunita Taneja](#)<sup>1</sup>, [Ranadip Chowdhury](#)<sup>1</sup>, [Neeta Dhabhai](#)<sup>1</sup>, [Ravi Prakash Upadhyay](#)<sup>1</sup>, [Sarmila Mazumder](#)<sup>1</sup>, [Sitanshi Sharma](#)<sup>1</sup>, [Kiran Bhatia](#)<sup>1</sup>, [Harish Chellani](#)<sup>2</sup>, [Rupali Dewan](#)<sup>3</sup>, [Pratima Mittal](#)<sup>3</sup>, [M K Bhan](#)<sup>4</sup>, [Rajiv Bahl](#)<sup>5</sup>, [Nita Bhandari](#)<sup>1</sup>, [WINGS Study Group](#)

## Abstract

**Objective:** To determine the effect of integrated and concurrent delivery of health, nutrition, water, sanitation and hygiene (WaSH), and psychosocial care interventions during the preconception period alone, during pregnancy and early childhood, and throughout preconception, pregnancy, and early childhood on birth outcomes and linear growth at 24 months of age compared with routine care.

**Design:** Individually randomised factorial trial.

**Setting:** Low and middle income neighbourhoods of Delhi, India.

**Participants:** 13 500 women were randomised to receive preconception interventions (n=6722) or routine care (n=6778). 2652 and 2269 pregnant women were randomised again to receive pregnancy and early childhood interventions or routine care. The analysis of birth outcomes included 1290 live births for the preconception, pregnancy, and early childhood interventions (group A), 1276 for the preconception intervention (group B), 1093 for the pregnancy and early childhood interventions (group C), and 1093 for the control (group D). Children aged 24 months by 30 June 2021 were included in the 24 month outcome analysis (453 in group A, 439 in B, 293 in C, and 271 in D).

**Interventions:** Health, nutrition, psychosocial care and support, and WaSH interventions were delivered during preconception, pregnancy, and early childhood periods.

**Main outcome measures:** The primary outcomes were low birth weight, small for gestational age, preterm, and mean birth weight. At 24 months, the outcomes were mean length-for-age z scores and proportion stunted. Three prespecified comparisons were made: preconception intervention groups (A+B) versus no preconception intervention groups (C+D); pregnancy and early childhood intervention groups (A+C) versus routine care during pregnancy and early childhood (B+D) and preconception, pregnancy, and early childhood interventions groups (A) versus control group (D).

**Results:** The proportion with low birth weight was lower in the preconception intervention groups (506/2235) than in the no preconception intervention groups (502/1889; incidence rate ratio 0.85, 98.3% confidence interval 0.75 to 0.97; absolute risk reduction -3.80%, 98.3% confidence interval -6.99% to -0.60%). The proportion with low birth weight was lower in the pregnancy intervention groups (502/2096) than in the no pregnancy intervention groups (506/2028) but the upper limit of the confidence interval crossed null effect (0.87, 0.76 to 1.01; -1.71%, -4.96% to 1.54%). There was a larger effect on proportion with low birth weight in the group that received interventions in the preconception and pregnancy periods (267/1141) compared with the control group (267/934; 0.76, 0.62 to 0.91; -5.59%, -10.32% to -0.85%). The proportion stunted at 24 months of age was substantially lower in the pregnancy and early childhood intervention groups (79/746) compared with the groups that did not receive these interventions (136/710; 0.51, 0.38 to 0.70; -8.32%, -12.31% to -4.32%), and in the group that received preconception, pregnancy, and early childhood interventions (47/453) compared with the control group (51/271; 0.49, 0.32 to 0.75; -7.98%, -14.24% to -1.71%). No effect on stunting at 24 months was observed in the preconception intervention groups (132/892) compared with the no preconception intervention groups (83/564).

**Conclusions:** An intervention package delivered during preconception, pregnancy, and early childhood substantially reduced low birth weight and stunting at 24 months. Pregnancy and early childhood interventions alone had lower but important effects on birth outcomes and 24 month outcomes. Preconception interventions alone had an important effect on birth outcomes but not on 24 month outcomes.

Int J Hyg Environ Health. 2023 May;250:114149.

doi: 10.1016/j.ijheh.2023.114149. Epub 2023 Mar 11.

**Assessing sustained uptake of latrine and child feces management interventions: Extended follow-up of a cluster-randomized controlled trial in rural Bangladesh 1-3.5 years after intervention initiation**

[Mahfuza Islam<sup>1</sup>](#), [Mahbubur Rahman<sup>2</sup>](#), [Mohammad Abdullah Heel Kafi<sup>3</sup>](#), [Leanne Unicomb<sup>2</sup>](#), [Mostafizur Rahman<sup>2</sup>](#), [Andrew Mertens<sup>4</sup>](#), [Jade Benjamin-Chung<sup>4</sup>](#), [Benjamin F Arnold<sup>5</sup>](#), [John M Colford Jr<sup>4</sup>](#), [Stephen P Luby<sup>6</sup>](#), [Ayse Ercumen<sup>7</sup>](#)

**Abstract**

**Background:** Sanitation interventions typically result in modest increases in latrine access, and any gains in latrine access and use are often not sustained over time. Sanitation programs also rarely include child-focused interventions such as potties. We aimed to assess the sustained effect of a multi-component sanitation intervention on access to and use of latrines and child feces management tools in rural Bangladesh.

**Methods:** We conducted a longitudinal substudy nested within the WASH Benefits randomized controlled trial. The trial provided latrine upgrades, child potties and sani-scoops for feces removal, along with behavior change promotion to encourage use of the delivered hardware. Promotion visits to intervention recipients were frequent during the first 2 years after intervention initiation, decreased in frequency between years 2-3, and ceased after 3 years. We enrolled a random subset of 720 households from the sanitation and control arms of the trial in a substudy and visited them quarterly between 1 and 3.5 years after intervention initiation. At each visit, field staff recorded sanitation-related behaviors through spot-check observations and structured questionnaires. We assessed intervention effects on observed indicators of hygienic latrine access, potty use and sani-scoop use and investigated whether these effects were modified by duration of follow-up, ongoing behavior change promotion and household characteristics.

**Results:** The intervention increased hygienic latrine access from 37% among controls to 94% in the sanitation arm ( $p < 0.001$ ). Access among intervention recipients remained high 3.5 years after intervention initiation, including periods with no active promotion. Gains in access were higher among households with less education, less wealth and larger number of residents. The intervention increased availability of child potties from 29% among controls to 98% in the sanitation arm ( $p < 0.001$ ). However, fewer than 25% of intervention households reported exclusive child defecation in a potty or had observed indicators of potty and sani-scoop use, and gains in potty use declined over the follow-up period, even with ongoing promotion.

**Conclusion:** Our findings from an intervention that provided free products and intensive initial behavior change promotion suggest a sustained increase in hygienic latrine access up to 3.5 years after intervention initiation but infrequent use of child feces management tools. Studies should investigate strategies to ensure sustained adoption of safe child feces management practices.

Trop Med Int Health. 2022 Sep;27(9):795-802.

doi: 10.1111/tmi.13799. Epub 2022 Aug 14.

**Effects of a community-driven water, sanitation, and hygiene programme on COVID-19 symptoms, vaccine acceptance and non-COVID illnesses: A cluster-randomised controlled trial in rural Democratic Republic of Congo**

[Kevin Croke](#)<sup>1</sup>, [Aidan Coville](#)<sup>2</sup>, [Eric Mvukiyehe](#)<sup>3</sup>, [Caleb Jeremie Dohou](#)<sup>2</sup>, [Jean-Paul Zibika](#)<sup>2</sup>, [Luca Stanus Ghib](#)<sup>2</sup>, [Michele Andreottola](#)<sup>2</sup>, [Yannick Lokaya Bokasola](#)<sup>2</sup>, [John Paul Quattrochi](#)<sup>4</sup>

**Abstract**

**Objective:** The government of the Democratic Republic of Congo (DRC) responded to COVID-19 with policy measures, such as business and school closures and distribution of vaccines, which rely on citizen compliance. In other settings, prior experience with effective government programmes has increased compliance with public health measures. We study the effect of a national water, sanitation, and hygiene programme on compliance with COVID-19 policies.

**Methods:** Prior to the COVID-19 pandemic, 332 communities were randomly assigned to the Villages et Écoles Assainis (VEA) programme or control. After COVID-19 reached DRC, individuals who owned phones (590/1312; 45%) were interviewed by phone three times between May 2020 and August 2021. Primary outcomes were COVID symptoms, non-COVID illness symptoms, child health, psychological well-being, and vaccine acceptance. Secondary outcomes included COVID-19 preventive behaviour and knowledge, and perceptions of governmental performance, including COVID response. All outcomes were self-reported. Outcomes were compared between treatment and control villages using linear models.

**Results:** The VEA programme did not affect respondents' COVID symptoms (-0.11, 95% CI -0.55 to 0.33), non-COVID illnesses (-0.01, 95% CI -0.05 to 0.03), child health (0.07, 95% CI -0.19 to 0.33), psychological well-being (-0.05, 95% CI -0.35 to 0.24), or vaccine acceptance (-0.04, 95% CI -0.19 to 0.10). There was no effect on village-level COVID-19 preventive behaviour (0.03, 95% CI -0.23 to 0.29), COVID-19 knowledge (0.16, 95% CI -0.08 to 0.39), or trust in institutions.

**Conclusions:** Although the VEA programme increased access to improved water and sanitation, we found no evidence that it increased trust in government or compliance with COVID policies, or reduced illness.

PLoS Negl Trop Dis. 2022 Sep 12;16(9):e0010702.

doi: 10.1371/journal.pntd.0010702. eCollection 2022 Sep.

**Acceptability measures of water, sanitation and hygiene interventions in low- and middle-income countries, a systematic review**

[Rose Hosking](#)<sup>1</sup>, [Suji Y O'Connor](#)<sup>1</sup>, [Kinley Wangdi](#)<sup>1</sup>, [Johanna Kurscheid](#)<sup>2</sup>, [Aparna Lal](#)<sup>1</sup>

**Abstract**

**Background:** Inadequate access to water, sanitation, and hygiene (WASH) is an environmental risk factor for poor health outcomes globally, particularly for children in low- and middle-income countries (LMIC). Despite technological advancements, many interventions aimed at improving WASH access return less than optimal results on long term impact, efficacy and sustainability. Research focus in the 'WASH sector' has recently expanded from investigating 'which interventions work' to 'how they are best implemented'. The 'acceptability' of an intervention is a key component of implementation that can influence initial uptake and sustained use. Acceptability assessments are increasingly

common for health interventions in clinical settings. A broad scale assessment of how acceptability has been measured in the WASH sector, however, has not yet been conducted.

**Methods/principal findings:** We conducted a systematic literature review of intervention studies published between 1990 and 2021 that evaluated the acceptability of WASH interventions in LMIC settings. Using an implementation science approach, focused outcomes included how acceptability was measured and defined, and the timing of acceptability assessment. We conducted quality assessment for all included studies using the Cochrane Risk of Bias tool for randomised studies, and the Newcastle-Ottawa Scale for non-randomised studies. Of the 1238 records; 36 studies were included for the analysis, 22 of which were non-randomized interventions and 16 randomized or cluster-randomized trials. We found that among the 36 studies, four explicitly defined their acceptability measure, and six used a behavioural framework to inform their acceptability study design. There were few acceptability evaluations in schools and healthcare facilities. While all studies reported measuring WASH acceptability, the measures were often not comparable or described.

**Conclusions:** As focus in WASH research shifts towards implementation, a consistent approach to including, defining, and measuring acceptability is needed.

## Health worker education

Hum Resour Health. 2023 Feb 24;21(1):13.

doi: 10.1186/s12960-023-00799-4.

### [Health worker education during the COVID-19 pandemic: global disruption, responses and lessons for the future-a systematic review and meta-analysis](#)

[Aikaterini Dedeilia](#)<sup>1,2,3</sup>, [Michail Papapanou](#)<sup>#3,4,5</sup>, [Andreas N Papadopoulos](#)<sup>#3,6</sup>, [Nina-Rafailia Karela](#)<sup>3,4</sup>, [Anastasia Androutsou](#)<sup>3,4</sup>, [Dimitra Mitsopoulou](#)<sup>3,4</sup>, [Melina Nikolakea](#)<sup>3,4</sup>, [Christos Konstantinidis](#)<sup>3,7</sup>, [Manthia Papageorgakopoulou](#)<sup>3,8</sup>, [Michail Sideris](#)<sup>9</sup>, [Elizabeth O Johnson](#)<sup>10</sup>, [Siobhan Fitzpatrick](#)<sup>11</sup>, [Giorgio Cometto](#)<sup>11</sup>, [Jim Campbell](#)<sup>11</sup>, [Marinos G Sotiropoulos](#)<sup>12,13,14</sup>

#### Abstract

**Background:** This systematic review and meta-analysis identified early evidence quantifying the disruption to the education of health workers by the COVID-19 pandemic, ensuing policy responses and their outcomes.

**Methods:** Following a pre-registered protocol and PRISMA/AMSTAR-2 guidelines, we systematically screened MEDLINE, EMBASE, Web of Science, CENTRAL, clinicaltrials.gov and Google Scholar from January 2020 to July 2022. We pooled proportion estimates via random-effects meta-analyses and explored subgroup differences by gender, occupational group, training stage, WHO regions/continents, and study end-year. We assessed risk of bias (Newcastle-Ottawa scale for observational studies, RoB2 for randomized controlled trials [RCT]) and rated evidence certainty using GRADE.

**Results:** Of the 171 489 publications screened, 2 249 were eligible, incorporating 2 212 observational studies and 37 RCTs, representing feedback from 1 109 818 learners and 22 204 faculty. The sample mostly consisted of undergraduates, medical doctors, and studies from institutions in Asia. Perceived training disruption was estimated at 71.1% (95% confidence interval 67.9-74.2) and learner redeployment at 29.2% (25.3-33.2). About one in three



learners screened positive for anxiety (32.3%, 28.5-36.2), depression (32.0%, 27.9-36.2), burnout (38.8%, 33.4-44.3) or insomnia (30.9%, 20.8-41.9). Policy responses included shifting to online learning, innovations in assessment, COVID-19-specific courses, volunteerism, and measures for learner safety. For outcomes of policy responses, most of the literature related to perceptions and preferences. More than two-thirds of learners (75.9%, 74.2-77.7) were satisfied with online learning (postgraduates more than undergraduates), while faculty satisfaction rate was slightly lower (71.8%, 66.7-76.7). Learners preferred an in-person component: blended learning 56.0% (51.2-60.7), face-to-face 48.8% (45.4-52.1), and online-only 32.0% (29.3-34.8). They supported continuation of the virtual format as part of a blended system (68.1%, 64.6-71.5). Subgroup differences provided valuable insights despite not resolving the considerable heterogeneity. All outcomes were assessed as very-low-certainty evidence.

**Conclusion:** The COVID-19 pandemic has severely disrupted health worker education, inflicting a substantial mental health burden on learners. Its impacts on career choices, volunteerism, pedagogical approaches and mental health of learners have implications for educational design, measures to protect and support learners, faculty and health workers, and workforce planning. Online learning may achieve learner satisfaction as part of a short-term solution or integrated into a blended model in the post-pandemic future.

## Haematological disorders

(See also Anaemia and iron deficiency, Malaria: treatment of uncomplicated malaria for study in sickle-cell disease patients)

### Sickle cell disease

Blood. 2023 Feb 23;141(8):825-834.

doi: 10.1182/blood.2022016620.

#### [Hydroxyurea for secondary stroke prevention in children with sickle cell anemia in Nigeria: a randomized controlled trial](#)

[Shehu U Abdullahi](#)<sup>1</sup>, [Surayya Sunusi](#)<sup>2</sup>, [Mohammed Sani Abba](#)<sup>3</sup>, [Saifuddeen Sani](#)<sup>4</sup>, [Hauwau Aminu Inuwa](#)<sup>5</sup>, [Safiya Gambo](#)<sup>6</sup>, [Awwal Gambo](#)<sup>6</sup>, [Bilya Musa](#)<sup>4</sup>, [Brittany V Covert Greene](#)<sup>7</sup>, [Adetola A Kassim](#)<sup>8</sup>, [Mark Rodeghier](#)<sup>9</sup>, [Nafiu Hussaini](#)<sup>10</sup>, [Mariana Ciobanu](#)<sup>11</sup>, [Muktar H Aliyu](#)<sup>12</sup>, [Lori C Jordan](#)<sup>11</sup>, [Michael R DeBaun](#)<sup>7</sup>

#### Abstract

We tested the hypothesis that fixed oral moderate-dose hydroxyurea (20 mg/kg per day) for initial treatment of secondary stroke prevention results in an 80% relative risk reduction of stroke or death when compared with fixed oral low-dose hydroxyurea (10 mg/kg per day) in a phase 3 double-blind, parallel-group, randomized controlled trial in children with sickle cell anemia (SCA) living in Nigeria. A total of 101 participants were randomly allocated to low-dose (n = 49) and moderate-dose (n = 52) hydroxyurea treatment groups. The median participant follow-up was 1.6 years (interquartile range, 1.0-2.3), with a planned minimum follow-up of 3.0 years. A total of 6 recurrent strokes and 2 deaths vs 5 recurrent strokes and 3 deaths occurred in the low- and moderate-dose groups, respectively. The incidence rate

ratio (IRR) of the primary outcome measure of stroke or death in the low- and moderate-dose hydroxyurea treatment groups was 0.98 (95% confidence interval [CI], 0.32-3.00; P = .97). The trial was stopped early owing to no clinical difference in the incidence rates of the primary outcome measure. The incidence rates of recurrent strokes were 7.1 and 6.0 per 100 person-years in the low- and moderate-dose groups, respectively, (IRR, 1.18; 95% CI, 0.30-4.88; P = .74). As a measure of adherence to the oral hydroxyurea therapy, the median percent of returned pills was 3.0% and 2.6% in the low- and moderate-dose groups, respectively. No participant had hydroxyurea therapy stopped for myelosuppression. For children with SCA in low-income settings without access to regular blood transfusion therapy, initial low-dose hydroxyurea is a minimum known efficacious dose for secondary stroke prevention.

Blood Adv. 2023 Jul 11;7(13):3023-3031.

doi: 10.1182/bloodadvances.2022008539.

**[Zinc for infection prevention in children with sickle cell anemia: a randomized double-blind placebo-controlled trial](#)**

[Ruth Namazzi](#)<sup>1,2</sup>, [Robert Opoka](#)<sup>1,2</sup>, [Andrea L Conroy](#)<sup>3</sup>, [Dibyadyuti Datta](#)<sup>3</sup>, [Abner Tagoola](#)<sup>4</sup>, [Caitlin Bond](#)<sup>3</sup>, [Michael J Goings](#)<sup>3</sup>, [Moon-Suhn Ryu](#)<sup>5</sup>, [Sarah E Cusick](#)<sup>6</sup>, [Nancy F Krebs](#)<sup>7</sup>, [Jeong Hoon Jang](#)<sup>8</sup>, [Wanzhu Tu](#)<sup>9</sup>, [Russell E Ware](#)<sup>10</sup>, [Chandy C John](#)<sup>3</sup>

**Abstract**

Data from small clinical trials in the United States and India suggest zinc supplementation reduces infection in adolescents and adults with sickle cell anemia (SCA), but no studies of zinc supplementation for infection prevention have been conducted in children with SCA living in Africa. We conducted a randomized double-blind placebo-controlled trial to assess zinc supplementation for prevention of severe or invasive infections in Ugandan children 1.00-4.99 years with SCA. Of 252 enrolled participants, 124 were assigned zinc (10 mg) and 126 assigned placebo once daily for 12 months. The primary outcome was incidence of protocol-defined severe or invasive infections. Infection incidence did not differ between treatment arms (282 vs. 270 severe or invasive infections per 100 person-years, respectively, incidence rate ratio of 1.04 [95% confidence interval (CI), 0.81, 1.32, p=0.78]), adjusting for hydroxyurea treatment. There was also no difference between treatment arms in incidence of serious adverse events or SCA-related events. Children receiving zinc had increased serum levels after 12-months, but at study exit, 41% remained zinc deficient (<65 µg/dL). In post-hoc analysis, occurrence of stroke or death was lower in the zinc treatment arm (adjusted hazard ratio (95% CI), 0.22 (0.05, 1.00); p=0.05). Daily 10 mg zinc supplementation for 12 months did not prevent severe or invasive infections in Ugandan children with SCA, but many supplemented children remained zinc deficient. Optimal zinc dosing and the role of zinc in preventing stroke or death in SCA warrant further investigation.

Blood. 2022 Sep 29;140(13):1470-1481.

doi: 10.1182/blood.2021014095.

**[Ticagrelor vs placebo for the reduction of vaso-occlusive crises in pediatric sickle cell disease: the HESTIA3 study](#)**

[Matthew M Heeney](#)<sup>1</sup>, [Miguel R Abboud](#)<sup>2</sup>, [Jessie Githanga](#)<sup>3</sup>, [Baba P D Inusa](#)<sup>4</sup>, [Julie Kanter](#)<sup>5</sup>, [Alan D Michelson](#)<sup>6</sup>, [Videlis Nduba](#)<sup>7</sup>, [Victor Musiime](#)<sup>8,9</sup>, [Mohini Apte](#)<sup>10</sup>, [Adlette Inati](#)<sup>11</sup>, [Amar M Taksande](#)<sup>12</sup>, [Marielle Andersson](#)<sup>13</sup>, [Magnus Åstrand](#)<sup>14</sup>, [Noha Maklad](#)<sup>15</sup>, [Mohammad Niazi](#)<sup>14</sup>, [Anders Himmelmann](#)<sup>13</sup>, [Anders R Berggren](#)<sup>13</sup>

## Abstract

The phase 3 HESTIA3 study assessed the efficacy and safety of the reversible P2Y12 inhibitor ticagrelor vs placebo in preventing vaso-occlusive crises in pediatric patients with sickle cell disease (SCD). Patients aged 2 to 17 years were randomly assigned 1:1 to receive weight-based doses of ticagrelor or matching placebo. The primary end point was the rate of vaso-occlusive crises, a composite of painful crises and/or acute chest syndrome (ACS). Key secondary end points included number and duration of painful crises, number of ACS events, and number of vaso-occlusive crises requiring hospitalization or emergency department visits. Exploratory end points included the effect of ticagrelor on platelet activation. In total, 193 patients (ticagrelor, n = 101; placebo, n = 92) underwent randomization at 53 sites across 16 countries. The study was terminated 4 months before planned completion for lack of efficacy. Median ticagrelor exposure duration was 296.5 days. The primary end point was not met: estimated yearly incidence of vaso-occlusive crises was 2.74 in the ticagrelor group and 2.60 in the placebo group (rate ratio, 1.06; 95% confidence interval, 0.75-1.50; P = .7597). There was no evidence of efficacy for ticagrelor vs placebo across secondary end points. Median platelet inhibition with ticagrelor at 6 months was 34.9% predose and 55.7% at 2 hours' postdose. Nine patients (9%) in the ticagrelor group and eight patients (9%) in the placebo group had at least one bleeding event. In conclusion, no reduction of vaso-occlusive crises was seen with ticagrelor vs placebo in these pediatric patients with SCD.

Lancet Child Adolesc Health. 2022 Sep;6(9):606-613.

doi: 10.1016/S2352-4642(22)00153-5. Epub 2022 Jul 2.

## [Sickle cell anaemia and severe Plasmodium falciparum malaria: a secondary analysis of the Transfusion and Treatment of African Children Trial \(TRACT\)](#)

[Sophie Uyoga](#)<sup>1</sup>, [Peter Olupot-Olupot](#)<sup>2</sup>, [Roisin Connon](#)<sup>3</sup>, [Sarah Kiguli](#)<sup>4</sup>, [Robert O Opoka](#)<sup>4</sup>, [Florence Alaroker](#)<sup>5</sup>, [Rita Muhindo](#)<sup>6</sup>, [Alexander W Macharia](#)<sup>1</sup>, [Arjen M Dondorp](#)<sup>7</sup>, [Diana M Gibb](#)<sup>3</sup>, [A Sarah Walker](#)<sup>3</sup>, [Elizabeth C George](#)<sup>3</sup>, [Kathryn Maitland](#)<sup>8</sup>, [Thomas N Williams](#)<sup>9</sup>

## Abstract

**Background:** Sickle cell anaemia (SCA) has historically been associated with high levels of childhood mortality in Africa. Although malaria has a major contribution to this mortality, to date, the clinical pathology of malaria among children with SCA has been poorly described. We aimed to explore the relationship between SCA and Plasmodium falciparum malaria in further detail by investigating the burden and severity of malaria infections among children recruited with severe anaemia to the TRACT trial of blood transfusion in Africa.

**Methods:** This study is a post-hoc secondary analysis of the TRACT trial data, conducted after trial completion. TRACT was an open-label, multicentre, factorial, randomised controlled trial enrolling children aged 2 months to 12 years who presented with severe anaemia (haemoglobin <6.0 g/dL) to four hospitals in Africa. This secondary analysis is restricted to Uganda, where the birth prevalence of SCA is approximately 1% and malaria transmission is high. Children were classified as normal (HbAA), heterozygous (HbAS), or homozygous (HbSS; SCA) for the rs334 A→T sickle mutation in HBB following batch-

genotyping by PCR at the end of the trial. To avoid confounding from SCA-specific medical interventions, we considered children with an existing diagnosis of SCA (known SCA) separately from those diagnosed at the end of the trial (unknown SCA). The outcomes considered in this secondary analysis were measures of *P falciparum* parasite burden, features of severe malaria, and mortality at day 28 in malaria-positive children.

**Findings:** Between Sept 17, 2014, and May 15, 2017, 3944 children with severe anaemia were enrolled into the TRACT trial. 3483 children from Uganda were considered in this secondary analysis. Overall, 1038 (30%) of 3483 Ugandan children had SCA. 1815 (78%) of 2321 children without SCA (HbAA) tested positive for *P falciparum* malaria, whereas the prevalence was significantly lower in children with SCA (347 [33%] of 1038;  $p < 0.0001$ ). Concentrations of plasma *P falciparum* histidine-rich protein 2 (PfHRP2), a marker of the total burden of malaria parasites within an individual, were significantly lower in children with either known SCA (median 8 ng/mL; IQR 0-57) or unknown SCA (7 ng/mL; 0-50) than in HbAA children (346 ng/mL; 21-2121;  $p < 0.0001$ ). In contrast to HbAA children, few HbSS children presented with classic features of severe and complicated malaria, but both the frequency and severity of anaemia were higher in HbSS children. We found no evidence for increased mortality at day 28 in those with SCA compared with those without SCA overall (hazard ratios 1.07 [95% CI 0.31-3.76] for known SCA and 0.67 [0.15-2.90] for unknown SCA).

**Interpretation:** The current study suggests that children with SCA are innately protected against classic severe malaria. However, it also shows that even low-level infections can precipitate severe anaemic crises that would likely prove fatal without rapid access to blood transfusion services.

PLoS Med. 2022 Oct 10;19(10):e1004104.

doi: 10.1371/journal.pmed.1004104. eCollection 2022 Oct.

[\*\*Monthly sulfadoxine/pyrimethamine-amodiaquine or dihydroartemisinin-piperazine as malaria chemoprevention in young Kenyan children with sickle cell anemia: A randomized controlled trial\*\*](#)

[Steve M Taylor<sup>1,2,3</sup>](#), [Sarah Korwa<sup>4</sup>](#), [Angie Wu<sup>2</sup>](#), [Cynthia L Green<sup>2,5</sup>](#), [Betsy Freedman<sup>1</sup>](#), [Sheila Clapp<sup>2</sup>](#), [Joseph Kipkoech Kirui<sup>4</sup>](#), [Wendy P O'Meara<sup>1,3</sup>](#), [Festus M Njuguna<sup>4,6</sup>](#)

**Abstract**

**Background:** Children with sickle cell anemia (SCA) in areas of Africa with endemic malaria transmission are commonly prescribed malaria chemoprevention. Chemoprevention regimens vary between countries, and the comparative efficacy of prevention regimens is largely unknown.

**Methods and findings:** We enrolled Kenyan children aged 1 to 10 years with homozygous hemoglobin S (HbSS) in a randomized, open-label trial conducted between January 23, 2018, and December 15, 2020, in Homa Bay, Kenya. Children were assigned 1:1:1 to daily Proguanil (the standard of care), monthly sulfadoxine/pyrimethamine-amodiaquine (SP-AQ), or monthly dihydroartemisinin-piperazine (DP) and followed monthly for 12 months. The primary outcome was the cumulative incidence of clinical malaria at 12 months, and the main secondary outcome was the cumulative incidence of painful events by self-report. Secondary outcomes included other parasitologic, hematologic, and general events. Negative binomial models were used to estimate incidence rate ratios (IRRs) per patient-year (PPY) at risk relative to Proguanil. The primary analytic population was the As-Treated

population. A total of 246 children were randomized to daily Proguanil (n = 81), monthly SP-AQ (n = 83), or monthly DP (n = 82). Overall, 53.3% (n = 131) were boys and the mean age was  $4.6 \pm 2.5$  years. The clinical malaria incidence was 0.04 episodes/PPY; relative to the daily Proguanil group, incidence rates were not significantly different in the monthly SP-AQ (IRR: 3.05, 95% confidence interval [CI]: 0.36 to 26.14; p = 0.39) and DP (IRR: 1.36, 95% CI: 0.21 to 8.85; p = 0.90) groups. Among secondary outcomes, relative to the daily Proguanil group, the incidence of painful events was not significantly different in the monthly SP-AQ and DP groups, while monthly DP was associated with a reduced rate of dactylitis (IRR: 0.47; 95% CI: 0.23 to 0.96; p = 0.038). The incidence of Plasmodium falciparum infection relative to daily Proguanil was similar in the monthly SP-AQ group (IRR 0.46; 95% CI: 0.17 to 1.20; p = 0.13) but reduced with monthly DP (IRR 0.21; 95% CI: 0.08 to 0.56; p = 0.002). Serious adverse events were common and distributed between groups, although compared to daily Proguanil (n = 2), more children died receiving monthly SP-AQ (n = 7; hazard ratio [HR] 5.44; 95% CI: 0.92 to 32.11; p = 0.064) but not DP (n = 1; HR 0.61; 95% CI 0.04 to 9.22; p = 0.89), although differences did not reach statistical significance for either SP-AQ or DP. Study limitations include the unexpectedly limited transmission of P. falciparum in the study setting, the high use of hydroxyurea, and the enhanced supportive care for trial participants, which may limit generalizability to higher-transmission settings where routine sickle cell care is more limited. **Conclusions:** In this study with limited malaria transmission, malaria chemoprevention in Kenyan children with SCA with monthly SP-AQ or DP did not reduce clinical malaria, but DP was associated with reduced dactylitis and P. falciparum parasitization. Pragmatic studies of chemoprevention in higher malaria transmission settings are warranted.

Am J Respir Crit Care Med. 2022 Jul 1;206(1):70-80.

doi: 10.1164/rccm.202108-1930OC.

[Arginine Therapy and Cardiopulmonary Hemodynamics in Hospitalized Children with Sickle Cell Anemia: A Prospective, Double-blinded, Randomized Placebo-controlled Clinical Trial](#)

[Richard Onalo](#)<sup>1</sup>, [Antoinette Cilliers](#)<sup>2</sup>, [Peter Cooper](#)<sup>3</sup>, [Claudia R Morris](#)<sup>4,5,6</sup>

**Abstract**

**Rationale:** Acute changes in cardiopulmonary hemodynamics that include tricuspid regurgitant jet velocity (TRV) elevation measured by Doppler echocardiography are often encountered during sickle cell vasoocclusive pain and acute chest syndrome (ACS). Arginine and nitric oxide depletion develop in patients with these complications. Arginine administration may therefore improve nitric oxide bioavailability and potentiate pulmonary vasodilatation. **Objectives:** To evaluate effects of l-arginine supplementation on Doppler indices of cardiopulmonary hemodynamics in children with sickle cell anemia experiencing pain. **Methods:** This was a prospective, double-blinded, randomized placebo-controlled trial of oral arginine in children with sickle cell anemia age 5-17 years hospitalized with severe pain and/or ACS. **Measurements and Main Results:** Blood biomarkers and Doppler echocardiographic indices of cardiopulmonary hemodynamics were measured before and after supplementation. The mean change in TRV, pulmonary artery systolic pressure, mean pulmonary artery pressure, and other indices of cardiopulmonary hemodynamics were tested with paired Student's *t* test and correlated with markers of arginine bioavailability using Pearson correlation. Sixty-six children were randomized into arginine versus placebo groups. An elevated TRV  $\geq 2.5$  m/s was seen in 40 (61%) patients. A Day 5 Doppler



echocardiogram was performed in 47 patients who remained hospitalized. A greater reduction in median TRV occurred in the arginine group than placebo (22.2%,  $n = 22$  vs. 3.8%,  $n = 25$ ;  $p < 0.01$ ). A larger percentage increase in global arginine bioavailability was associated with a lower TRV after 5 days of supplementation ( $r = -0.533$ ;  $P = 0.001$ ). Significant differences in multiple indices of cardiopulmonary hemodynamics and mean N-terminal pro B-type brain natriuretic peptide were also noted after arginine therapy. **Conclusions:** Oral arginine supplementation improves cardiopulmonary hemodynamics during sickle cell disease vasoocclusive pain and ACS.

Ann Hematol. 2022 Sep;101(9):1931-1940.

doi: 10.1007/s00277-022-04901-z. Epub 2022 Jul 27.

**[Anticoagulation strategies and recurrence of venous thromboembolic events in patients with sickle cell disease: a systematic review and meta-analysis](#)**

[Nadirah El-Amin](#)<sup>1</sup>, [Audra Inness](#)<sup>2</sup>, [John W Cyrus](#)<sup>3</sup>, [India Sisler](#)<sup>1</sup>, [Oliver Karam](#)<sup>4</sup>

**Abstract**

Sickle cell disease (SCD) results in many complications including an increased risk of developing venous thromboembolic events (VTEs) and an increased risk of mortality as a result. We conducted a systematic review using multiple databases to compare the efficacy of different anticoagulation in preventing recurrence, development of bleeding, progression of thrombus, and mortality in patients with SCD and a venous thrombotic event. Eight hundred seventy-one studies were screened and six studies were included. Among patients with SCD who experienced a VTE and were anticoagulated, the overall recurrence of VTE was 27.6% (95%CI 23.5-31.9). The overall progression to pulmonary embolism (PE) was 11.7% (95%CI 4.3-22.1). The overall bleeding rate was 14.1% (95%CI 7.8-21.9) and the overall mortality was 3.7% (95%CI 0.8-8.5). Based on observational studies, there did not appear to be differences between anticoagulant classes for the above adverse outcomes. Significant heterogeneity in the patient population and outcome measures limited the interpretation of the results. More studies, specifically randomized trials, are needed to help direct appropriate management of VTE's in patients with sickle cell disease (PROSPERO ID: 236,208).

Blood Adv. 2022 Nov 16;bloodadvances.2022008623.

doi: 10.1182/bloodadvances.2022008623. Online ahead of print.

**[Underweight children over 5 years with sickle cell anemia are at risk for early mortality in a low-resource setting](#)**

[Lauren Jane Klein](#)<sup>1</sup>, [Shehu Abdullahi](#)<sup>2</sup>, [Safiya Gambo](#)<sup>3</sup>, [Virginia A Stallings](#)<sup>4</sup>, [Sari Acra](#)<sup>1</sup>, [Mark Rodeghier](#)<sup>5</sup>, [Michael R DeBaun](#)<sup>6</sup>

**Abstract**

Undernutrition is a risk factor for under 5 mortality and is also postulated to be a risk factor for mortality in older children and adults with sickle cell anemia. We tested the hypothesis that underweight (weight-for-age z-score  $\leq -1$ ) is associated with mortality in children aged 5-12 years with sickle cell anemia. We performed a secondary analysis of participants in the Primary Prevention of Stroke in Children with Sickle Cell Disease in Nigeria trial, a double-blind, parallel-group randomized controlled trial for low-dose ( $n=109$ ) or moderate-dose



(n=111) hydroxyurea in children with abnormal transcranial Doppler velocities and a comparison group (n=211) of participants with non-elevated transcranial Doppler velocities in northern Nigeria ([NCT02560935](#)). Nutritional status was classified as underweight (weight-for-age z-score), stunting (height-for-age z-score), and wasting (body mass index z-score) using the World Health Organization growth reference. The mean weight-for-age z-score was lower in children who died during the study than in those who survived (-2.6 vs. -2.1, p=0.016). Otherwise, the baseline characteristics of children who died during the study were not significantly different from those who survived. A pooled analysis of participants demonstrated that a lower weight-for-age z-score was associated with an increased hazard of death (HR=0.580, p=0.004, 95%CI 0.399-0.843). Underweight participants (weight-for-age z-score <-1) had a greater probability of death during follow-up than those not underweight (p=0.043). Underweight status in school-aged children with sickle cell anemia is a previously unrecognized risk factor for early mortality in Nigeria and can be easily applied to screen children at risk for death.

## Thalassaemia

Blood Adv. 2023 Feb 28;7(4):611-619.

doi: 10.1182/bloodadvances.2021006778.

### [Deferiprone for transfusional iron overload in sickle cell disease and other anemias: open-label study of up to 3 years](#)

[Mohsen S Elalfy](#)<sup>1</sup>, [Mona Hamdy](#)<sup>2</sup>, [Amal El-Beshlawy](#)<sup>3</sup>, [Fatma S E Ebeid](#)<sup>1</sup>, [Mohamed Badr](#)<sup>4</sup>, [Julie Kanter](#)<sup>5</sup>, [Baba Inusa](#)<sup>6</sup>, [Amira A M Adly](#)<sup>1</sup>, [Suzan Williams](#)<sup>7</sup>, [Yurdanur Kilinc](#)<sup>8</sup>, [David Lee](#)<sup>9</sup>, [Caroline Fradette](#)<sup>9</sup>, [Anna Rozova](#)<sup>9</sup>, [Noemi Toiber Temin](#)<sup>9</sup>, [Fernando Tricta](#)<sup>9</sup>, [Janet L Kwiatkowski](#)<sup>10</sup>

#### Abstract

Long-term safety and efficacy data on the iron chelator deferiprone in sickle cell disease (SCD) and other anemias are limited. FIRST-EXT was a 2-year extension study of FIRST (Ferriprox in Patients With Iron Overload in Sickle Cell Disease Trial), a 1-year, randomized noninferiority study of deferiprone vs deferoxamine in these populations. Patients who entered FIRST-EXT continued to receive, or were switched to, deferiprone. Altogether, 134 patients were enrolled in FIRST-EXT (mean age: 16.2 years), with mean (SD) exposure to deferiprone of 2.1 (0.8) years over the 2 studies. The primary end point was safety. Secondary end points were change in liver iron concentration (LIC), cardiac T2\*, serum ferritin (SF), and the proportion of responders ( $\geq 20\%$  improvement in efficacy measure). The most common adverse events considered at least possibly related to deferiprone were neutropenia (9.0%) and abdominal pain (7.5%). LIC (mg/g dry weight) decreased over time, with mean (SD) changes from baseline at each time point (year 1, -2.64 [4.64]; year 2, -3.91 [6.38]; year 3, -6.64 [7.72], all  $P < .0001$ ). Mean SF levels ( $\mu\text{g/L}$ ) decreased significantly after year 2 (-771,  $P = .0008$ ) and year 3 (-1016,  $P = .0420$ ). Responder rates for LIC and SF increased each year (LIC: year 1, 46.5%; year 2, 57.1%; year 3, 66.1%; SF: year 1, 35.2%; year 2, 55.2%; year 3, 70.9%). Cardiac T2\* remained normal in all patients. In conclusion, long-term therapy with deferiprone was not associated with new safety concerns and led to continued and progressive reduction in iron load in individuals with SCD or other anemias.

Cochrane Database Syst Rev. 2023 Jan 13;1(1):CD013767.

doi: 10.1002/14651858.CD013767.pub2.

**Foetal haemoglobin inducers for reducing blood transfusion in non-transfusion-dependent beta-thalassaemias**

[Wai Cheng Foong<sup>1</sup>](#), [C Khai Loh<sup>2</sup>](#), [Jacqueline J Ho<sup>1</sup>](#), [Doris Sc Lau<sup>2</sup>](#)

**Abstract**

**Background:** Non-transfusion-dependent  $\beta$ -thalassaemia (NTD $\beta$ T) is a subset of inherited haemoglobin disorders characterised by reduced production of the  $\beta$ -globin chain of haemoglobin leading to anaemia of varying severity. Although blood transfusion is not a necessity for survival, it may be required to prevent complications of chronic anaemia, such as impaired growth and hypercoagulability. People with NTD $\beta$ T also experience iron overload due to increased iron absorption from food sources which becomes more pronounced in those requiring blood transfusion. People with a higher foetal haemoglobin (HbF) level have been found to require fewer blood transfusions, thus leading to the emergence of treatments that could increase its level. HbF inducers stimulate HbF production without altering any gene structures. Evidence for the possible benefits and harms of these inducers is important for making an informed decision on their use.

**Objectives:** To compare the effectiveness and safety of the following for reducing blood transfusion for people with NTD $\beta$ T: 1. HbF inducers versus usual care or placebo; 2. single HbF inducer with another HbF inducer, and single dose with another dose; and 3. combination of HbF inducers versus usual care or placebo, or single HbF inducer.

**Search methods:** We used standard, extensive Cochrane search methods. The latest search date was 21 August 2022.

**Selection criteria:** We included randomised controlled trials (RCTs) or quasi-RCTs comparing single HbF inducer with placebo or usual care, with another single HbF inducer or with a combination of HbF inducers; or comparing different doses of the same HbF inducer.

**Data collection and analysis:** We used standard Cochrane methods. Our primary outcomes were blood transfusion and haemoglobin levels. Our secondary outcomes were HbF levels, the long-term sequelae of NTD $\beta$ T, quality of life and adverse events.

**Main results:** We included seven RCTs involving 291 people with NTD $\beta$ T, aged two to 49 years, from five countries. We reported 10 comparisons using eight different HbF inducers (four pharmacological and four natural): three RCTs compared a single HbF inducer to placebo and seven to another HbF inducer. The duration of the intervention lasted from 56 days to six months. Most studies did not adequately report the randomisation procedures or whether and how blinding was achieved. HbF inducer against placebo or usual care Three HbF inducers, HQK-1001, Radix Astragali or a 3-in-1 combined natural preparation (CNP), were compared with a placebo. None of the comparisons reported the frequency of blood transfusion. We are uncertain whether Radix Astragali and CNP increase haemoglobin at three months (mean difference (MD) 1.33 g/dL, 95% confidence interval (CI) 0.54 to 2.11; 1 study, 2 interventions, 35 participants; very low-certainty evidence). We are uncertain whether Radix Astragali and CNP have any effect on HbF (MD 12%, 95% CI -0.74% to 24.75%; 1 study, 2 interventions, 35 participants; very low-certainty evidence). Only medians on haemoglobin and HbF levels were reported for HQK-1001. Adverse effects reported for HQK-1001 were nausea, vomiting, dizziness and suprapubic pain. There were no prespecified adverse effects for Radix Astragali and CNP. HbF inducer versus another HbF inducer Four studies compared a single inducer with another over three to six months. Comparisons

included hydroxyurea versus resveratrol, hydroxyurea versus thalidomide, hydroxyurea versus decitabine and Radix Astragali versus CNP. No study reported our prespecified outcomes on blood transfusion. Haemoglobin and HbF were reported for the comparison Radix Astragali versus CNP, but we are uncertain whether there were any differences (1 study, 24 participants; low-certainty evidence). Different doses of the same HbF inducer Two studies compared two different types of HbF inducers at different doses over two to six months. Comparisons included hydroxyurea 20 mg/kg/day versus 10 mg/kg/day and HQK-1001 10 mg/kg/day, 20 mg/kg/day, 30 mg/kg/day and 40 mg/kg/day. Blood transfusion, as prespecified, was not reported. In one study (61 participants) we are uncertain whether the lower levels of both haemoglobin and HbF at 24 weeks were due to the higher dose of hydroxyurea (haemoglobin: MD -2.39 g/dL, 95% CI -2.80 to -1.98; very low-certainty evidence; HbF: MD -10.20%, 95% CI -16.28% to -4.12%; very low-certainty evidence). The study of the four different doses of HQK-1001 did not report results for either haemoglobin or HbF. We are not certain if major adverse effects may be more common with higher hydroxyurea doses (neutropenia: risk ratio (RR) 9.93, 95% CI 1.34 to 73.97; thrombocytopenia: RR 3.68, 95% CI 1.12 to 12.07; very low-certainty evidence). Taking HQK-1001 20 mg/kg/day may result in the fewest adverse effects. A combination of HbF inducers versus a single HbF inducer Two studies compared three combinations of two inducers with a single inducer over six months: hydroxyurea plus resveratrol versus resveratrol or hydroxyurea alone, and hydroxyurea plus l-carnitine versus hydroxyurea alone. Blood transfusion was not reported. Hydroxyurea plus resveratrol may reduce haemoglobin compared with either resveratrol or hydroxyurea alone (MD -0.74 g/dL, 95% CI -1.45 to -0.03; 1 study, 54 participants; low-certainty evidence). We are not certain whether the gastrointestinal disturbances, headache and malaise more commonly reported with hydroxyurea plus resveratrol than resveratrol alone were due to the interventions. We are uncertain whether hydroxyurea plus l-carnitine compared with hydroxyurea alone may increase mean haemoglobin, and reduce pulmonary hypertension (1 study, 60 participants; very low-certainty evidence). Adverse events were reported but not in the intervention group. None of the comparisons reported the outcome of HbF.

**Authors' conclusions:** We are uncertain whether any of the eight HbF inducers in this review have a beneficial effect on people with NTD $\beta$ T. For each of these HbF inducers, we found only one or at the most two small studies. There is no information on whether any of these HbF inducers have an effect on our primary outcome, blood transfusion. For the second primary outcome, haemoglobin, there may be small differences between intervention groups, but these may not be clinically meaningful and are of low- to very low-certainty evidence. Data on adverse effects and optimal doses are limited. Five studies are awaiting classification, but none are ongoing.

## Heart disease

### Rheumatic heart disease

## Congenital heart disease and cardiac surgery

(see also Intensive care)

Ann Card Anaesth. 2022 Jul-Sep;25(3):270-278.

doi: 10.4103/aca.aca\_51\_22.

### [Effect of perioperative use of oral triiodothyronine for infants undergoing complex congenital cardiac surgeries under cardiopulmonary bypass: A double-blinded randomised controlled study](#)

[Sujithareddy Karri<sup>1</sup>](#), [Banashree Mandal<sup>1</sup>](#), [Bhupesh Kumar<sup>1</sup>](#), [Govardandutt Puri<sup>1</sup>](#), [Shyam Thingnam<sup>2</sup>](#), [Hemant Kumar<sup>3</sup>](#), [V S Unnikrishnan<sup>4</sup>](#)

#### Abstract

**Background:** Thyroid hormone metabolism disrupts after cardiopulmonary bypass both in adults and pediatric patients. This is known as Euthyroid sick syndrome, and it is more evident in pediatric patients who were undergoing complex cardiac surgeries compared to adults. This decrease in serum T3 levels increases the incidence of low cardiac output, requirement of inotropes, prolonged mechanical ventilation, and prolonged intensive care unit (ICU) stay.

**Aims and objectives:** The primary objective was to compare the mean Vasoactive-inotropic score (VIS) at 72 hours postoperatively between T3 and Placebo groups.

**Materials and methods:** One hundred patients were screened, and 88 patients were included in the study. Triiodothyronine 1 mic/kg 10 doses 8<sup>th</sup> hourly was given orally postoperatively to cases and sugar sachets to controls. The blood samples for analysis of FT3, FT4, and TSH were taken every 24 hours postoperatively, and baseline values were taken after induction. Mean VIS scores, ejection Fraction (EF), Left ventricular outflow tract velocity time integral (LVOT VTI), hemodynamics and partial pressure of oxygen/ fraction of inspired oxygen (PaO<sub>2</sub>/FiO<sub>2</sub>) were recorded daily.

**Results:** The Mean VIS scores at 72 Hours postoperatively were significantly less in the T3 group (5.49 ± 6.2) compared to the Placebo group (13.6 ± 11.7). The PaO<sub>2</sub>/FiO<sub>2</sub> ratios were comparatively more in the T3 group than the Placebo group. The serum levels of FT3 FT4 were significantly higher in the T3-supplemented group than the Placebo group. The VIS scores were significantly lower from 48 hours postoperatively in children < 6 months of age.

**Conclusion:** In this study, we observed that supplementing T3 postoperatively decreases the inotropic requirement from 72 hours postoperatively. This is more useful in children <6 months of age undergoing complex cardiac surgeries.

Thyroid. 2022 Aug;32(8):879-896.

doi: 10.1089/thy.2021.0609. Epub 2022 May 24.

### [Efficacy and Safety of Triiodothyronine Treatment in Cardiac Surgery or Cardiovascular Diseases: A Systematic Review and Meta-Analysis of Randomized Controlled Trials](#)

[Mathuri Tharmapoopathy<sup>1</sup>](#), [Abishan Thavarajah<sup>1</sup>](#), [Ryan P W Kenny<sup>2</sup>](#), [Alessandro Pingitore<sup>3</sup>](#), [Giorgio Iervasi<sup>3</sup>](#), [John Dark<sup>1</sup>](#), [Arjola Bano<sup>4,5</sup>](#), [Salman Razvi<sup>1</sup>](#)

#### Abstract

**Background:** Low levels of the active thyroid hormone triiodothyronine (T3) in cardiac patients are associated with worse outcomes. The aim of this analysis was to assess if T3 treatment is beneficial and safe in patients undergoing cardiac surgery or those with

cardiovascular diseases in whom there is observed or expected reduction in serum T3 levels. **Methods:** A systematic review and meta-analysis of randomized controlled trials (RCTs) was performed as per the PRISMA guidelines. Pubmed, EMBASE, and Web of Science databases were searched for RCTs published between January 1, 1960 and March 30, 2022 that evaluated the effects of T3 therapy in patients undergoing cardiac surgery or with cardiovascular diseases. The primary outcomes were measures of cardiac function. Weighted mean difference (MD) or relative risk was calculated using a random effects model. PROSPERO registration number CRD42020211966. **Results:** Of the 3181 full-text articles screened, 34 studies with 2547 participants (number ranging between 13 and 223, mean ages between 0.5 and 73 years, mean percentage of women between 7% and 64%) were included. In 12 RCTs with 1093 adults undergoing cardiac surgery T3 therapy was associated with improvement in cardiac index (MD [95% confidence interval], 0.24 [0.08 to 0.40] L/min/m<sup>2</sup>, I<sup>2</sup> = 74%). The quality of evidence was high to moderate. In 3 RCTs with 188 children undergoing cardiac surgery, 3 RCTs with 131 adult cardiac donors, 3 RCTs with 83 adult patients with heart failure, and 2 RCTs with 89 adults with acute myocardial infarction, T3 therapy did not improve cardiac index or left ventricular function; the quality of evidence ranged from high (pediatric cardiac surgery) to low (other groups). No detrimental effect of T3 therapy was observed on heart rate, risk of in-hospital atrial fibrillation, or mortality. **Conclusions:** Short-term T3 therapy is safe and trials in adults undergoing cardiac surgical procedures to evaluate longer term clinical endpoints are required. Current data do not support the routine use of T3 therapy in children undergoing cardiac surgery or in cardiac donors. Adequately designed trials are required to determine if T3 therapy improves cardiac function and clinical outcomes in patients with heart failure or acute myocardial infarction.

Ann Card Anaesth. 2022 Oct-Dec;25(4):466-471.

doi: 10.4103/aca.aca\_42\_21.

[Effects of recombinant erythropoietin on hemoglobin levels and blood transfusion needs in patients with preoperative anemia undergoing cardiac surgery](#)

[Ziae Totonchi](#)<sup>1</sup>, [Feridoun Noohi](#)<sup>2</sup>, [Farzaneh Futuhi](#)<sup>3</sup>, [Rasoul Azarfarin](#)<sup>4</sup>, [Pooyan Radbin](#)<sup>1</sup>

**Abstract**

**Introduction:** Preoperative anemia is an important and relatively common problem in patients undergoing cardiac surgery, and its treatment is crucial in improving postoperative outcomes. The use of recombinant erythropoietin is one of the suggested methods in this field. Therefore, in the present study, we sought to evaluate the effects of recombinant erythropoietin on hemoglobin (Hb) levels and blood transfusion needs in cardiac surgery in patients with preoperative anemia.

**Methods:** This randomized nonblind clinical trial was performed on patients with mild-to-moderate anemia (Hb <12 g/dL in men and Hb <11 g/dL in women) undergoing cardiac surgery at a referral heart hospital (Tehran, Iran). The patients were randomly divided into two groups of 33 patients. In the intervention group, recombinant erythropoietin was administered at a dose of 500 IU/kg one to three days before surgery. Intra- and postoperative Hb levels and the need for blood transfusion were recorded during surgery and for 3 days afterward.

**Results:** The use of packed red blood cells in the operating room was similar in the intervention and control groups (P = 0.156), but it was significantly lower in the intensive care unit in the intervention group (P = 0.030). The mean Hb, which was initially identical in the

two groups ( $P > 0.05$ ), showed a significantly lower decrease in the intervention group ( $P = 0.001$ ). No significant differences were observed concerning other variables.

**Conclusions:** The use of recombinant erythropoietin (500 IU/kg/day) one to three days before cardiac surgery in our anemic patients blunted a reduction in Hb levels and decreased blood transfusion needs.

J Cardiothorac Vasc Anesth. 2022 Oct;36(10):3841-3846.

doi: 10.1053/j.jvca.2022.04.044. Epub 2022 May 3.

**[Bivalirudin anticoagulation in neonates and infants undergoing cardiac surgery](#)**

[Suruchi Hasija](#)<sup>1</sup>, [Milind P Hote](#)<sup>2</sup>, [Neeti Makhija](#)<sup>3</sup>, [Sandeep Chauhan](#)<sup>3</sup>, [Poonam Malhotra](#)<sup>3</sup>, [Maroof Ahmad Khan](#)<sup>4</sup>, [Gaurav Sharma](#)<sup>5</sup>

**Abstract**

**Objectives:** To determine the dosage of bivalirudin as the anticoagulant for cardiac surgery in neonates and infants.

**Design:** Pilot study.

**Setting:** Tertiary-care hospital.

**Participants:** Twenty-five neonates and infants with congenital heart disease (CHD) undergoing cardiac surgery.

**Interventions:** The children received a 1 mg/kg bivalirudin bolus followed by a 2.5 mg/kg/h infusion as the anticoagulant for cardiac surgery. The dose was adjusted subsequently to maintain an activated clotting time (ACT)  $>480$  s.

**Measurements and main results:** The mean age and weight were 5.3 months and 5.2 kg, respectively. Out of the 25 children, 16 were cyanotic. Baseline rotational thromboelastometry (ROTEM) (Tem Innovations GmbH, Munich, Germany) analysis revealed an underlying coagulation defect across EXTEM, INTEM, FIBTEM, and ADPTEM parameters. The dose of anticoagulant required was 1 mg/kg, followed by a  $2.2 \pm 0.4$  mg/kg/h infusion. Only 1 child required an additional bolus dose. The ACT remained elevated for 4 hours after discontinuation of infusion. The mean 24-h postoperative chest tube drainage was  $92 \pm 36$  mL. Excessive bleeding occurred in 4 children, 1 of whom required re-exploration. The platelet count remained low for 5 days, and, postoperatively, the prothrombin time and activated partial thromboplastin time remained low for 2 days.

**Conclusions:** Effective anticoagulation was achieved with bivalirudin in the neonates and infants undergoing cardiac surgery. The dose required to maintain an ACT  $>480$  s was 1.0 mg/kg, followed by  $2.2 \pm 0.4$  mg/kg/h. The ACT remained elevated for 4 h after the discontinuation of bivalirudin infusion, resulting in an increased chest-tube output in some patients. Randomized, controlled trials are needed to further evaluate the safety of bivalirudin in the neonates and infants with complex congenital heart disease undergoing cardiac surgery with cardiopulmonary bypass.

Pediatr Pulmonol. 2023 Jul;58(7):2132-2139.

doi: 10.1002/ppul.26451. Epub 2023 May 3.

**[Comparison of the efficacy of inhaled versus infused milrinone in the management of persistent pulmonary hypertension of the newborn in resource-limited settings: A randomized clinical trial](#)**



[Farhad Abolhasan Choobdar<sup>1</sup>](#), [Peyman Shahhosseini<sup>2</sup>](#), [Zahra Vahedi<sup>3</sup>](#), [Nastaran Khosravi<sup>1</sup>](#), [Nasrin Khalesi<sup>1</sup>](#), [Maral Ghassemzadeh<sup>4</sup>](#)

### Abstract

**Background:** The standard treatment for persistent pulmonary hypertension of the newborn (PPHN) is inhaled nitric oxide (iNO), which is not available in Iran. Consequently, other drugs, such as milrinone, are prescribed. So far, no study has investigated the effectiveness of inhaled milrinone in the management of PPHN. The present study aimed to improve the management of PPHN in the absence of iNO.

**Methods:** In this randomized clinical trial, neonates with PPHN, admitted to the neonatal intensive care unit of Hazrat Ali-Asghar and Akbar-Abadi hospitals, were treated with intravenous dopamine infusion and randomly divided into two groups, receiving milrinone through inhalation or infusion route. The neonates were evaluated by Doppler echocardiography, clinical examinations, and oxygen demand test. The neonates were also evaluated for the clinical symptoms and mortality in the follow-up.

**Results:** A total of 31 infants, with a median age of 2 days (interquartile range = 4), were included in this study. There was a significant decrease in the peak systolic and mean pulmonary arterial pressure in both inhalation and infusion groups following milrinone administration, with no significant difference between the groups ( $p = 0.584$  and  $p = 0.147$ , respectively). There was no significant difference between the two groups regarding the mean systolic blood pressure before and after treatment. Additionally, diastolic blood pressure was significantly lower in the infusion group after treatment ( $p = 0.020$ ); however, the amount of reduction was not significantly different between the groups ( $p = 0.928$ ). Overall, 83.9% of the participants achieved full recovery, 75% of whom were in the infusion group and 93.3% in the inhalation group ( $p = 0.186$ ).

**Conclusion:** Milrinone inhalation can have similar effects to milrinone infusion as an adjunct treatment in the management of PPHN. Also, infusion and inhalation of milrinone showed similar safety.

Eur J Pediatr. 2022 Dec 8.

doi: 10.1007/s00431-022-04721-3. Online ahead of print.

### [Effect of high-energy and/or high-protein feeding in children with congenital heart disease after cardiac surgery: a systematic review and meta-analysis](#)

[Ping Ni<sup>1</sup>](#), [XiuLi Wang<sup>2</sup>](#), [ZhuoMing Xu<sup>1</sup>](#), [Wenyi Luo<sup>3</sup>](#)

### Abstract

High-energy or high-protein feeding offers a promising approach to improving malnutrition in children after congenital heart surgery. However, the effect of high-energy or high-protein feeding in this population has not yet been systematically reviewed. Therefore, we aimed to assess the safety and effectiveness of high-energy or high-protein feeding in children after congenital heart surgery. Five electronic databases (PubMed, Embase, CENTRAL, CINAHL, and Scopus) were searched from inception to April 23, 2022. After screening the literature according to inclusion and exclusion criteria, a risk of bias assessment was performed using version 2 of the Cochrane risk-of-bias tool for randomized trials, and the certainty of the evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations system. Finally, the random effects model was used to perform a meta-analysis of all data. A total of 609 subjects from 9 studies were included for qualitative

analysis, and meta-analyses were performed on data from 8 of these studies. The results showed that high-energy and/or high-protein feeding did not increase feeding intolerance (RR = 1.09, 95% CI: 0.80, 1.48) or fluid intake (MD = - 12.50 ml/kg/d, 95% CI: - 36.10, 11.10); however, the intervention was beneficial in increasing weight (MD = 0.5 kg, 95% CI: 0.23, 0.77) and reducing the duration of mechanical ventilation (MD = - 17.45 h, 95% CI: - 27.30, - 7.60), intensive care unit (ICU) stay (MD = - 1.45 days, 95% CI: - 2.36, - 0.54) and hospital stay (MD = - 2.82 days, 95% CI: - 5.22, - 0.43). However, high-energy and/or protein feeding did not reduce the infection rate (RR = 0.68, 95% CI: 0.25, 1.87) or mortality (RR = 1.50, 95% CI: 0.47, 4.82).

**Conclusion:** The certainty of the evidence was graded as moderate to high, which suggests that high-energy and/or high-protein feeding may be safe in children after congenital heart surgery. Furthermore, this intervention improves nutrition and reduces the duration of mechanical ventilation, length of ICU stay, and length of hospital stay. However, the overall conclusion of this meta-analysis will need to be confirmed in a cohort of patients with different cardiac physiologies.

## HIV / AIDS

### Antiretroviral therapy (ART)

Lancet HIV. 2022 Sep;9(9):e638-e648.

doi: 10.1016/S2352-3018(22)00163-1.

#### [Once-daily dolutegravir-based antiretroviral therapy in infants and children living with HIV from age 4 weeks: results from the below 14 kg cohort in the randomised ODYSSEY trial](#)

[Pauline Amuge<sup>1</sup>](#), [Abbas Lugemwa<sup>2</sup>](#), [Ben Wynne<sup>3</sup>](#), [Hilda A Mujuru<sup>4</sup>](#), [Avy Violari<sup>5</sup>](#), [Cissy M Kityo<sup>6</sup>](#), [Moherndran Archary<sup>7</sup>](#), [Ebrahim Variava<sup>5</sup>](#), [Ellen White<sup>3</sup>](#), [Rebecca M Turner<sup>3</sup>](#), [Clare Shakeshaft<sup>3</sup>](#), [Shabinah Ali<sup>3</sup>](#), [Kusum J Nathoo<sup>4</sup>](#), [Lorna Atwine<sup>2</sup>](#), [Afaaf Liberty<sup>5</sup>](#), [Dickson Bbuye<sup>1</sup>](#), [Elizabeth Kaudha<sup>6</sup>](#), [Rosie Mngqibisa<sup>7</sup>](#), [Modehei Mosala<sup>5</sup>](#), [Vivian Mumbiro<sup>4</sup>](#), [Annet Nanduudu<sup>6</sup>](#), [Rogers Ankunda<sup>2</sup>](#), [Lindiwe Maseko<sup>5</sup>](#), [Adeodata R Kekitiinwa<sup>1</sup>](#), [Carlo Giaquinto<sup>8</sup>](#), [Pablo Rojo<sup>9</sup>](#), [Diana M Gibb<sup>3</sup>](#), [Anna Turkova<sup>3</sup>](#), [Deborah Ford<sup>10</sup>](#), [ODYSSEY Trial Team](#)

#### Abstract

**Background:** Young children living with HIV have few treatment options. We aimed to assess the efficacy and safety of dolutegravir-based antiretroviral therapy (ART) in children weighing between 3 kg and less than 14 kg.

**Methods:** ODYSSEY is an open-label, randomised, non-inferiority trial (10% margin) comparing dolutegravir-based ART with standard of care and comprises two cohorts (children weighing  $\geq 14$  kg and  $< 14$  kg). Children weighing less than 14 kg starting first-line or second-line ART were enrolled in seven HIV treatment centres in South Africa, Uganda, and Zimbabwe. Randomisation, which was computer generated by the trial statistician, was stratified by first-line or second-line ART and three weight bands. Dispersible 5 mg dolutegravir was dosed according to WHO weight bands. The primary outcome was the Kaplan-Meier estimated proportion of children with virological or clinical failure by 96 weeks, defined as: confirmed viral load of at least 400 copies per mL after week 36; absence of virological suppression by 24 weeks followed by a switch to second-line or third-line ART; all-

cause death; or a new or recurrent WHO stage 4 or severe WHO stage 3 event. The primary outcome was assessed by intention to treat in all randomly assigned participants. A primary Bayesian analysis of the difference in the proportion of children meeting the primary outcome between treatment groups incorporated evidence from the higher weight cohort ( $\geq 14$  kg) in a prior distribution. A frequentist analysis was also done of the lower weight cohort ( $< 14$  kg) alone. Safety analyses are presented for all randomly assigned children in this study ( $< 14$  kg cohort). ODYSSEY is registered with ClinicalTrials.gov, [NCT02259127](https://clinicaltrials.gov/ct2/show/study/NCT02259127).

**Findings:** Between July 5, 2018, and Aug 26, 2019, 85 children weighing less than 14 kg were randomly assigned to receive dolutegravir ( $n=42$ ) or standard of care ( $n=43$ ; 32 [74%] receiving protease inhibitor-based ART). Median age was 1.4 years (IQR 0.6-2.0) and median weight 8.1 kg (5.4-10.0). 72 (85%) children started first-line ART and 13 (15%) started second-line ART. Median follow-up was 124 weeks (112-137). By 96 weeks, treatment failure occurred in 12 children in the dolutegravir group (Kaplan-Meier estimated proportion 31%) versus 21 (48%) in the standard-of-care group. The Bayesian estimated difference in treatment failure (dolutegravir minus standard of care) was -10% (95% CI -19% to -2%;  $p=0.020$ ), demonstrating superiority of dolutegravir. The frequentist estimated difference was -18% (-36% to 2%;  $p=0.057$ ). 15 serious adverse events were reported in 11 (26%) children in the dolutegravir group, including two deaths, and 19 were reported in 11 (26%) children in the standard-of-care group, including four deaths (hazard ratio [HR] 1.08 [95% CI 0.47-2.49];  $p=0.86$ ). 36 adverse events of grade 3 or higher were reported in 19 (45%) children in the dolutegravir group, versus 34 events in 21 (49%) children in the standard-of-care group (HR 0.93 [0.50-1.74];  $p=0.83$ ). No events were considered related to dolutegravir.

**Interpretation:** Dolutegravir-based ART was superior to standard of care (mainly protease inhibitor-based) with a lower risk of treatment failure in infants and young children, providing support for global dispersible dolutegravir roll-out for younger children and allowing alignment of adult and paediatric treatment.

Clin Infect Dis. 2023 Jun 6;ciad346.

doi: 10.1093/cid/ciad346. Online ahead of print.

### [Pharmacokinetic data of dolutegravir in second-line treatment of children living with HIV: results from the CHAPAS4-trial](#)

[Lisanne Bevers](#)<sup>1</sup>, [Hylke Waalewijn](#)<sup>1,2</sup>, [Alexander Szubert](#)<sup>3</sup>, [Chishala Chabala](#)<sup>4</sup>, [Mutsa Bwakura-Dangarembizi](#)<sup>5</sup>, [Shafic Makumbi](#)<sup>6</sup>, [Joan Nangiya](#)<sup>7</sup>, [Vivian Mumbiro](#)<sup>5</sup>, [Veronica Mulenga](#)<sup>4</sup>, [Victor Musiime](#)<sup>7</sup>, [David Burger](#)<sup>1</sup>, [Diana Gibb](#)<sup>3</sup>, [Angela Colbers](#)<sup>1</sup>; [CHAPAS4-TRIAL TEAM](#)

#### **Abstract**

**Background:** Dolutegravir (DTG), combined with a backbone of two NRTIs, is currently the preferred first-line treatment for HIV in childhood. CHAPAS4 is an ongoing randomized controlled trial (#SRCTN22964075) investigating second-line treatment options for children with HIV. We did a nested PK substudy within CHAPAS4 to evaluate the DTG exposure in children with HIV taking DTG with food, as part of their second-line treatment.

**Methods:** Additional consent was required for children on DTG enrolled in the CHAPAS4-trial to participate in this PK substudy. Children weighing 14-19.9 kg took 25 mg DTG as dispersible tablets (DT) and children  $\geq 20$  kg took 50 mg film-coated tablets (FCT). Steady-state 24 h DTG plasma concentration-time PK profiling was done at  $t = 0$  and 1, 2, 4, 6, 8, 12, and 24 h after observed DTG intake with food. Reference adult PK data and paediatric data

from the ODYSSEY-trial was used primarily for comparison. The individual target trough concentration (C<sub>trough</sub>) was defined as 0.32 mg/L.

**Results:** 39 children on DTG were included in this PK substudy. The Geometric Mean (GM), (CV%) AUC<sub>0-24h</sub> was 57.1 h\*mg/L (38.4%) which was approximately 8% below the average AUC<sub>0-24h</sub> in children in the ODYSSEY-trial with comparable dosages, but above the adult reference. The GM (CV%) C<sub>trough</sub> was 0.82 mg/L (63.8%) which was comparable to ODYSSEY and adult reference values.

**Conclusions:** This nested PK substudy shows that the exposure of DTG taken with food in children on second-line treatment is comparable with that of children in the ODYSSEY-trial and adult references.

J Antimicrob Chemother. 2023 Mar 3;dkad043.

doi: 10.1093/jac/dkad043. Online ahead of print.

**Population pharmacokinetics of unbound and total dolutegravir concentrations in children aged 12 years and older: a PK substudy of the SMILE trial**

[Seef Abdalla<sup>1,2</sup>](#), [Alexandra Compagnucci<sup>3</sup>](#), [Yi Zheng<sup>2</sup>](#), [Jean-Marc Tréluyer<sup>1,2,4</sup>](#), [Yacine Saidi<sup>3</sup>](#), [José T Ramos<sup>5,6</sup>](#), [Alexandra Coelho<sup>3</sup>](#), [Yoann Riault<sup>3</sup>](#), [Tim R Cressey<sup>7</sup>](#), [Déborah Hirt<sup>1,2</sup>](#); [SMILE study group](#)

**Abstract**

**Background:** SMILE, a multicentre randomized trial, compared the efficacy and safety of switching virologically suppressed children and adolescents with HIV to a once-daily dual regimen of dolutegravir plus ritonavir-boosted darunavir versus continuing standard ART. Within a nested pharmacokinetic (PK) substudy, we performed a population PK analysis to describe total and unbound dolutegravir plasma concentrations in children and adolescents receiving this dual therapy.

**Methods:** Sparse blood samples were obtained during follow-up for dolutegravir quantification. A population PK model was developed to simultaneously describe total and unbound dolutegravir concentrations. Simulations were performed and were compared with the protein-adjusted 90% inhibitory concentration (IC<sub>90</sub>) and the in vitro IC<sub>50</sub>, respectively. Dolutegravir exposures in children aged ≥12 years were also compared with values in treatment-experienced adults.

**Results:** Four hundred and fifty-five samples from 153 participants aged between 12 and 18 years were collected for this PK analysis. A one-compartment model with first-order absorption and elimination best described unbound dolutegravir concentrations. The relationship between unbound and total dolutegravir concentrations was best characterized by a non-linear model. Unbound dolutegravir apparent clearance was significantly influenced by total bilirubin concentrations and by Asian ethnicity. All children and adolescents had trough concentrations well above the protein-adjusted IC<sub>90</sub> and the in vitro IC<sub>50</sub> values. Dolutegravir concentrations and exposures were also similar to those obtained in adults receiving dolutegravir 50 mg once daily.

**Conclusions:** A once-daily 50 mg dolutegravir dose for children and adolescents produces adequate total and unbound concentrations when used as part of dual therapy with ritonavir-boosted darunavir.

Lancet HIV. 2022 Sep;9(9):e627-e637.

doi: 10.1016/S2352-3018(22)00160-6. Epub 2022 Jul 19.

**[Dolutegravir twice-daily dosing in children with HIV-associated tuberculosis: a pharmacokinetic and safety study within the open-label, multicentre, randomised, non-inferiority ODYSSEY trial](#)**

[Anna Turkova](#)<sup>1</sup>, [Hylke Waalewijn](#)<sup>2</sup>, [Man K Chan](#)<sup>3</sup>, [Pauline D J Bollen](#)<sup>2</sup>, [Mutsa F Bwakura-Dangarembizi](#)<sup>4</sup>, [Adeodata R Kekitiinwa](#)<sup>5</sup>, [Mark F Cotton](#)<sup>6</sup>, [Abbas Lugemwa](#)<sup>7</sup>, [Ebrahim Variava](#)<sup>8</sup>, [Grace Miriam Ahimbisibwe](#)<sup>9</sup>, [Ussanee Srirompotong](#)<sup>10</sup>, [Vivian Mumbiro](#)<sup>4</sup>, [Pauline Amuge](#)<sup>5</sup>, [Peter Zuidewind](#)<sup>6</sup>, [Shabinah Ali](#)<sup>3</sup>, [Cissy M Kityo](#)<sup>11</sup>, [Moherndran Archary](#)<sup>12</sup>, [Rashida A Ferrand](#)<sup>13</sup>, [Avy Violari](#)<sup>8</sup>, [Diana M Gibb](#)<sup>3</sup>, [David M Burger](#)<sup>2</sup>, [Deborah Ford](#)<sup>3</sup>, [Angela Colbers](#)<sup>2</sup>, [ODYSSEY Trial Team](#)

**Abstract**

**Background:** Children with HIV-associated tuberculosis (TB) have few antiretroviral therapy (ART) options. We aimed to evaluate the safety and pharmacokinetics of dolutegravir twice-daily dosing in children receiving rifampicin for HIV-associated TB.

**Methods:** We nested a two-period, fixed-order pharmacokinetic substudy within the open-label, multicentre, randomised, controlled, non-inferiority ODYSSEY trial at research centres in South Africa, Uganda, and Zimbabwe. Children (aged 4 weeks to <18 years) with HIV-associated TB who were receiving rifampicin and twice-daily dolutegravir were eligible for inclusion. We did a 12-h pharmacokinetic profile on rifampicin and twice-daily dolutegravir and a 24-h profile on once-daily dolutegravir. Geometric mean ratios for trough plasma concentration ( $C_{\text{trough}}$ ), area under the plasma concentration time curve from 0 h to 24 h after dosing ( $AUC_{0-24\text{ h}}$ ), and maximum plasma concentration ( $C_{\text{max}}$ ) were used to compare dolutegravir concentrations between substudy days. We assessed rifampicin  $C_{\text{max}}$  on the first substudy day. All children within ODYSSEY with HIV-associated TB who received rifampicin and twice-daily dolutegravir were included in the safety analysis. We described adverse events reported from starting twice-daily dolutegravir to 30 days after returning to once-daily dolutegravir. This trial is registered with ClinicalTrials.gov ([NCT02259127](#)), EudraCT (2014-002632-14), and the ISRCTN registry (ISRCTN91737921).

**Findings:** Between Sept 20, 2016, and June 28, 2021, 37 children with HIV-associated TB (median age 11·9 years [range 0·4-17·6], 19 [51%] were female and 18 [49%] were male, 36 [97%] in Africa and one [3%] in Thailand) received rifampicin with twice-daily dolutegravir and were included in the safety analysis. 20 (54%) of 37 children enrolled in the pharmacokinetic substudy, 14 of whom contributed at least one evaluable pharmacokinetic curve for dolutegravir, including 12 who had within-participant comparisons. Geometric mean ratios for rifampicin and twice-daily dolutegravir versus once-daily dolutegravir were 1·51 (90% CI 1·08-2·11) for  $C_{\text{trough}}$ , 1·23 (0·99-1·53) for  $AUC_{0-24\text{ h}}$ , and 0·94 (0·76-1·16) for  $C_{\text{max}}$ . Individual dolutegravir  $C_{\text{trough}}$  concentrations were higher than the 90% effective concentration (ie, 0·32 mg/L) in all children receiving rifampicin and twice-daily dolutegravir. Of 18 children with evaluable rifampicin concentrations, 15 (83%) had a  $C_{\text{max}}$  of less than the optimal target concentration of 8 mg/L. Rifampicin geometric mean  $C_{\text{max}}$  was 5·1 mg/L (coefficient of variation 71%). During a median follow-up of 31 weeks (IQR 30-40), 15 grade 3 or higher adverse events occurred among 11 (30%) of 37 children, ten serious adverse events occurred among eight (22%) children, including two deaths (one tuberculosis-related death, one death due to traumatic injury); no adverse events, including deaths, were considered related to dolutegravir.



**Interpretation:** Twice-daily dolutegravir was shown to be safe and sufficient to overcome the rifampicin enzyme-inducing effect in children, and could provide a practical ART option for children with HIV-associated TB.

Lancet Child Adolesc Health. 2022 Oct;6(10):692-704.

doi: 10.1016/S2352-4642(22)00213-9. Epub 2022 Sep 2.

**[Safety and efficacy of abacavir for treating infants, children, and adolescents living with HIV: a systematic review and meta-analysis](#)**

[Julie Jesson](#)<sup>1</sup>, [Laura Saint-Lary](#)<sup>2</sup>, [Marc Harris Dassi Tchoupa Revegue](#)<sup>2</sup>, [John O'Rourke](#)<sup>3</sup>, [Claire L Townsend](#)<sup>3</sup>, [Françoise Renaud](#)<sup>3</sup>, [Martina Penazzato](#)<sup>3</sup>, [Valérie Leroy](#)<sup>2</sup>

**Abstract**

**Background:** Abacavir is a nucleoside reverse transcriptase inhibitor recommended in paediatric HIV care. We assessed the safety and efficacy profile of abacavir used in first, second, or subsequent lines of treatment for infants, children, and adolescents living with HIV to inform 2021 WHO paediatric ART recommendations.

**Methods:** In this systematic review and meta-analysis, we included observational and experimental studies conducted in infants aged 0-1 year, children aged 1-10 years, and adolescents aged 10-19 years living with HIV; with data on safety or efficacy, or both, of abacavir-based antiretroviral therapy (ART); published in English or French between Jan 1, 2009, and Oct 1, 2020, plus an updated search to incorporate studies published between Oct 1, 2020, and May 15, 2022. Studies could be non-randomised or non-comparative and include patients who are treatment-naïve or those who previously received abacavir (only if abacavir was combined with other ART). Case studies, studies in adults aged 18 years or older, and those assessing the effect of maternal ART exposure were excluded. We extracted data related to study identifier, study design, study period, setting, population characteristics, ART treatment, and safety (any hypersensitivity reaction, death, grade 3 or 4 adverse events, treatment discontinuation, any other morbidities, and serious adverse events), and efficacy outcomes (HIV viral load and CD4 counts reported at 6 and 12 months after ART initiation). Using random-effect models, we estimated weighted pooled incidence and relative risk (RR) of outcomes. The protocol is published in PROSPERO (CRD42022309230).

**Findings:** Of 1777 records identified, 1475 (83%) were screened after removing duplicates and a further 1421 (96%) were excluded. Of 54 full-text articles assessed for eligibility, 33 (61%) were excluded. Four records were identified from grey literature plus one duplicate from database searching, resulting in 24 studies included (two randomised controlled trials, one single-arm trial, 12 prospective cohorts, seven retrospective cohorts, and two cross-sectional studies). 19 studies described safety data and 15 described efficacy data. 18 (75%) studies were conducted in ART-naïve participants. The risk of bias was considered moderate to high for most studies, and all outcomes had significant between-study heterogeneity. Data from 24 265 participants were included, of whom 7236 (30%) received abacavir. Abacavir hypersensitivity reaction was reported in nine (38%) studies, with an incidence ranging from 0.00% to 8.26% ( $I^2=85%$ ;  $p<0.0001$ ). The incidence of death (reported in seven studies) following abacavir treatment varied from 0.00% to 5.49% ( $I^2=58%$ ;  $p=0.026$ ). Viral suppression (<400 copies per mL) varied from 50% to 70% at 6 months ( $I^2=92%$ ,  $p<0.0001$ ) and from 57% to 78% at 12 months ( $I^2=88%$ ,  $p<0.0001$ ).



**Interpretation:** Toxic effects due to abacavir use remain rare and manageable. Despite scarce data on efficacy, this meta-analysis supports the use of abacavir as a preferred first-line regimen for infants and children living with HIV.

AIDS Res Hum Retroviruses. 2022 Oct;38(10):774-778.

doi: 10.1089/AID.2021.0140. Epub 2022 Sep 7.

### **Tenofovir, Lamivudine, and Dolutegravir Among Rural Adolescents in Zimbabwe: A Cautionary Tale**

[Vinie Kouamou<sup>1</sup>](#), [Rhoderick Machekano<sup>2</sup>](#), [Tichaona Mapangisana<sup>2</sup>](#), [Caroline Maposhere<sup>3</sup>](#), [Shungu Munyati<sup>3</sup>](#), [Junior Mutsvangwa<sup>3</sup>](#), [Tinei Shamu<sup>4,5,6</sup>](#), [Kathy McCarty<sup>7</sup>](#), [David Katzenstein<sup>3</sup>](#), [Justen Manasa<sup>8,9</sup>](#)

#### **Abstract**

Tenofovir disoproxil fumarate, lamivudine, and dolutegravir (TLD) as a safe and more effective single daily dose regimen is rolling out in Africa for people living with HIV. Although access to viral load (VL) testing is improving, patients may still be transitioned to TLD with virological failure and potential drug resistance. We reviewed annual VL test results of 390 children and adolescents who had enrolled in a community-based antiretroviral therapy program in rural Zimbabwe between 2018 and 2019. VL testing was done by the near point of care simplified amplification-based assays at Chidamoyo Christian Hospital and rate of virological suppression (VS) on TLD (VL <1,000 copies/mL) was assessed. Overall, 184 children and adolescents on TLD were enrolled in this study. The median [interquartile range (IQR)] age was 15 (11-19) years, above half of the participants were female (57%). Before switching to TLD, rate of VS was 76% (139/184). After a median (IQR) duration of 6.9 (5.5-9.1) months on TLD, VS was observed in 95% (174/184) of the participants. Of the 10 participants with VL ≥1,000 copies/mL on TLD, 90% (9/10) were failing on their previous regimens, 6 of 9 (67%) having been on boosted protease inhibitor-based regimens. A high rate (95%) of VS was observed among children and adolescents on TLD in rural Zimbabwe. TLD may address the problems of virological failure and emergence of resistance in Africa. However, longer follow-up might be needed to ascertain sustained VS in this vulnerable population.

## **Viral load monitoring**

Lancet Child Adolesc Health. 2022 Oct;6(10):681-691.

doi: 10.1016/S2352-4642(22)00191-2. Epub 2022 Aug 18.

### **Point-of-care HIV viral load and targeted drug resistance mutation testing versus standard care for Kenyan children on antiretroviral therapy (Opt4Kids): an open-label, randomised controlled trial**

[Rena C Patel<sup>1</sup>](#), [Patrick Oyaro<sup>2</sup>](#), [Katherine K Thomas<sup>3</sup>](#), [James Wagude<sup>4</sup>](#), [Irene Mukui<sup>5</sup>](#), [Evelyn Brown<sup>6</sup>](#), [Shukri A Hassan<sup>7</sup>](#), [Eunice Kinywa<sup>8</sup>](#), [Frederick Oluoch<sup>8</sup>](#), [Francesca Odhiambo<sup>9</sup>](#), [Boaz Oyaro<sup>10</sup>](#), [Leonard Kingwara<sup>11</sup>](#), [Enericah Karauki<sup>6</sup>](#), [Nashon Yongo<sup>6</sup>](#), [Lindah Otieno<sup>9</sup>](#), [Grace C John-Stewart<sup>12</sup>](#), [Lisa L Abuogi<sup>13</sup>](#)

#### **Abstract**

**Background:** Feasible, scalable, and cost-effective approaches to ensure virological suppression among children living with HIV are urgently needed. The aim of the Opt4Kids study was to determine the effect of point of care viral load and targeted drug resistance

mutation testing in improving virological suppression among children on antiretroviral therapy (ART) in Kenya.

**Methods:** In this open-label, individually randomised controlled trial, we enrolled children living with HIV aged 1-14 years and who were either newly initiating or already receiving ART at five study facilities in Kenya. Participants were randomly allocated 1:1 to receive the intervention of point-of-care viral load testing every 3 months, targeted drug resistance mutation testing, and clinical decision support (point-of-care testing) or to receive the standard care (control group), stratified by facility site and age groups (1-9 years vs 10-14 years). Investigators were masked to the randomised group. The primary efficacy outcome was virological suppression (defined as a viral load of <1000 copies per mL) by point-of-care viral load testing at 12 months after enrolment in all participants with an assessment. This study is registered with ClinicalTrials.gov, [NCT03820323](https://clinicaltrials.gov/ct2/show/study/NCT03820323).

**Findings:** Between March 7, 2019, and December 31, 2020, we enrolled 704 participants. Median age at enrolment was 9 years (IQR 7-12), 344 (49%) participants were female and 360 (51%) were male, and median time on ART was 5.8 years (IQR 3.1-8.6). 536 (76%) of 704 had documented virological suppression at enrolment. At 12 months after enrolment, the proportion of participants achieving virological suppression in the intervention group (283 [90%] of 313 participants with a 12 month point-of-care viral load test) did not differ from that in the control group (289 [92%] of 315; risk ratio [RR] 0.99, 95% CI 0.94-1.03; p=0.55). We identified 138 episodes of viraemia in intervention participants, of which 107 (89%) samples successfully underwent drug resistance mutation testing and 91 (85%) had major drug resistance mutations. The median turnaround time for viral load results was 1 day (IQR 0-1) in the intervention group and 15 days (10-21) in the control group.

**Interpretation:** Point-of-care viral load testing decreased turnaround time and targeted drug resistance mutation testing identified a high prevalence of HIV drug resistance mutations in children living with HIV, but the combined approach did not increase rates of virological suppression. Further research in combination interventions, including point-of-care viral load and drug resistance mutation testing coupled with psychosocial support, is needed to optimise virological suppression for children living with HIV.

PLoS One. 2023 Feb 14;18(2):e0281279.

doi: 10.1371/journal.pone.0281279. eCollection 2023.

**[Clinic-based SAMBA-II vs centralized laboratory viral load assays among HIV-1 infected children, adolescents and young adults in rural Zimbabwe: A randomized controlled trial](#)**

[Vinie Kouamou](#)<sup>1</sup>, [Rhoderick Machezano](#)<sup>2</sup>, [Tichaona Mapangisana](#)<sup>2</sup>, [Caroline Maposhere](#)<sup>3</sup>, [Reggie Mutetwa](#)<sup>3</sup>, [Justen Manasa](#)<sup>4,5</sup>, [Tinei Shamu](#)<sup>6,7,8</sup>, [Kathy McCarty](#)<sup>9</sup>, [Shungu Munyati](#)<sup>3</sup>, [Junior Mutsvangwa](#)<sup>3</sup>, [Mampedi Bogoshi](#)<sup>10</sup>, [Dennis Israelski](#)<sup>11</sup>, [David Katzenstein](#)<sup>3,12</sup>

**Abstract**

**Background:** In Zimbabwe, children, adolescents and young adults living with HIV (CALWH) who are on public health antiretroviral therapy (ART) have inadequate viral load (VL) suppression. We assessed whether a clinic-based VL monitoring could decrease 12-month virologic failure rates among these CALWH.

**Methods:** The study was registered on ClinicalTrials.gov: [NCT03986099](https://clinicaltrials.gov/ct2/show/study/NCT03986099). CALWH in care at Chidamoyo Christian Hospital (CCH) and 8 rural outreach sites (ROS) on long-term

community-based ART were randomized (1:1) to 6 monthly VL monitoring by COBAS®Ampliprep®/Taqman48® HIV-1 at the provincial referral laboratory (PRL) as per standard of care (SOC) or by the clinic-based SAMBA II assay, Diagnostics for the Real World, at CCH. VL suppression, turn-around-time (TAT) for VL results, drug switching and drug resistance in second-line failure were assessed at 12 months.

**Results:** Of 390 CALWH enrolled 347 (89%) completed 12 months follow-up. Median (IQR) age and ART duration were 14.1 (9.7-18.2) and 6.4 (3.7-7.9) years, respectively. Over half (57%) of the participants were female. At enrolment, 78 (20%) had VL  $\geq 1,000$  copies/ml and VL suppression of 80% was unchanged after 12 months, with no significant difference between the SOC (81%) and the clinic-based (80%) arms ( $p = 0.528$ ). Median (IQR) months to confirmatory VL result at CCH vs PRL was 4.0 (2.1-4.4) vs 4.5 (3.5-6.3) respectively;  $p = 0.027$  at 12 months. Drug switching was documented among 26/347 (7%) participants with no difference between the median (IQR) time to switch in SOC vs clinic-based arms (5.1 (3.9-10.0) months vs 4.4 (2.5-8.4) respectively;  $p = 0.569$ ). Out of 24 confirmed second-line failures, only 4/19 (21%) had protease inhibitor resistance.

**Conclusion:** In rural Zimbabwe, the clinic-based SAMBA II assay was able to provide confirmatory VL results faster than the SOC VL assay at the PRL. However, this rapid TAT did not allow for a more efficient drug switch among these CALWH.

BMC Public Health. 2023 Jul 3;23(1):1280.

doi: 10.1186/s12889-023-16181-x.

[\*\*Effectiveness of a community-based intervention \(Konga model\) to address factors contributing to low viral load suppression among children living with HIV in Tanzania: a preliminary, cluster, randomized clinical trial report\*\*](#)

[Kihulya Mageda<sup>1</sup>](#), [Khamis Kulemba<sup>2</sup>](#), [Edwin Kilimba<sup>3</sup>](#), [Leonard K Katalambula<sup>4</sup>](#), [Ntuli Kapologwe<sup>4</sup>](#), [Pammla Petrucka<sup>5</sup>](#)

**Abstract**

**Background:** Despite effective antiretroviral therapy (ART) coverage in other groups living with human immunodeficiency virus (HIV) in Tanzania, virologic suppression among HIV-positive children receiving ART remains unacceptably low. This study evaluated the effectiveness of a community-based intervention (Konga model) in addressing the factor contributing to low viral load suppression among children living with HIV in the Simiyu region, Tanzania.

**Methods:** This study used a parallel cluster randomized trial. The cluster was only eligible if the health facility provided HIV care and treatment. All eligible resident children aged 2–14 years who attended the cluster with a viral load  $> 1,000$  cells/mm were enrolled. The intervention included three distinct activities: adherence counseling, psychosocial support, and co-morbidity screening such as tuberculosis. The evaluation was based on patient-centered viral load outcomes measured at baseline and 6 months later. Using a pre- and post-test design, we compared the means of participants in the intervention and control groups. We performed an analysis of covariance. The effect of a Konga was calculated using omega-squared. We used F-tests, with their corresponding p-values, as measures of improvement.

**Results:** We randomly assigned 45 clusters to the treatment (15) and control (30) groups. We enrolled 82 children with a median age of 8.8 years (interquartile range (IQR); 5.5-11.2), and a baseline median viral load of 13,150 cells/mm (interquartile range (IQR); 3600-59,200). After

the study, both children in each group had good adherence, with children in the treatment group scoring slightly higher than those in the control group, 40 (97.56%) versus 31(75%61), respectively. At the end of the study, the difference in viral load suppression between the two groups was significant. The median viral load suppression at the end of the study was 50 cells/mm [IQR, (20-125)]. After adjusting for the viral load before the intervention, the effect size of the Konga intervention explained 4% (95% confidence interval [0%, 14.1%]) of the viral load variation at the end of the intervention.

**Conclusion:** The Konga model demonstrated significant positive effects that improved viral load suppression. We recommend implementing the Konga model trial in other regions to improve the consistency of results.

## HIV diagnosis

Lancet HIV. 2023 Apr;10(4):e220-e229.

doi: 10.1016/S2352-3018(23)00001-2. Epub 2023 Mar 2.

### [The effect of the Xpert HIV-1 Qual test on early infant diagnosis of HIV in Myanmar and Papua New Guinea: a pragmatic, cluster-randomised, stepped-wedge, open-label trial](#)

[Yasmin Mohamed<sup>1</sup>](#), [Hla Htay<sup>2</sup>](#), [Janet Gare<sup>3</sup>](#), [Andrew J BValley<sup>4</sup>](#), [Angela Kelly-Hanku<sup>4</sup>](#), [Win Lei Yee<sup>2</sup>](#), [Paul A Agius<sup>5</sup>](#), [Steven G Badman<sup>6</sup>](#), [Minh Duc Pham<sup>7</sup>](#), [Claire Nightingale<sup>8</sup>](#), [Xiang-Sheng Chen<sup>9</sup>](#), [Zure Kombati<sup>10</sup>](#), [Amelia Koata<sup>3</sup>](#), [Gloria Munnall<sup>10</sup>](#), [Selina Silim<sup>3</sup>](#), [Win Thein<sup>11</sup>](#), [Tin Maung Zaw<sup>12</sup>](#), [Latt Latt Kyaw<sup>11</sup>](#), [Mark Stoové<sup>13</sup>](#), [Suzanne M Crowe<sup>13</sup>](#), [David Anderson<sup>13</sup>](#), [Htay Htay Tin<sup>11</sup>](#), [Stanley Luchters<sup>14</sup>](#)

#### **Abstract**

**Background:** Despite proven benefits for child health, coverage of early infant diagnosis of HIV remains suboptimal in many settings. We aimed to assess the effect of a point-of-care early infant diagnosis test on time-to-results communication for infants vertically exposed to HIV.

**Methods:** This pragmatic, cluster-randomised, stepped-wedge, open-label trial assessed the effect of the Xpert HIV-1 Qual early infant diagnosis test (Cepheid) on time-to-results communication, compared with standard care laboratory-based testing of dried blood spots using PCR. Hospitals were the unit of randomisation for one-way crossover from control to intervention phase. Each site had between 1 month and 10 months of control phase before transitioning to the intervention, with a total of 33 hospital-months in the control phase and 45 hospital-months in the intervention phase. We enrolled infants vertically exposed to HIV at six public hospitals: four in Myanmar and two in Papua New Guinea. Infants had to have mothers with confirmed HIV infection, be younger than 28 days, and required HIV testing to be eligible for enrolment. Health-care facilities providing prevention of vertical transmission services were eligible for participation. The primary outcome was communication of early infant diagnosis results to the infant's caregiver by 3 months of age, assessed by intention to treat. This completed trial was registered with the Australian and New Zealand Clinical Trials Registry, 12616000734460.

**Findings:** In Myanmar, recruitment took place between Oct 1, 2016, and June 30, 2018; in Papua New Guinea, recruitment was between Dec 1, 2016, and Aug 31, 2018. A total of 393 caregiver-infant pairs were enrolled in the study across both countries. Independent of study time, the Xpert test reduced time to early infant diagnosis results communication by 60%, compared with the standard of care (adjusted time ratio 0.40, 95% CI 0.29-0.53,  $p < 0.0001$ ). In the control phase, two (2%) of 102 study participants received an early infant diagnosis test result by 3 months of age compared with 214 (74%) of 291 in the intervention phase. No safety and adverse events were reported related to the diagnostic testing intervention.

**Interpretation:** This study reinforces the importance of scaling up point-of-care early infant diagnosis testing in resource-constrained and low HIV-prevalence settings, typical of the UNICEF East Asia and Pacific region.

Clin Infect Dis. 2022 Aug 25;75(2):260-268.

doi: 10.1093/cid/ciab923.

### [A Randomized Trial of Point-of-Care Early Infant Human Immunodeficiency Virus \(HIV\) Diagnosis in Zambia](#)

[Carla J Chibwasha<sup>1,2</sup>](#), [Katie R Mollan<sup>3</sup>](#), [Catherine E Ford<sup>1,2</sup>](#), [Aaron Shibemba<sup>4</sup>](#), [Pooja T Saha<sup>3</sup>](#), [Mildred Lusaka<sup>2</sup>](#), [Felistas Mbewe<sup>2</sup>](#), [Andrew G Allmon<sup>3</sup>](#), [Rose Lungu<sup>2</sup>](#), [Hans M L Spiegel<sup>5</sup>](#), [Emmanuel Mweni<sup>2</sup>](#), [Humphrey Mwape<sup>2</sup>](#), [Chipepo Kankasa<sup>6</sup>](#), [Benjamin H Chi<sup>1,2</sup>](#), [Jeffrey S A Stringer<sup>1,2</sup>](#)

#### **Abstract**

**Background:** Point-of-care (POC) early infant diagnosis (EID) provides same-day results and the potential for immediate initiation of antiretroviral therapy (ART).

**Methods:** We conducted a pragmatic trial at 6 public clinics in Zambia. HIV-exposed infants were individually randomized to either (1) POC EID (onsite testing with the Alere q HIV-1/2 Detect) or (2) enhanced standard of care (SOC) EID (off-site testing at a public laboratory). Infants with HIV were referred for ART and followed for 12 months. Our primary outcome was defined as alive, in care, and virally suppressed at 12 months.

**Results:** Between March 2016 and November 2018, we randomized 4000 HIV-exposed infants to POC ( $n=1989$ ) or SOC ( $n=2011$ ). All but 2 infants in the POC group received same-day results, while the median time to result in the SOC group was 27 (interquartile range: 22-30) days. Eighty-one (2%; 95% confidence interval [CI]: 1.6-2.5%) infants were diagnosed with HIV. Although ART initiation was high, there were 15 (19%) deaths, 15 (19%) follow-up losses, and 31 (38%) virologic failures. By 12 months, only 20 of 81 (25%; 95% CI: 15-34%) infants with HIV were alive, in care, and virally suppressed: 13 (30%; 16-43%) infants in the POC group vs 7 (19%; 6-32%) in the SOC group (RR: 1.56; .7-3.50).

**Conclusions:** POC EID eliminated diagnostic delays and accelerated ART initiation but did not translate into definitive improvement in 12-month outcomes. In settings where centralized EID is well functioning, POC EID is unlikely to improve pediatric HIV outcomes.

BMC Health Serv Res. 2022 Dec 5;22(1):1480.

doi: 10.1186/s12913-022-08828-z.

**[The cost of implementing the Systems Analysis and Improvement Approach for a cluster randomized trial integrating HIV testing into family planning services in Mombasa County, Kenya](#)**

[Dorothy Thomas](#)<sup>1</sup>, [George Wanje](#)<sup>2</sup>, [McKenna C Eastment](#)<sup>3</sup>, [R Scott McClelland](#)<sup>2,3,4,5</sup>, [Emily Mwaringa](#)<sup>6</sup>, [Shem Patta](#)<sup>6</sup>, [Walter Jaoko](#)<sup>5</sup>, [John Kinuthia](#)<sup>2,7</sup>, [Aisha Abubakar](#)<sup>6</sup>, [Kenneth Sherr](#)<sup>2,4,8</sup>, [Ruanne V Barnabas](#)<sup>9,10</sup>

**Abstract**

**Background:** Although HIV testing in family planning (FP) clinics is a promising approach for engaging women in HIV treatment and prevention services, HIV testing rates are low in FP clinics in Kenya. In 2018, a cluster randomized trial was implemented in Mombasa, Kenya applying the Systems Analysis and Improvement Approach (SAIA) to integrate HIV testing into FP services (1K24HD088229-01). We estimated the incremental costs and explored cost drivers of the FP HIV SAIA implementation in Mombasa, Kenya.

**Methods:** We conducted a costing evaluation from the payer perspective for the FP HIV SAIA randomized control trial. We identified relevant activities for the intervention including start-up, training, research and FP HIV SAIA. We estimated activity time burden using a time-and motion study. We derived unit costs through staff interviews and programmatic budgets. We present cost estimates for two different scenarios: as-implemented including research and projected costs for a Ministry of Health-supported intervention. All costs are reported in 2018 USD.

**Results:** For an annual program output of 36,086 HIV tests administered to new FP clients, we estimated the total annual program cost to be \$91,994 with an average cost per new FP client served of \$2.55. Personnel and HIV rapid testing kits comprised 55% and 21% of programmatic costs, respectively. Assuming no changes to program outputs and with efficiency gains under the MOH scenario, the estimated cost per new FP client served decreased to \$1.30 with a programmatic cost reduction of 49%.

**Conclusion:** FP HIV SAIA is a low-cost and flexible implementation strategy for facilitating integrated delivery of HIV testing alongside FP services. Although cost implications of the FP HIV SAIA intervention must continue to be evaluated over time, these findings provide context-specific cost data useful for budget planning and decision-making regarding intervention delivery and expansion.

## Cotrimoxazole preventative therapy

J Pediatr. 2022 Jul;246:266-270.e2.

doi: 10.1016/j.jpeds.2022.03.031. Epub 2022 Mar 26.

**[Prolonged Cotrimoxazole Prophylaxis Has No Impact on Child Growth in the First Two Years of Life: Findings from a Randomized Controlled Trial in Botswana](#)**

[Aamirah Mussa](#)<sup>1</sup>, [Kathleen M Powis](#)<sup>2</sup>, [Shahin Lockman](#)<sup>3</sup>, [Gbolahan Ajibola](#)<sup>4</sup>, [Chelsea Morroni](#)<sup>5</sup>, [Laura Smeaton](#)<sup>6</sup>, [Mompoti Mmalane](#)<sup>4</sup>, [Joseph Makhema](#)<sup>4</sup>, [Roger L Shapiro](#)<sup>7</sup>

**Abstract**

We investigated the impact of prolonged cotrimoxazole prophylaxis on growth in 2848 HIV-exposed uninfected children enrolled in the Mpepu study, a randomized, placebo-controlled trial in Botswana. No significant differences in mean weight-for-age, length-for-age, or



weight-for-length z scores between placebo and cotrimoxazole arms were observed overall through 18 months.

## HIV-exposed and uninfected infants

BMJ Open. 2022 Dec 30;12(12):e069116.

doi: 10.1136/bmjopen-2022-069116.

### [Mitigating Infectious morbidity and Growth deficits in HIV-exposed uninfected infants with human Milk Oligosaccharide \(MIGH-T MO\): a randomised trial protocol](#)

[Rupak Shivakoti](#)<sup>#1</sup>, [Amy L Slogrove](#)<sup>#2,3</sup>, [Barbara Laughton](#)<sup>2</sup>, [Mehr Shafiq](#)<sup>4</sup>, [Elisma Schoeman](#)<sup>2</sup>, [Richard H Glashoff](#)<sup>5</sup>, [Cheng-Shiun Leu](#)<sup>6</sup>, [Shuang Wang](#)<sup>6</sup>, [Lars Bode](#)<sup>7</sup>, [Grace Aldrovandi](#)<sup>8</sup>, [Louise Kuhn](#)<sup>4,9</sup>

#### Abstract

**Introduction:** Children who are HIV-exposed uninfected (HEU), that is, children who do not acquire HIV infection despite being born to mothers with HIV, have a higher risk of mortality, infectious morbidity and growth deficits than children who are HIV-unexposed uninfected (HUU). Prior research has focused on breast feeding and has pointed to changes in human milk oligosaccharides (HMOs) associated with maternal HIV that may influence the infant microbiome and thereby lead to these adverse outcomes. However, to our knowledge, no study has attempted to intervene along this pathway to reduce the occurrence of the adverse outcomes in children HEU. We will conduct a double-blind, randomised trial of a synbiotic intervention, which combines an HMO and probiotic, in breastfed infants HEU in South Africa to evaluate whether this intervention has promise to reduce excess infectious morbidity and growth faltering compared with controls.

**Methods and analysis:** One hundred and forty-four breastfed infants HEU, aged 4 weeks, will be 1:1 randomised to receive either a daily synbiotic or an identical-looking placebo through age 24 weeks. Infants will be followed until age 48 weeks and outcomes of infectious morbidity, growth and biological measurements (eg, microbiota, inflammation and metabolome) will be assessed. Analyses will follow intention-to-treat principles comparing the cohorts as randomised. Infants HEU will be compared across arms with respect to the occurrence of infectious morbidity and growth outcomes through 4-24 weeks and 4-48 weeks using appropriate parametric and non-parametric statistical tests. Additionally, an observational cohort of 40 breastfed infants HUU will be recruited as a comparator group with no intervention.

## Nutrition, growth, and development of children with HIV

BMC Med. 2023 Apr 28;21(1):162.

doi: 10.1186/s12916-023-02862-2.

### [Impact of oral intervention on the oral and overall health of children living with HIV in Cambodia: a randomized controlled trial](#)

[Kimiyo Kikuchi<sup>1</sup>](#), [Sovannary Tuot<sup>2,3,4</sup>](#), [Junko Yasuoka<sup>5</sup>](#), [Makoto Murayama<sup>6</sup>](#), [Sumiyo Okawa<sup>7</sup>](#), [Akira Shibamura<sup>3</sup>](#), [Keiko Nanishi<sup>8</sup>](#), [Sothearith Eng<sup>2,9</sup>](#), [Chantheany Huot<sup>10</sup>](#), [Siyan Yj<sup>2,11,12</sup>](#)

## Abstract

**Background:** Maintaining oral health is essential for improving overall health of children living with HIV. Therefore, we evaluated the effectiveness of an oral health intervention for improving their oral and overall health. In addition, we examined their longitudinal association between changes in oral and overall health.

**Methods:** We conducted a 2-year randomized controlled trial involving children living with HIV in Cambodia. Children aged 3-15 years and their caregivers were randomly allocated either to the intervention (group A) or control (group B) arm. A second control arm (group C) included children without HIV. The group A children received oral health education sessions and practiced home-based daily care.

**Results:** In the baseline survey, 482 children participated (group A: n = 160, group B: n = 168, group C: n = 154), and 350 completed the endline survey. An interaction effect in teeth brushing duration was observed in children in group A relative to group B (AOR = 2.69, 95% CI: 1.37-5.31) and group C (AOR = 3.78, 95% CI: 1.70-8.40). Longitudinal associations were observed between changes in oral hygiene and overall health, as presented by alterations in dental caries in permanent teeth with viral load detection (adjusted odds ratio = 3.58, 95% CI: 1.10 - 11.73), in salivary flow quantity with the overall quality of life ( $\beta = 0.07$ , 95% CI: < 0.01 - 0.13), as well as in dental caries, salivary pH, debris index with body mass index for age among group A children.

**Conclusions:** Oral health intervention may improve oral care behaviors and potentially enhance overall health among children living with HIV in antiretroviral therapy in a resource-constrained setting.

## Prevention of mother to child transmission of HIV and maternal-infant HIV care

AIDS Behav. 2023 Jun 12.

doi: 10.1007/s10461-023-04097-x. Online ahead of print.

### [Why do Integrated Maternal HIV and Infant Healthcare Services work? A Secondary Analysis of a Randomised Controlled Trial in South Africa](#)

[Kirsty Brittain<sup>1</sup>](#), [Karryn Brown<sup>2</sup>](#), [Tamsin Phillips<sup>2</sup>](#), [Allison Zerbe<sup>3</sup>](#), [Jennifer Pellowski<sup>4,5</sup>](#), [Robert H Remien<sup>6</sup>](#), [Claude A Mellins<sup>6</sup>](#), [Elaine J Abrams<sup>3,7,8</sup>](#), [Landon Myer<sup>2</sup>](#)

## Abstract

In a randomised trial, we found that integrated maternal HIV and infant health services through the end of breastfeeding were significantly associated with the primary outcome of engagement in HIV care and viral suppression at 12 months postpartum, compared to the standard of care. Here, we quantitatively explore potential psychosocial modifiers and mediators of this association. Our findings suggest that the intervention was significantly more effective among women experiencing an unintended pregnancy but did not improve outcomes among women reporting risky alcohol use. Although not statistically significant, our results suggest that **the intervention may also be more effective among women experiencing higher levels of poverty and HIV-related stigma**. We observed no definitive

mediator of the intervention effect, but women allocated to integrated services reported better relationships with their healthcare providers through 12 months postpartum. These findings point to high-risk groups that may benefit the most from integrated care, as well as groups for whom these benefits are hampered and that warrant further attention in intervention development and evaluation.

J Acquir Immune Defic Syndr. 2022 Dec 1;91(4):403-409.

doi: 10.1097/QAI.0000000000003081.

**Effects of Initiating Raltegravir-Based Versus Efavirenz-Based Antiretroviral Regimens During Pregnancy on Weight Changes and Perinatal Outcomes: NICHD P1081**

[Conrado Milani Coutinho<sup>1</sup>](#), [Meredith G Warshaw<sup>2</sup>](#), [Geraldo Duarte<sup>1</sup>](#), [Alice Stek<sup>3</sup>](#), [Avy Violari<sup>4</sup>](#), [Cristina B Hofer<sup>5</sup>](#), [Jaime G Deville<sup>6</sup>](#), [James Samwel Ngocho<sup>7</sup>](#), [José Henrique Pilotto<sup>8</sup>](#), [Mario Dias Correa Jr<sup>9</sup>](#), [David E Shapiro<sup>2</sup>](#), [Trevon L Fuller<sup>10,11</sup>](#), [Nahida Chakhtoura<sup>12</sup>](#), [Mark Mirochnick<sup>13</sup>](#), [Esaú C João<sup>10</sup>](#)

**Abstract**

**Background:** Integrase inhibitors have been associated with excess gestational weight gain that may lead to adverse pregnancy outcomes (APOs). This post hoc analysis of NICHD P1081 compared antepartum changes in weight and body mass index (BMI) in pregnant women initiating raltegravir- or efavirenz-based combined antiretroviral therapy (cART) and examined associations between rates of weight gain and APOs.

**Setting:** NICHD P1081 enrolled antiretroviral-naïve pregnant women living with HIV in the second and third trimester in Brazil, Tanzania, South Africa, Thailand, Argentina, and the United States.

**Methods:** Two hundred eighty-one women enrolled between 20 and 31 gestational weeks were randomized to raltegravir- or efavirenz-based cART and followed for  $\geq 4$  weeks. A low rate of weight gain was defined as  $< 0.18$  kg/wk and high as  $> 0.59$  kg/wk. We compared weight gain and BMI increase between treatment arms using Kruskal-Wallis tests. Logistic regression was used to investigate the association between weight gain and APOs.

**Results:** Raltegravir-based cART was associated with significantly higher antepartum weight gain (median 0.36 kg/wk versus 0.29 kg/wk,  $P = 0.01$ ) and BMI increase (median 0.14 kg/m<sup>2</sup>/wk versus 0.11 kg/m<sup>2</sup>/wk,  $P = 0.01$ ) compared with efavirenz-based treatment. Women on raltegravir had less low weight gain (18% versus 36%) and more high weight gain (21% versus 12%) ( $P = 0.001$ ). Women with low weight gain were more likely than those with normal weight gain to have small for gestational age infants or a composite of APOs.

**Conclusions:** A raltegravir-based antiretroviral regimen was associated with significantly higher antepartum rate of weight gain and BMI increase compared with efavirenz-based treatment in antiretroviral-naïve pregnant women.

J Acquir Immune Defic Syndr. 2023 May 15.

doi: 10.1097/QAI.0000000000003218. Online ahead of print.

**Bone and renal health in infants with or without breastmilk exposure to tenofovir-based maternal antiretroviral treatment in the PROMISE randomized trial**

[Tichaona Vhembo<sup>1</sup>](#), [Kristin Baltrusaitis<sup>2</sup>](#), [Camlin Tierney<sup>2</sup>](#), [Maxensia Owor<sup>3</sup>](#), [Sufia Dadabhai<sup>4</sup>](#), [Avy Violari<sup>5</sup>](#), [Gerhard Theron<sup>6</sup>](#), [Dhayendre Moodley<sup>7</sup>](#), [Cynthia Mukwasi-](#)

[Kahari<sup>8</sup>](#), [Kathleen George<sup>9</sup>](#), [John Shepherd<sup>10</sup>](#), [George K Siberry<sup>11</sup>](#), [Renee Browning<sup>12</sup>](#), [Mary Glenn Fowler<sup>13</sup>](#), [Lynda Stranix-Chibanda<sup>1,14</sup>](#); [IMPAACT P1084s study team](#)

## Abstract

**Background:** We assessed bone and kidney outcomes in infants randomized post-delivery as mother-infant pairs within the IMPAACT PROMISE trial to maternal TDF-based ART (mART) or infant nevirapine prophylaxis (iNVP) to prevent breastfeeding HIV transmission.

**Methods:** Infants were co-enrolled in the P1084s substudy on randomization day and followed through Week 74. Lumbar spine bone mineral content (LS-BMC) was assessed at entry (6-21 days of life) and Week 26 by dual-energy x-ray absorptiometry. Creatinine clearance (CrCl) was calculated at entry and Weeks 10, 26, and 74. Student t-tests compared mean LS-BMC and CrCl at Week 26 and mean change from entry between arms.

**Results:** Of 400 enrolled infants, mean (standard deviation (sd); n) for entry LS-BMC was 1.68g (0.35; n=363) and CrCl was 64.2mL/min/1.73m<sup>2</sup> (24.6; n=357). At Week 26, 98% of infants were breastfeeding and 96% were on their assigned HIV prevention strategy. Mean (sd) Week 26 LS-BMC was 2.64g (0.48) for mART and 2.77g (0.44) for iNVP; mean difference (95% confidence interval (CI)) -0.13g (-0.22, -0.04), P=0.007, n=375/398 (94%). Mean absolute (-0.14g (-0.23, -0.06)) and percent (-10.88% (-18.53, -3.23)) increase in LS-BMC from entry was smaller for mART than iNVP. At Week 26, mean (sd) CrCl was 130.0mL/min/1.73m<sup>2</sup> (34.9) for mART vs. 126.1mL/min/1.73m<sup>2</sup> (30.0) for iNVP; mean difference (95% CI) 3.8 (-3.0, 10.7), P=0.27, n=349/398 (88%).

**Conclusion:** Week 26 mean LS-BMC was lower in infants in the mART group compared with the iNVP group. However, this difference (~0.23g) was less than the one-half sd considered potentially clinically relevant. No infant renal safety concerns were observed.

BMC Pregnancy Childbirth. 2023 Jan 17;23(1):34.

doi: 10.1186/s12884-022-05341-3.

## [Prevalence of neurotoxicity symptoms among postpartum women on isoniazid preventive therapy and efavirenz-based treatment for HIV: an exploratory objective of the IMPAACT P1078 randomized trial](#)

[Patricia Mandima<sup>#1</sup>](#), [Kristin Baltrusaitis<sup>#2</sup>](#), [Grace Montepiedra<sup>2</sup>](#), [Lisa Aaron<sup>2</sup>](#), [Jyoti Mathad<sup>3</sup>](#), [Carolyn Onyango-Makumbi<sup>4</sup>](#), [Mandisa Nyati<sup>5</sup>](#), [James Ngocho<sup>6</sup>](#), [Gift Chareka<sup>7</sup>](#), [Ponego Ponatshego<sup>8</sup>](#), [Gaerolwe Masheto<sup>8</sup>](#), [Katie McCarthy<sup>9</sup>](#), [Patrick Jean-Philippe<sup>10</sup>](#), [Amita Gupta<sup>11</sup>](#), [Lynda Stranix-Chibanda<sup>1,12</sup>](#); [IMPAACT P1078 T. B. APPRISE study team](#)

## Abstract

**Background:** This exploratory analysis investigates the prevalence and risk factors of neurocognitive toxicity in postpartum women on HIV treatment in response to a concern of an Isoniazid Preventive Therapy (IPT)/Efavirenz interaction.

**Trial design:** Pregnant women on HIV treatment from countries with high TB prevalence were randomized in IMPAACT P1078 to 28 weeks of IPT started either during pregnancy or at 12 weeks postpartum. Partway through study implementation, the Patient Health Questionnaire 9, the cognitive complaint questionnaire, and the Pittsburgh Sleep Quality Index were added to evaluate depression, cognitive function, and sleep quality at postpartum weeks. Screening for peripheral neuropathy was conducted throughout the study.

**Methods:** We summarized percentages of women with depression symptoms, cognitive dysfunction, poor sleep quality and peripheral neuropathy and assessed the association of 11 baseline risk factors of neurotoxicity using logistic regression, adjusted for gestational age stratum.

**Results:** Of 956 women enrolled, 749 (78%) had at least one neurocognitive evaluation. During the postpartum period, the percentage of women reporting at least mild depression symptoms, cognitive complaint and poor sleep quality peaked at 13%, 8% and 10%, respectively, at 12 weeks, and the percentage of women reporting peripheral neuropathy peaked at 13% at 24 weeks. There was no evidence of study arm differences in odds of all four neurotoxic symptoms.

**Conclusions:** Timing of IPT initiation and EFV use were not associated with symptoms of neurotoxicity. Further study is advised to formally assess risk factors of neurotoxicity.

Soc Sci Med. 2023 Mar;320:115684.

doi: 10.1016/j.socscimed.2023.115684. Epub 2023 Jan 14.

**[Economic costs and cost-effectiveness of conditional cash transfers for the uptake of services for the prevention of vertical HIV transmissions in a resource-limited setting](#)**

**[Steven P Masiano](#)<sup>1</sup>, **[Bienvenu Kawende](#)**<sup>2</sup>, **[Noro Lantoniana Rosa Ravelomanana](#)**<sup>3</sup>, **[Tiffany L Green](#)**<sup>4</sup>, **[Bassam Dahman](#)**<sup>5</sup>, **[Harsha Thirumurthy](#)**<sup>6</sup>, **[April D Kimmel](#)**<sup>7</sup>, **[Marcel Yotebieng](#)**<sup>3</sup>**

**Abstract**

**Background:** Prevention of mother-to-child transmission (PMTCT) is critical for halting the HIV epidemic. However, innovative approaches to improve PMTCT uptake may be resource-intensive. We examined the economic costs and cost-effectiveness of conditional cash transfers (CCTs) for the uptake of PMTCT services in the Democratic Republic of Congo.

**Methods:** We leveraged data from a randomized controlled trial of CCTs (n = 216) versus standard PMTCT care alone (standard of care (SOC), n = 217). Economic cost data came from multiple sources, with costs analyzed from the societal perspective and reported in 2016 international dollars (I\$). Effectiveness outcomes included PMTCT uptake (i.e., accepting all PMTCT visits and services) and retention (i.e., in HIV care at six weeks post-partum). Generalized estimating equations estimated effectiveness (relative risk) and incremental costs, with incremental effectiveness reported as the number of women needing CCTs for an additional PMTCT uptake or retention. We evaluated the cost-effectiveness of the CCTs at various levels of willingness-to-pay and assessed uncertainty using deterministic sensitivity analysis and cost-effectiveness acceptability curves.

**Results:** Mean costs per participant were I\$516 (CCTs) and I\$431 (SOC), representing an incremental cost of I\$85 (95% CI: 59, 111). PMTCT uptake was more likely for CCTs vs SOC (68% vs 53%, p < 0.05), with seven women needing CCTs for each additional PMTCT service uptake; twelve women needed CCTs for an additional PMTCT retention. The incremental cost-effectiveness of CCTs vs SOC was I\$595 (95% CI: I\$550, I\$638) for PMTCT uptake and I\$1028 (95% CI: I\$931, I\$1125) for PMTCT retention. CCTs would be an efficient use of resources if society's willingness-to-pay for an additional woman who takes up PMTCT services is at least I\$640. In the worst-case scenario, the findings remained relatively robust.

**Conclusions:** Given the relatively low cost of the CCTs, policies supporting CCTs may decrease onward HIV transmission and expedite progress toward ending the epidemic.

Sci Rep. 2023 Jun 9;13(1):9389.

doi: 10.1038/s41598-023-35817-x.

**The effect of an interactive weekly text-messaging intervention on retention in prevention of mother-to-child transmission of HIV care: a randomised controlled trial (WelTel PMTCT)**

[Björn Nordberg](#) <sup>#1,2</sup>, [Mia Liisa van der Kop](#) <sup>#3</sup>, [Winfred Mwangi](#) <sup>3,4</sup>, [Jonathan Mwangi](#) <sup>3</sup>, [Eunice Kaguiru](#) <sup>5</sup>, [Katrine J Chamorro de Angeles](#) <sup>3</sup>, [Richard T Lester](#) <sup>6</sup>, [Erin E Gabriel](#) <sup>7</sup>, [Susanne Rautiainen](#) <sup>3,8</sup>, [Patricia Opondo Awiti](#) <sup>3</sup>, [Anna E Kågesten](#) <sup>3</sup>, [Edwin Were](#) <sup>9</sup>, [Anna Mia Ekström](#) <sup>3,10</sup>

**Abstract**

Retention in prevention of mother-to-child transmission (PMTCT) care is critical to prevent vertical HIV transmission and reduce morbidity and mortality of mother-infant pairs. We investigated whether weekly, interactive text-messaging improved 18-month postpartum retention in PMTCT care. This randomised, two-armed, parallel trial was conducted at six PMTCT clinics in western Kenya. Pregnant women with HIV at least 18 years of age with access to a mobile phone, able to text-message, or had somebody who could text on their behalf, were eligible. Participants were randomly assigned at a 1:1 ratio in block sizes of four to the intervention or control group. The intervention group received weekly text messages asking "How are you?" ("Mambo?" in Swahili) and were requested to respond within 48 h. Healthcare workers called women who indicated a problem or did not respond. The intervention was administered up to 24 months after delivery. Both groups received standard care. The primary outcome was retention in care at 18 months postpartum (i.e., clinic attendance 16-24 months after delivery based on data from patient files, patient registers and Kenya's National AIDS and STI Control Programme database), which was analysed by intention-to-treat. Researchers and data collectors were masked to group assignment, while healthcare workers were not. Between June 25th, 2015, and July 5th, 2016, we randomly assigned 299 women to the intervention and 301 to standard care only. Follow-up concluded on July 26th, 2019. The proportion of women retained in PMTCT care at 18 months postpartum was not significantly different between the intervention (n = 210/299) and control groups (n = 207/301) (risk ratio 1.02, 95% confidence interval 0.92-1.14, p = 0.697). No adverse events related to the mobile phone intervention were reported. Weekly, interactive text-messaging was not associated with improved retention in PMTCT care at 18 months postpartum or linkage to care up to 30 months postpartum in this setting.

AIDS Behav. 2022 Dec;26(12):3834-3847.

doi: 10.1007/s10461-022-03712-7. Epub 2022 Jun 15.

**Real-time Feedback to Improve HIV Treatment Adherence in Pregnant and Postpartum Women in Uganda: A Randomized Controlled Trial**

[Lora L Sabin](#) <sup>1</sup>, [Elizabeth Simmons](#) <sup>2,3</sup>, [Nafisa Halim](#) <sup>2</sup>, [Davidson H Hamer](#) <sup>2,4</sup>, [Allen L Gifford](#) <sup>4,5,6</sup>, [Rebecca L West](#) <sup>2</sup>, [Anna Larson](#) <sup>2</sup>, [Rachael Bonawitz](#) <sup>2</sup>, [Philip Aroda](#) <sup>7</sup>, [Bolangle Banigbe](#) <sup>2</sup>, [Alayna J Holderman](#) <sup>8</sup>, [Lisa Murray](#) <sup>9</sup>, [Mary B DeSilva](#) <sup>10</sup>, [Julia Gasuza](#) <sup>7</sup>, [Barbara Mukasa](#) <sup>7</sup>, [Lisa J Messersmith](#) <sup>2</sup>

**Abstract**

We assessed an intervention aimed at improving adherence to antiretroviral therapy (ART) among pregnant and postpartum women living with HIV (PPWLH). We randomized 133



pregnant women initiating ART in Uganda to receive text reminders generated by real time-enabled electronic monitors and data-informed counseling through 3 months postpartum (PPM3) or standard care. Intention-to-treat analyses found low adherence levels and no intervention impact. Proportions achieving  $\geq 95\%$  adherence in PPM3 were 16.4% vs. 9.1% ( $t = -1.14$ ,  $p = 0.26$ ) in intervention vs. comparison groups, respectively; 30.9% vs. 29.1% achieved  $\geq 80\%$  adherence. Additional analyses found significant adherence declines after delivery, and no effect on disease progression (CD4-cell count, viral load), though treatment interruptions were significantly fewer in intervention participants. Per-protocol analyses encompassing participants who used adherence monitors as designed experienced better outcomes, suggesting potential benefit for some PPWLH.

J Acquir Immune Defic Syndr. 2023 Jan 1;92(1):76-83.

doi: 10.1097/QAI.0000000000003102. Epub 2022 Sep 28.

**Self-reported Antiretroviral Adherence: Association With Maternal Viral Load Suppression in Postpartum Women Living With HIV-1 From Promoting Maternal and Infant Survival Everywhere, a Randomized Controlled Trial in Sub-Saharan Africa and India**

[Neetal Nevrekar<sup>1</sup>](#), [Kevin Butler<sup>2</sup>](#), [David E Shapiro<sup>2</sup>](#), [Patience Atuhaire<sup>3</sup>](#), [Taha E Taha<sup>4</sup>](#), [Bonus Makanani<sup>5</sup>](#), [Lameck Chinula<sup>6</sup>](#), [Maxensia Owor<sup>3</sup>](#), [Dhayendre Moodley<sup>7,8</sup>](#), [Tsongai Chipato<sup>9</sup>](#), [Katie McCarthy<sup>10</sup>](#), [Patricia M Flynn<sup>11</sup>](#), [Judith Currier<sup>12</sup>](#), [Mary Glenn Fowler<sup>13</sup>](#), [Amita Gupta<sup>14</sup>](#), [Nishi Suryavanshi<sup>1</sup>](#)

**Abstract**

**Introduction:** Optimal adherence to antiretroviral therapy (ART) is crucial to promoting maternal-infant health.

**Setting:** Fourteen sites in 7 countries within sub-Saharan Africa and India.

**Methods:** The multicomponent, open-label strategy PROMISE trial enrolled breastfeeding mother-infant pairs not meeting in-country criteria for maternal ART (mART) initiation in the postpartum component within 5 days of delivery. Randomization was to mART versus infant NVP (iNVP) prophylaxis. Infants in the mART arm also received 6 weeks of iNVP. Self-reported adherence was assessed in a secondary analysis. Time-to-event analyses were performed to explore the association between adherence and maternal viral load (mVL) in the mART arm.

**Results:** Two thousand four hundred thirty-one mother-infant pairs were enrolled between 2011 and 2014; the baseline maternal median CD4 was 686 (IQR 553-869), and the median mVL was 322 copies/mL (IQR 40-1422). Self-reported adherence was lower in the mART arm compared with the iNVP arm (no missed doses within 4 weeks of all study visits: 66% vs 83%; within 2 weeks: 71% vs 85%;  $P < 0.0001$ ). The iNVP adherence at week 6 was high in both arms: 97% in mART arm; 95% in iNVP arm. Time-to-event analyses showed that adherence to mART was associated with time to first mVL  $\geq 400$  copies/mL ( $P < 0.0001$ ). Missing 1 full day of doses over 3 days was associated with a 66% risk of mVL  $\geq 1000$  copies/mL (HR: 1.66; 95% CI: 1.37, 1.99).

**Conclusions:** Postpartum women were less adherent to their own ART than mothers providing their infant's nevirapine prophylaxis. The self-reported missed mART doses were associated with high mVL. Strategies to optimize postpartum mART adherence are urgently needed.

Lancet HIV. 2023 Mar;10(3):e154-e163.

doi: 10.1016/S2352-3018(22)00369-1. Epub 2023 Feb 3.

**[Pregnancy and neonatal safety outcomes of timing of initiation of daily oral tenofovir disoproxil fumarate and emtricitabine pre-exposure prophylaxis for HIV prevention \(CAP016\): an open-label, randomised, non-inferiority trial](#)**

[Dhayendre Moodley](#)<sup>1</sup>, [Carl Lombard](#)<sup>2</sup>, [Vani Govender](#)<sup>3</sup>, [Megeshinee Naidoo](#)<sup>3</sup>, [Alicia C Desmond](#)<sup>3</sup>, [Kimesh Naidoo](#)<sup>4</sup>, [Ottacia Mhlongo](#)<sup>5</sup>, [Motshedisi Sebitloane](#)<sup>6</sup>, [Marie-Louise Newell](#)<sup>7</sup>, [Richard Clark](#)<sup>8</sup>, [James F Rooney](#)<sup>8</sup>, [Glenda Gray](#)<sup>9</sup>; [CAP016 Team](#)

**Abstract**

**Background:** The safety of tenofovir disoproxil fumarate and emtricitabine as pre-exposure prophylaxis (PrEP) in pregnant women not living with HIV is uncertain. We aimed to compare pregnancy and neonatal outcomes in women exposed and not exposed to PrEP during pregnancy.

**Methods:** In this single-site, open-label, randomised, non-inferiority trial in Durban, South Africa, we evaluated pregnancy and neonatal outcomes in pregnant women aged 18 years or older, not living with HIV, and at 14-28 weeks' gestation at the time of enrolment. Eligible participants were randomly assigned (1:1) using a computer-generated permuted block (block size of ten) randomisation list to immediate initiation or deferred initiation of PrEP until breastfeeding cessation. Participants in the immediate PrEP group received a monthly supply of once daily oral tenofovir disoproxil fumarate 300 mg and emtricitabine 200 mg. Participants in the deferred PrEP group received standard of care for HIV prevention. The primary outcomes were the occurrence of preterm live birth (<37 weeks gestational age) and very preterm birth (<34 weeks gestational age) determined by menstrual dating, low birthweight (<2500 g), very low birthweight (<1500 g), stillbirth ( $\geq 20$  weeks gestational age), and small for gestational age (birthweight less than the tenth percentile). Post-natal safety outcomes will be reported elsewhere. We used binomial regression models to estimate risk differences and two-sided 90% CIs. Immediate PrEP was non-inferior to deferred PrEP if the upper bound of the 90% CI of the risk difference was less than the upper predefined non-inferiority margin for preterm birth (7.5%), very preterm birth (2.6%), low birthweight (5.5%), very low birthweight (1.2%), stillbirth (1.0%), and small for gestational age (3.7%). All outcomes were analysed in the intention-to-treat population. This study is registered with ClinicalTrials.gov, [NCT3227731](#).

**Findings:** Between Sept 25, 2017, and Dec 6, 2019, we screened 693 women, of whom 540 were randomly assigned to immediate PrEP (n=271) or deferred PrEP (n=269). The median gestational age was 19 weeks (IQR 15-23 for immediate PrEP and 16-23 for deferred PrEP). The risk difference between the immediate PrEP group and the deferred PrEP group for preterm birth was -4.7% (90% CI -10.7 to 1.2; immediate PrEP was non-inferior), for very preterm birth was 0.6% (-3.4 to 4.6; upper limit exceeded the non-inferiority margin), for low birthweight was 2.5% (-1.6 to 6.6; upper limit exceeded the non-inferiority margin), for very low birthweight was 0% (-1.4 to 1.4; upper limit exceeded the non-inferiority margin), for stillbirth was 1.2% (-1.5 to 3.8; upper limit exceeded the non-inferiority margin), and for small for gestational age was 0.9% (-1.2 to 2.9; immediate PrEP was non-inferior).

**Interpretation:** In our study, PrEP was not associated with preterm birth or small for gestational age infants. Our data support the use of tenofovir disoproxil fumarate and emtricitabine in pregnancy and our reassuring findings can be used to allay safety concerns among pregnant women.

J Acquir Immune Defic Syndr. 2022 Dec 1;91(4):397-402.

doi: 10.1097/QAI.0000000000003078.

### [Pregnancy in Women With HIV in a Tuberculosis Preventive Therapy Trial](#)

[Priya Singh](#)<sup>1</sup>, [Lawrence H Moulton](#)<sup>2</sup>, [Grace L Barnes](#)<sup>1</sup>, [Amrita Gupta](#)<sup>1</sup>, [Reginah Msandiwa](#)<sup>3</sup>, [Richard E Chaisson](#)<sup>1</sup>, [Neil A Martinson](#)<sup>3</sup>

#### **Abstract**

**Background:** Tuberculosis preventive therapy (TPT) is recommended for people with HIV infection, including during pregnancy. The effect of TPT exposure at conception and during pregnancy is poorly documented.

**Methods:** We report pregnancy outcomes among South African women with HIV enrolled in a randomized trial of 4 TPT regimens (two 3-month regimens, rifapentine/isoniazid [3HP] or rifampin/isoniazid [3HR], isoniazid for 6 months, or isoniazid continuously). Descriptive statistics and risk ratios were assessed to examine relationships between study regimens and outcomes.

**Results:** 216/896 women (24%) conceived during the study. Women who conceived were younger (27.9 vs 31.3 years) and had higher mean CD4 counts (589.1 vs 536.7). The odds of pregnancy were higher in women in the rifamycin-isoniazid arms than those in the isoniazid arms (3HP: relative risk [RR] 1.73, P = 0.001; 3HR:RR 1.55, P = 0.017) despite increased contraceptive use compared with the standard 6H therapy. Thirty-four women became pregnant while taking preventive treatment (8 rifamycin and 26 isoniazid monotherapy). Pregnancy outcomes in these women were as follows: 17 (50%) mother/baby healthy, 3 (9%) spontaneous abortions, 6 (18%) elective abortions, 1 (3%) premature delivery, 2 (6%) neonatal deaths [1 rifamycin-isoniazid and 1 isoniazid], and 5 (15%) unknown.

**Conclusions:** Pregnancy was common in women who had received TPT and more frequent in women who had received rifamycin-isoniazid-based regimens.

## **HIV vaccine**

(see Vaccine – HIV vaccine)

## **Helminth infections**

(See also Anaemia, Diarrhoea, Micronutrients and food fortification, Malaria and HIV)

PLoS Negl Trop Dis. 2023 Apr 10;17(4):e0010401.

doi: 10.1371/journal.pntd.0010401. Online ahead of print.

### [Overestimation of school-based deworming coverage resulting from school-based reporting](#)

[William Sheahan](#)<sup>1</sup>, [Roy Anderson](#)<sup>2</sup>, [Kumudha Aruldas](#)<sup>3</sup>, [Euripide Avokpaho](#)<sup>4</sup>, [Sean Galagan](#)<sup>5</sup>, [Jeanne Goodman](#)<sup>5</sup>, [Parfait Houngbegnon](#)<sup>4</sup>, [Gideon John Israel](#)<sup>3</sup>, [Venkateshprabhu Janagaraj](#)<sup>3</sup>, [Saravanakumar Puthupalayam Kaliappan](#)<sup>3</sup>, [Arianna Rubin Means](#)<sup>5</sup>, [Chloe Morozoff](#)<sup>5</sup>, [Emily Pearman](#)<sup>5</sup>, [Rohan Michael Ramesh](#)<sup>3</sup>, [Amy Roll](#)<sup>5</sup>, [Alexandra Schaefer](#)<sup>5</sup>, [James](#)

[Simwanza<sup>6</sup>](#), [Stefan Witek-McManus<sup>7</sup>](#), [Sitara S R Ajjampur<sup>3</sup>](#), [Robin Bailey<sup>6</sup>](#), [Moudachirou Ibikounlé<sup>4</sup>](#), [Khumbo Kalua<sup>6</sup>](#), [Adrian J F Luty<sup>8</sup>](#), [Rachel Pullan<sup>7</sup>](#), [Judd L Walson<sup>5,9,10</sup>](#), [Kristjana Hrönn Ásbjörnsdóttir<sup>5,11</sup>](#)

## Abstract

**Background:** Soil Transmitted Helminths (STH) infect over 1.5 billion people globally and are associated with anemia and stunting, resulting in an annual toll of 1.9 million Disability-Adjusted Life Years (DALYs). School-based deworming (SBD), via mass drug administration (MDA) campaigns with albendazole or mebendazole, has been recommended by the World Health Organization to reduce levels of morbidity due to STH in endemic areas. DeWorm3 is a cluster-randomized trial, conducted in three study sites in Benin, India, and Malawi, designed to assess the feasibility of interrupting STH transmission with community-wide MDA as a potential strategy to replace SBD. This analysis examines data from the DeWorm3 trial to quantify discrepancies between school-level reporting of SBD and gold standard individual-level survey reporting of SBD.

**Methodology/principal findings:** Population-weighted averages of school-level SBD calculated at the cluster level were compared to aggregated individual-level SBD estimates to produce a Mean Squared Error (MSE) estimate for each study site. In order to estimate individual-level SBD coverage, these MSE values were applied to SBD estimates from the control arm of the DeWorm3 trial, where only school-level reporting of SBD coverage had been collected. In each study site, SBD coverage in the school-level datasets was substantially higher than that obtained from individual-level datasets, indicating possible overestimation of school-level SBD coverage. When applying observed MSE to project expected coverages in the control arm, SBD coverage dropped from 89.1% to 70.5% (p-value < 0.001) in Benin, from 97.7% to 84.5% (p-value < 0.001) in India, and from 41.5% to 37.5% (p-value < 0.001) in Malawi.

**Conclusions/significance:** These estimates indicate that school-level SBD reporting is likely to significantly overestimate program coverage. These findings suggest that current SBD coverage estimates derived from school-based program data may substantially overestimate true pediatric deworming coverage within targeted communities.

Lancet Infect Dis. 2023 Mar;23(3):331-340.

doi: 10.1016/S1473-3099(22)00589-8. Epub 2022 Oct 28.

[Efficacy and safety of moxidectin and albendazole compared with ivermectin and albendazole coadministration in adolescents infected with \*Trichuris trichiura\* in Tanzania: an open-label, non-inferiority, randomised, controlled, phase 2/3 trial](#)

[Sophie Welsche<sup>1</sup>](#), [Emmanuel C Mrimi<sup>2</sup>](#), [Jan Hattendorf<sup>1</sup>](#), [Eveline Hürlimann<sup>1</sup>](#), [Said M Ali<sup>3</sup>](#), [Jennifer Keiser<sup>4</sup>](#)

## Abstract

**Background:** Control efforts against soil-transmitted helminths focus on preventive chemotherapy with albendazole and mebendazole, however these drugs yield unsatisfactory results against *Trichuris trichiura* infections. We aimed to assess the efficacy and safety of moxidectin and albendazole compared with ivermectin and albendazole against *T trichiura* in adolescents living on Pemba Island, Tanzania.

**Methods:** This open-label, non-inferiority, randomised, controlled, phase 2/3 trial was done in four secondary schools (Kilindi, Kwale, Ndagoni [Chake Chake District], and Kiuyu [Wete District]) on Pemba Island, Tanzania. Adolescents aged 12-19 years who tested positive for *T*

trichiura in at least two of four Kato-Katz slides with a mean infection intensity of 48 eggs per gram (EPG) of stool or higher were considered for inclusion. Participants were randomly assigned (21:21:2:2:8) to five treatment groups (8 mg moxidectin and 400 mg albendazole [group 1], 200 µg/kg ivermectin and 400 mg albendazole [group 2], 400 mg albendazole [group 3], 200 µg/kg ivermectin [group 4], or 8 mg moxidectin [group 5]) using a computer-generated randomisation code, stratified by baseline T trichiura infection intensity. Study site investigators and participants were not masked to study treatment; however, allocation was concealed to participants. The primary outcome was egg reduction rate (ERR) of T trichiura 14-21 days after treatment in the available case population. Moxidectin and albendazole was considered non-inferior to ivermectin and albendazole (control group) when the lower limit of the two-sided 95% CI of the difference was higher than the non-inferiority margin of -2 percentage points. This study is registered with ClinicalTrials.gov, [NCT04700423](https://clinicaltrials.gov/ct2/show/study/NCT04700423).

**Findings:** Between March 1 and April 30, 2021, 771 participants were assessed for eligibility. 221 (29%) of 771 participants were ineligible and a further 14 (2%) were excluded. 207 (39%) of 536 participants were randomly assigned to moxidectin and albendazole, 211 (39%) to ivermectin and albendazole, 19 (4%) to albendazole, 19 (4%) to ivermectin, and 80 (15%) to moxidectin. Primary outcome data were available for all 536 participants. The geometric mean ERR of T trichiura after 14-21 days was 96.8% (95% CI 95.8 to 97.6) with moxidectin and albendazole and 99.0% (98.7 to 99.3) with ivermectin and albendazole (difference of -2.2 percentage points [-4.2 to -1.4]). No serious adverse events were reported during the study. The most reported adverse events were headache (160 [34%] of 465), abdominal pain (78 [17%]), itching (44 [9%]), and dizziness (26 [6%]).

**Interpretation:** Our findings show inferiority of moxidectin and albendazole to ivermectin and albendazole against T trichiura. However, given the high efficacy, moxidectin coadministration might complement treatment programmes, particularly in areas in which ivermectin is not available FUNDING: Bill and Melinda Gates Foundation, reference number OPP1153928.

## Hepatitis and liver disease

Liver Int. 2022 Nov;42(11):2492-2500.

doi: 10.1111/liv.15398. Epub 2022 Aug 25.

### [Rotational thromboelastometry-guided blood component use in cirrhotic children undergoing invasive procedures: Randomized controlled trial](#)

[Arjun Maria](#)<sup>1</sup>, [Bikrant B Lal](#)<sup>1</sup>, [Rajeev Khanna](#)<sup>1</sup>, [Vikrant Sood](#)<sup>1</sup>, [Amar Mukund](#)<sup>2</sup>, [Meenu Bajpai](#)<sup>3</sup>, [Seema Alam](#)<sup>1</sup>

#### Abstract

**Background & aims:** This randomized controlled trial (RCT) was conducted with the aim to evaluate the efficacy and safety of using ROTEM-based transfusion strategy in cirrhotic children undergoing invasive procedures.

**Methods:** This was an open-label, RCT which included (i) children under 18 years of age with liver cirrhosis; (ii) INR between 1.5 and 2.5; and/or (iii) platelet count between  $20 \times 10^9$  /L and  $50 \times 10^9$  /L (for procedures other than liver biopsy) and between  $40 \times 10^9$  /L and  $60 \times 10^9$  /L (for

liver biopsy); and (iv) listed for invasive procedures. Stratified randomization was done for children undergoing liver biopsies. Patients randomized to the ROTEM and conventional groups received blood component transfusion using predefined criteria.

**Results:** A total of 423 invasive procedures were screened for inclusion of which 60 were randomized (30 in each group with comparable baseline parameters). The volume of total blood components, fresh frozen plasma (FFP) and platelets transfused was significantly lower in ROTEM as compared to conventional group. Only 46.7% of children in ROTEM group received a blood component compared to 100% in conventional group ( $p < .001$ ). The requirement of FFP (ROTEM: 43.3%, Conventional: 83.3%,  $p = .001$ ) was significantly lower in the patients receiving ROTEM-guided transfusions. There was no difference in procedure-related bleed and transfusion-related complications between the two groups. ROTEM was cost-effective ( $p = .002$ ) despite the additional cost of the test.

**Conclusion:** ROTEM-based transfusion strategies result in lower blood component transfusion in cirrhotic children undergoing invasive procedures without an increase in risk of procedure-related bleed. ROTEM-guided transfusion strategy is cost-effective.

## Injury prevention

J Trop Pediatr. 2023 Apr 5;69(3):fmad012.

doi: 10.1093/tropej/fmad012.

### [Effect of integrated intervention to prevent child drowning in rural areas of Guangdong, China: a cluster randomized controlled trial](#)

[Ruilin Meng](#)<sup>1</sup>, [Haofeng Xu](#)<sup>1</sup>, [Mingqu Zhang](#)<sup>2</sup>, [Pengpeng Ye](#)<sup>3</sup>, [Zhishan Zhou](#)<sup>4</sup>, [Xuhao Zhu](#)<sup>2</sup>, [Xingru Li](#)<sup>4</sup>, [Lifeng Lin](#)<sup>1</sup>

#### Abstract

**Background:** Drowning is the leading cause of death for children under the age of 15 years in Guangdong Province, China. This serious public health issue also exists in low- and middle-income countries (LMICs), which have few value-integrated intervention programs. The current study presents an integrated intervention project that aims to explore an effective pattern of prevention for child drowning in rural areas and feasibility to perform in other LMICs.

**Methods:** We conducted a cluster randomized controlled trial by comparing the incidence of non-fatal drowning among children in two groups in rural areas of southern China. We recruited the participants in two phases and reached a total of 10 687 students from 23 schools at two towns in Guangdong Province, China. At the first and second phases, 8966 and 1721 students were recruited, respectively.

**Results:** The final evaluation questionnaires were collected after 18 months of integrated intervention, where we obtained 9791 data from Grades 3-9. The incidence of non-fatal drowning between the intervention and control groups after intervention did not differ significantly from the baseline according to the total number of students, male students, female students and Grades 6-9 [0.81; 95% confidence interval (CI): [0.66, 1.00];  $p = 0.05$ , 1.17; 95% CI: [0.90, 1.51];  $p = 0.25$ , 1.40; 95% CI: [0.97, 2.02];  $p = 0.07$  and 0.97; 95% CI: [0.70, 1.34];  $p = 0.86$ ], except for Grades 3-5 (1.36; 95% CI: [1.02, 1.82];  $p = 0.037$ ). The study observed a significantly positive benefit of awareness and risk behaviours of non-fatal drowning



between the intervention and control groups (0.27, 95% CI: [0.21, 0.33];  $p = 0.00$ , -0.16; 95% CI: [-0.24, -0.08];  $p = 0.00$ ).

**Conclusions:** The integrated intervention exerted a significant impact on the prevention and management of child non-fatal drowning, especially in rural areas.

## Integrated management of Childhood Illness (IMCI)

### Iodine deficiency

### Kidney disease

Pediatr Nephrol. 2022 Oct 18.

doi: 10.1007/s00467-022-05769-x. Online ahead of print.

[Management and outcomes in children with lupus nephritis in the developing countries](#)

[Priyanka Khandelwal](#)<sup>1</sup>, [Srinivasavaradan Govindarajan](#)<sup>1</sup>, [Arvind Bagga](#)<sup>2</sup>

#### Abstract

**Background:** Lupus nephritis (LN) has variable prevalence, severity, and outcomes across the world.

**Objectives:** This review compares the outcomes of childhood LN in low- and middle-income countries (LMICs) and high-income countries (HICs) and aims to summarize long-term outcomes of pediatric LN from LMICs.

**Data sources:** A systematic literature search, conducted in PubMed, EMBASE, and Cochrane database in the last 30-years from January 1992, published in the English language, identified 113 studies including 52 from lower ( $n = 1336$ ) and upper MICs ( $n = 3014$ ).

**Study eligibility criteria:** Cohort studies or randomized controlled trials, of patients  $\leq 18$  years of age (or where such data can be separately extracted), with  $> 10$  patients with clinically or histologically diagnosed LN and outcomes reported beyond 12 months were included.

**Participants and interventions:** Patients  $\leq 18$  years of age with clinically or histologically diagnosed LN; effect of an intervention was not measured.

**Study appraisal and synthesis methods:** Two authors independently extracted data. We separately analyzed studies from developed countries (high income countries; HIC) and developing countries (LMICs). Middle-income countries were further classified as lower and upper MICs. Meta-analyses of data were performed by calculating a pooled estimate utilizing the random-effects model. Test for heterogeneity was applied using  $I^2$  statistics. Publication bias was assessed using funnel plots.

**Results:** Kidney remission was similar across MICs and HICs with 1-year pooled complete remission rates of 59% (95% CI 51-67%); one third of patients had kidney flares. The pooled 5-year survival free of stage 5 chronic kidney disease (CKD5) was lower in MICs, especially in lower MICs compared to HICs (83% vs. 93%;  $P = 0.002$ ). The pooled 5-year patient survival was significantly lower in MICs than HICs (85% vs. 94%;  $P < 0.001$ ). In patients with class IV LN, the 5- and 10-year respective risk of CKD5 was 14% and 30% in MICs; corresponding risks

in HICs were 8% and 17%. Long-term data from developing countries was limited. Sepsis (48.8%), kidney failure (14%), lupus activity (18.1%), and intracranial hemorrhage/infarct (5.4%) were chief causes of death; mortality due to complications of kidney failure was more common in lower MICs (25.6%) than HICs (6.4%).

**Limitations:** The review is limited by heterogenous approach to diagnosis and management that has changed over the period spanning the review. World Bank classification based on income might not correlate with the standards of medical care. The overall quality of evidence is low since included studies were chiefly retrospective and single center.

**Conclusions and implications of key findings:** Challenges in LMICs include limited access to pediatric nephrology care, dialysis, increased risk of infection-induced mortality, lack of frequent monitoring, and non-compliance due to cost of therapy. Attention to these issues might update the existing data and improve patient follow-up and outcomes.

Pediatr Nephrol. 2022 Dec;37(12):3117-3126.

doi: 10.1007/s00467-022-05475-8. Epub 2022 Mar 14.

**[Efficacy of rituximab versus tacrolimus in difficult-to-treat steroid-sensitive nephrotic syndrome: an open-label pilot randomized controlled trial](#)**

[Georgie Mathew](#)<sup>1</sup>, [Aditi Sinha](#)<sup>2</sup>, [Aijaz Ahmed](#)<sup>1</sup>, [Neetu Grewal](#)<sup>1</sup>, [Priyanka Khandelwal](#)<sup>1</sup>, [Pankaj Hari](#)<sup>1</sup>, [Arvind Bagga](#)<sup>1</sup>

**Abstract**

**Background:** Rituximab and tacrolimus are therapies reserved for patients with frequently relapsing or steroid-dependent nephrotic syndrome who have failed conventional steroid-sparing agents. Given their toxicities, demonstrating non-inferiority of rituximab to tacrolimus may enable choice between these medications.

**Methods:** This investigator-initiated, single-center, open-label, pilot randomized controlled trial examined the non-inferiority of two doses of intravenous (IV) rituximab given one-week apart to oral therapy with tacrolimus (1:1 allocation), in maintaining sustained remission over 12 months follow-up, in patients with difficult-to-treat steroid-sensitive nephrotic syndrome, defined as frequently relapsing or steroid-dependent disease that had failed  $\geq 2$  steroid-sparing strategies. Secondary outcomes included frequency of relapses, proportion with frequent relapses, time to relapse and frequent relapses, and adverse events (CTRI/2018/11/016342).

**Results:** Baseline characteristics were comparable for 41 patients randomized to receive rituximab (n = 21) or tacrolimus (n = 20). While 55% of patients in each limb were in sustained remission at 1 year, non-inferiority of rituximab to tacrolimus was not demonstrated (mean difference 0%; 95% CI - 30.8%, 30.8%; non-inferiority limit - 20%; P = 0.50). Frequent relapses were more common in patients administered rituximab compared to tacrolimus (risk difference 30%, 95% CI 7.0, 53.0, P = 0.023). Both groups showed similar reductions in relapse rates and prednisolone use. Common adverse events were infusion-related with rituximab and gastrointestinal symptoms with tacrolimus.

**Conclusions:** Therapy with rituximab was not shown to be non-inferior to 12-months treatment with tacrolimus in maintaining remission in patients with difficult-to-treat steroid-sensitive nephrotic syndrome. Frequent relapses were more common with rituximab. While effective, both agents require close monitoring for adverse events.

Eur J Pediatr. 2022 Oct 17.

doi: 10.1007/s00431-022-04655-w. Online ahead of print.

**[The diuretic effect of adding aminophylline or theophylline to furosemide in pediatric populations: a systematic review](#)**

[Paul Van Siang Lian Mang](#)<sup>1</sup>, [Jun Chuen Hui](#)<sup>1</sup>, [Rachel Si Jing Tan](#)<sup>2</sup>, [M Shahnaz Hasan](#)<sup>3</sup>, [Yao Mun Choo](#)<sup>4</sup>, [Mohammed F Abosamak](#)<sup>5</sup>, [Ka Ting Ng](#)<sup>6</sup>

**Abstract**

The diuretic effect of the combined furosemide and aminophylline/theophylline among pediatric patients remains unclear. The primary aim of this systematic review was to examine the clinical diuretic effects (urine output and fluid balance) of co-administration of furosemide and aminophylline/theophylline as compared to furosemide alone in pediatric population. Ovid MEDLINE, CENTRAL, and EMBASE were searched from its inception until March 2022 for observational studies and randomized controlled trials (RCTs) comparing the administration of furosemide versus furosemide and aminophylline/theophylline in pediatric population. Case reports, case series, commentaries, letters to editors, systematic reviews, and meta-analyses were excluded. Five articles with a total sample population of 187 patients were included in this systematic review. As compared to the furosemide alone, our pooled data demonstrated that co-administration of furosemide and aminophylline/theophylline was associated with higher urine output (mean difference: 2.91 [90% CI 1.54 to 4.27],  $p < 0.0001$ ,  $I^2 = 90\%$ ) and a more negative fluid balance (mean difference - 28.27 [95% CI: - 46.21 to - 10.33],  $p = 0.002$ ,  $I^2 = 56\%$ ) than those who received furosemide alone.

**Conclusion:** This is the first paper summarizing the evidence of combined use of furosemide with aminophylline/theophylline in pediatric population. Our systematic review demonstrated that the co-administration of furosemide and aminophylline/theophylline could potentially yield better diuretic effects of urine output and negative fluid balance than furosemide alone in pediatric patients with fluid overload. Given the substantial degree of heterogeneity and low level of evidence, future adequately powered trials are warranted to provide evidence regarding the combined use of aminophylline/theophylline and furosemide as diuretic in the pediatric population.

Eur J Pediatr. 2023 Jan;182(1):101-109.

doi: 10.1007/s00431-022-04650-1. Epub 2022 Oct 11.

**[Comparison of darbepoetin alpha and recombinant human erythropoietin for treatment of anemia in pediatric chronic kidney disease: a non-inferiority trial from India](#)**

[Rufaida Mazahir](#)<sup>1,2</sup>, [Kanav Anand](#)<sup>3</sup>, [P K Pruthi](#)<sup>3</sup>

**Abstract**

To determine whether or not Darbepoetin alpha (DA) was non-inferior to recombinant human erythropoietin (rHuEPO) in the treatment of anemia in children with chronic kidney disease (CKD) stage 3-5 (on or not on dialysis). This was a randomized, open-label, two-arm, parallel group, active-controlled, non-inferiority trial conducted at a tertiary care center in New Delhi, India. Fifty patients of either gender (aged 1-18 years) with CKD stage 3-5 (on or not on dialysis) who had baseline hemoglobin (Hb) between 9 and 12 g/dL and were on

stable erythropoietin therapy for at least 8 weeks were randomized (1:1) to either continue rHuEPO or switch to DA therapy for a period of 28 weeks. Doses were titrated in the initial 23 weeks to maintain the Hb between 11 and 12 g/dL, and efficacy was assessed between weeks 24 and 28. The primary efficacy outcome was the mean change in Hb between baseline and the evaluation period. In the intention-to-treat population (n = 50), the adjusted between-group difference in mean Hb change between the baseline and the evaluation period was 0.131 g/dL (95% CI: - 0.439 to 0.719, p = 0.629). The lower limit of the two-sided 95% CI for the difference in the mean change in Hb between the two treatment groups was well above the pre-specified non-inferiority margin of - 1.0 g/dL. Similar pattern of non-inferiority was seen for per protocol population. The safety profile of DA and rHuEPO was also comparable (injection site pain:rHuEPO-3, DA-7; p=0.296). Conclusion: DA is non-inferior to rHuEPO for the treatment of anemia of CKD (stage 3-5) in pediatric population with a comparable safety profile.

Pediatr Nephrol. 2023 Jun;38(6):1907-1913.

doi: 10.1007/s00467-022-05790-0. Epub 2022 Nov 2.

**Changes in bone biomarkers in response to different dosing regimens of cholecalciferol supplementation in children with chronic kidney disease**

Nivedita Kamath<sup>1</sup>, Arpana Iyengar<sup>2</sup>, Hamsa V Reddy<sup>2</sup>, Jyoti Sharma<sup>3</sup>, Jyoti Singhal<sup>3</sup>, Sudha Ekambaram<sup>4</sup>, Susan Uthup<sup>5</sup>, Sumithra Selvam<sup>6</sup>, Mandy Wan<sup>7</sup>, Anja Rahn<sup>8</sup>, Dagmar Christiane-Fischer<sup>8</sup>, Rukshana Shroff<sup>9</sup>

**Abstract**

**Background:** The effect of different dosing regimens of cholecalciferol supplementation on bone biomarkers has not been studied in children with chronic kidney disease (CKD).

**Methods:** This is a post hoc analysis of a multi-center randomized controlled trial which included children with CKD stages 2-4 with vitamin D deficiency (25-hydroxy vitamin D (25OHD) < 30 ng/ml) randomized 1:1:1 to receive an equivalent dose of oral cholecalciferol as daily, weekly or monthly treatment. Markers of bone formation (bone alkaline phosphatase (BAP), procollagen I N terminal peptide (PINP)), bone resorption (tartarate-resistant acid phosphatase 5b (TRAP), C terminal telopeptide (CTX)), and osteocyte markers (intact fibroblast growth factor 23 (iFGF23), sclerostin) and soluble klotho were measured at baseline and after 3 months of intensive replacement therapy. The change in biomarkers and ratio of markers of bone formation to resorption were compared between treatment arms. BAP and TRAP were expressed as age- and sex-specific z-scores.

**Results:** 25OHD levels increased with cholecalciferol supplementation, with 85% achieving normal levels. There was a significant increase in the BAP/TRAP ratio (p = 0.04), iFGF23 (p = 0.004), and klotho (p = 0.002) with cholecalciferol therapy, but this was comparable across all three therapy arms. The BAPz was significantly higher in the weekly arm (p = 0.01). The change in 25OHD ( $\Delta$ 25OHD) inversely correlated with  $\Delta$ PTH (r = - 0.4, p < 0.001).

**Conclusions:** Although cholecalciferol supplementation was associated with a significant increase in bone formation, the three dosing regimens of cholecalciferol supplementation have a comparable effect on the bone biomarker profile, suggesting that they can be used interchangeably to suit the patient's needs and optimize adherence to therapy

## Leishmaniasis

Clin Infect Dis. 2022 Sep 27;ciac643.

doi: 10.1093/cid/ciac643. Online ahead of print.

### [Paromomycin and Miltefosine Combination as an Alternative to Treat Patients With Visceral Leishmaniasis in Eastern Africa: A Randomized, Controlled, Multicountry Trial](#)

[Ahmed M Musa<sup>1</sup>](#), [Jane Mbui<sup>2</sup>](#), [Rezika Mohammed<sup>3</sup>](#), [Joseph Olobo<sup>4</sup>](#), [Koert Ritmeijer<sup>5</sup>](#), [Gabriel Alcoba<sup>6</sup>](#), [Gina Muthoni Ouattara<sup>7</sup>](#), [Thaddaeus Egondi<sup>7</sup>](#), [Prossy Nakanwagi<sup>7</sup>](#), [Truphosa Omollo<sup>7</sup>](#), [Monique Wasunna<sup>7</sup>](#), [Luka Verrest<sup>8</sup>](#), [Thomas P C Dorlo<sup>8</sup>](#), [Brima Musa Younis<sup>1</sup>](#), [Ali Nour<sup>1</sup>](#), [Elmukashfi Taha Ahmed Elmukashfi<sup>1</sup>](#), [Ahmed Ismail Omer Haroun<sup>1</sup>](#), [Eltahir A G Khalil<sup>1</sup>](#), [Simon Njenga<sup>2</sup>](#), [Helina Fikre<sup>3</sup>](#), [Tigist Mekonnen<sup>3</sup>](#), [Dagne Mersha<sup>9</sup>](#), [Kasaye Sisay<sup>9</sup>](#), [Patrick Sagaki<sup>10</sup>](#), [Jorge Alvar<sup>11</sup>](#), [Alexandra Solomos<sup>11</sup>](#), [Fabiana Alves<sup>11</sup>](#)

#### Abstract

**Background:** This study aimed to determine whether paromomycin plus miltefosine (PM/MF) is noninferior to sodium stibogluconate plus paromomycin (SSG/PM) for treatment of primary visceral leishmaniasis in eastern Africa.

**Methods:** An open-label, phase 3, randomized, controlled trial was conducted in adult and pediatric patients at 7 sites in eastern Africa. Patients were randomly assigned to either 20 mg/kg paromomycin plus allometric dose of miltefosine (14 days), or 20 mg/kg sodium stibogluconate plus 15 mg/kg paromomycin (17 days). The primary endpoint was definitive cure after 6 months.

**Results:** Of 439 randomized patients, 424 completed the trial. Definitive cure at 6 months was 91.2% (155 of 170) and 91.8% (156 of 170) in the PM/MF and SSG/PM arms in primary efficacy modified intention-to-treat analysis (difference, 0.6%; 97.5% confidence interval [CI], -6.2 to 7.4), narrowly missing the noninferiority margin of 7%. In the per-protocol analysis, efficacy was 92% (149 of 162) and 91.7% (155 of 169) in the PM/MF and SSG/PM arms (difference, -0.3%; 97.5% CI, -7.0 to 6.5), demonstrating noninferiority. Treatments were well tolerated. Four of 18 serious adverse events were study drug-related, and 1 death was SSG-related. Allometric dosing ensured similar MF exposure in children (<12 years) and adults.

**Conclusions:** PM/MF and SSG/PM efficacies were similar, and adverse drug reactions were as expected given the drugs safety profiles. With 1 less injection each day, reduced treatment duration, and no risk of SSG-associated life-threatening cardiotoxicity, PM/MF is a more patient-friendly alternative for children and adults with primary visceral leishmaniasis in eastern Africa.

## Lymphatic filariasis

Lancet Infect Dis. 2022 Aug;22(8):1200-1209.

doi: 10.1016/S1473-3099(22)00026-3. Epub 2022 May 6.

### [Mass drug administration of ivermectin, diethylcarbamazine, plus albendazole compared with diethylcarbamazine plus albendazole for reduction of lymphatic filariasis endemicity in Papua New Guinea: a cluster-randomised trial](#)

[Moses Laman<sup>1</sup>](#), [Livingstone Tavul<sup>1</sup>](#), [Stephan Karl<sup>2</sup>](#), [Bethuel Kotty<sup>1</sup>](#), [Zebede Kerry<sup>1</sup>](#), [Stephen Kumai<sup>1</sup>](#), [Anna Samuel<sup>1</sup>](#), [Lina Lorry<sup>1</sup>](#), [Lincoln Timinao<sup>1</sup>](#), [S Cade Howard<sup>3</sup>](#), [Leo Makita<sup>4</sup>](#), [Lucy John<sup>4</sup>](#), [Sibauk Bieb<sup>4</sup>](#), [James Wangi<sup>5</sup>](#), [Jeffrey M Albert<sup>6</sup>](#), [Michael Payne<sup>3</sup>](#), [Gary J Weil<sup>7</sup>](#), [Daniel J Tisch<sup>8</sup>](#), [Catherine M Bjerum<sup>3</sup>](#), [Leanne J Robinson<sup>9</sup>](#), [Christopher L King<sup>10</sup>](#)

## Abstract

**Background:** A single co-administered dose of a triple-drug regimen (ivermectin, diethylcarbamazine, and albendazole) has been shown to be safe and more efficacious for clearing *Wuchereria bancrofti* microfilariae than the standard two-drug regimen of diethylcarbamazine plus albendazole in clinical trials. However, the effectiveness of mass drug administration with the triple-drug regimen compared with the two-drug regimen is unknown. We compared the effectiveness of mass drug administration with the triple-drug and two-drug regimens for reducing microfilariae prevalence to less than 1% and circulating filarial antigen prevalence to less than 2%, levels that are unlikely to sustain transmission of lymphatic filariasis, in Papua New Guinea.

**Methods:** This open-label, cluster-randomised study was done in 24 villages in a district endemic for lymphatic filariasis in Papua New Guinea. Villages paired by population size were randomly assigned to receive mass drug administration with a single dose of the triple-drug oral regimen of ivermectin (200 µg per kg of bodyweight) plus diethylcarbamazine (6 mg per kg of bodyweight) plus albendazole (400 mg) or a single dose of the two-drug oral regimen of diethylcarbamazine (6 mg per kg of bodyweight) plus albendazole (400 mg). This is a follow-on study of a previously reported safety study (ClinicalTrials.gov [NCT02899936](#)). All residents aged 5 years or older and non-pregnant women were asked to participate. After cross-sectional night blood microfilariae and circulating filarial antigen surveys, mass drug administration was provided at baseline and repeated 12 months later. The primary outcomes were mean prevalence of microfilariae and circulating filarial antigen at 12 months and 24 months, assessed in all residents willing to participate at each timepoint. This study is registered with ClinicalTrials.gov, [NCT03352206](#).

**Findings:** Between Nov 18, 2016, and May 26, 2017, 4563 individuals were enrolled in 24 clusters; 12 clusters (2382 participants) were assigned to the triple-drug regimen and 12 clusters (2181 participants) to the two-drug regimen. Mean drug ingestion rates (of residents aged ≥5 years) were 66·1% at baseline and 63·2% at 12 months in communities assigned to the triple-drug regimen and 65·9% at baseline and 54·9% at 12 months in communities assigned to the two-drug regimen. Microfilariae prevalence in the triple-drug regimen group decreased from 105 (4·4%) of 2382 participants (95% CI 3·6-5·3) at baseline to nine (0·4%) of 2319 (0·1-0·7) at 12 months and four (0·2%) of 2086 (0·1-0·5) at 24 months. In the two-drug regimen group, microfilariae prevalence decreased from 93 (4·3%) of 2181 participants (95% CI 3·5-5·2) at baseline to 29 (1·5%) of 1963 (1·0-2·1) at 12 months and eight (0·4%) of 1844 (0·2-0·9) at 24 months (adjusted estimated risk ratio 4·5, 95% CI 1·4-13·8,  $p=0·0087$ , at 12 months; 2·9, 95% CI 1·0-8·8,  $p=0·058$ , at 24 months). The prevalence of circulating filarial antigen decreased from 523 (22·0%) of 2382 participants (95% CI 20·3-23·6) at baseline to 378 (16·3%) of 2319 (14·9-17·9) at 12 months and 156 (7·5%) of 2086 (6·4-8·7) at 24 months in the triple-drug regimen group and from 489 (22·6%) of 2168 participants (20·7-24·2) at baseline to 358 (18·2%) of 1963 (16·7-20·1) at 12 months and 184 (10·0%) of 1840 (8·7-11·5) at 24 months in the two-drug regimen group; after adjustment, differences between groups were not significant.

**Interpretation:** Mass administration of the triple-drug regimen was more effective than the two-drug regimen in reducing microfilariae prevalence in communities to less than the target



level of 1%, but did not reduce circulating filarial antigen prevalence to less than 2%. These results support the use of mass drug administration with the triple-drug regimen to accelerate elimination of lymphatic filariasis.

## Leprosy

## Malaria

### Insecticide-treated bed nets and other materials

Lancet Infect Dis. 2022 Sep 26;S1473-3099(22)00469-8.

doi: 10.1016/S1473-3099(22)00469-8. Online ahead of print.

[Effect of long-lasting insecticidal nets with and without piperonyl butoxide on malaria indicators in Uganda \(LLINEUP\): final results of a cluster-randomised trial embedded in a national distribution campaign](#)

[Catherine Maiteki-Sebuguzi<sup>1</sup>, Samuel Gonahasa<sup>2</sup>, Moses R Kamya<sup>3</sup>, Agaba Katureebe<sup>2</sup>, Irene Bagala<sup>2</sup>, Amy Lynd<sup>4</sup>, Peter Mutungi<sup>2</sup>, Simon P Kigozi<sup>2</sup>, Jimmy Opigo<sup>5</sup>, Janet Hemingway<sup>4</sup>, Grant Dorsey<sup>6</sup>, Martin J Donnelly<sup>7</sup>, Sarah G Staedke<sup>8</sup>](#)

#### Abstract

**Background:** Long-lasting insecticidal nets (LLINs) are the foundation of malaria control but resistance of mosquito vectors to pyrethroids threatens their effectiveness. We embedded a cluster-randomised trial into Uganda's 2017-18 campaign to distribute LLINs. LLINs with piperonyl butoxide (PBO) reduced parasite prevalence more effectively than conventional LLINs (without PBO) for 18 months. Here, we report the final 25-month survey results.

**Methods:** LLINEUP was a cluster-randomised trial conducted in 48 districts in eastern and western Uganda. 104 health subdistricts (clusters) without ongoing or planned indoor residual spraying with pirimiphos-methyl (Actellic, Basel, Switzerland) were eligible for inclusion in the trial. Clusters were randomly assigned to PBO LLINs (PermaNet 3.0 or Olyset Plus) and conventional LLINs (PermaNet 2.0 or Olyset Net) with proportionate randomisation using STATA version 14.2. LLINs were delivered from March 25, 2017, to March 18, 2018. Between April 23, 2019, and Sept 13, 2019, community surveys were conducted in 50 randomly selected households per cluster; ten households per cluster were randomly selected for entomology surveys. Mosquitoes were collected in the morning from indoor surfaces of households using Prokopack aspirators. Due to COVID-19 restrictions, only 90 of the 104 clusters were surveyed at 25 months. The primary outcome was parasite prevalence by microscopy in children aged 2-10 years, assessed in the as-treated population, determined using the results from the 6-month household survey on the type of LLINs received in each cluster. This trial is registered with ISRCTN, ISRCTN17516395, and is now completed.

**Findings:** In the as-treated analysis, two clusters were excluded (no predominant LLIN received) and four were reassigned; 40 PBO LLIN clusters (30 PermaNet 3.0, ten Olyset Plus) and 48 non-PBO LLIN (36 PermaNet 2.0, 12 Olyset Net) were included. Parasite prevalence

was 17·1% (506 of 2958 participants) in the PBO group and 19·8% (701 of 3534) in the non-PBO group (prevalence ratio adjusted for baseline 0·80 [95% CI 0·69-0·93],  $p=0\cdot0048$ ). Comparing within-treatment group parasite prevalence to baseline, parasite prevalence ratios were lower in the PBO groups at all timepoints, but the difference was greatest at 6 months (PBO LLINs parasite prevalence at baseline 28·8% [1001 of 3472, 95% CI 27·3-30·4] vs at 6 months 12·0% [361 of 3009, 10·9-13·2], prevalence ratio [PR] 0·43 [95% CI 0·36-0·52],  $p<0\cdot0001$ ; non-PBO LLINs parasite prevalence at baseline 25·4% [1015 of 4004, 24·0-26·7] vs 6 months 14·8% [526 of 3551, 13·7-16·0], PR 0·60 [0·54-0·68],  $p<0\cdot0001$ ) and 25 months (PBO LLINs parasite prevalence at 25 months 17·1% [506 of 2958, 15·8-18·5], PR 0·63 [95% CI 0·57-0·71],  $p<0\cdot0001$ ; non-PBO LLINs parasite prevalence at 25 months 19·8% [701 of 3534, 18·5-21·2], PR 0·79 [0·73-0·86],  $p<0\cdot0001$ ).

**Interpretation:** In Uganda, PBO LLINs outperformed pyrethroid-only LLINs for 25 months. WHO concluded that PBO LLINs are more effective against malaria than non-PBO LLINs when resistance to pyrethroids is high and issued a conditional recommendation suggesting PBO LLINs should be deployed in areas of pyrethroid resistance.

Lancet. 2023 Feb 11;401(10375):435-446.

doi: 10.1016/S0140-6736(22)02319-4. Epub 2023 Jan 24.

**[Efficacy of pyriproxyfen-pyrethroid long-lasting insecticidal nets \(LLINs\) and chlorfenapyr-pyrethroid LLINs compared with pyrethroid-only LLINs for malaria control in Benin: a cluster-randomised, superiority trial](#)**

[Manfred Accrombessi](#)<sup>1</sup>, [Jackie Cook](#)<sup>2</sup>, [Edouard Dangbenon](#)<sup>3</sup>, [Boulais Yovogan](#)<sup>3</sup>, [Hilaire Akpovi](#)<sup>3</sup>, [Arthur Sovi](#)<sup>4</sup>, [Constantin Adoha](#)<sup>3</sup>, [Landry Assongba](#)<sup>3</sup>, [Aboubacar Sidick](#)<sup>3</sup>, [Bruno Akinro](#)<sup>3</sup>, [Razaki Ossè](#)<sup>3</sup>, [Filémon Tokponnon](#)<sup>3</sup>, [Rock Aïkpon](#)<sup>5</sup>, [Aurore Ogouyemi-Hounto](#)<sup>5</sup>, [Germain Gil Padonou](#)<sup>3</sup>, [Immo Kleinschmidt](#)<sup>6</sup>, [Louisa A Messenger](#)<sup>4</sup>, [Mark Rowland](#)<sup>4</sup>, [Corine Ngufor](#)<sup>4</sup>, [Natacha Protopopoff](#)<sup>4</sup>, [Martin C Akogbeto](#)<sup>3</sup>

**Abstract**

**Background:** New classes of long-lasting insecticidal nets (LLINs) combining mixtures of insecticides with different modes of action could put malaria control back on track after rebounds in transmission across sub-Saharan Africa. We evaluated the relative efficacy of pyriproxyfen-pyrethroid LLINs and chlorfenapyr-pyrethroid LLINs compared with standard LLINs against malaria transmission in an area of high pyrethroid resistance in Benin.

**Methods:** We conducted a cluster-randomised, superiority trial in Zou Department, Benin. Clusters were villages or groups of villages with a minimum of 100 houses. We used restricted randomisation to randomly assign 60 clusters to one of three LLIN groups (1:1:1): to receive nets containing either pyriproxyfen and alpha-cypermethrin (pyrethroid), chlorfenapyr and alpha-cypermethrin, or alpha-cypermethrin only (reference). Households received one LLIN for every two people. The field team, laboratory staff, analyses team, and community members were masked to the group allocation. The primary outcome was malaria case incidence measured over 2 years after net distribution in a cohort of children aged 6 months-10 years, in the intention-to-treat population. This study is ongoing and is registered with ClinicalTrials.gov, [NCT03931473](#).

**Findings:** Between May 23 and June 24, 2019, 53 854 households and 216 289 inhabitants were accounted for in the initial census and included in the study. Between March 19 and 22, 2020, 115 323 LLINs were distributed to 54 030 households in an updated census. A cross-

sectional survey showed that study LLIN usage was highest at 9 months after distribution (5532 [76.8%] of 7206 participants), but decreased by 24 months (4032 [60.6%] of 6654). Mean malaria incidence over 2 years after LLIN distribution was 1.03 cases per child-year (95% CI 0.96-1.09) in the pyrethroid-only LLIN reference group, 0.84 cases per child-year (0.78-0.90) in the pyriproxyfen-pyrethroid LLIN group (hazard ratio [HR] 0.86, 95% CI 0.65-1.14;  $p=0.28$ ), and 0.56 cases per child-year (0.51-0.61) in the chlorfenapyr-pyrethroid LLIN group (HR 0.54, 95% CI 0.42-0.70;  $p<0.0001$ ).

**Interpretation:** Over 2 years, chlorfenapyr-pyrethroid LLINs provided greater protection from malaria than pyrethroid-only LLINs in an area with pyrethroid-resistant mosquitoes. Pyriproxyfen-pyrethroid LLINs conferred protection similar to pyrethroid-only LLINs. These findings provide crucial second-trial evidence to enable WHO to make policy recommendations on these new LLIN classes. This study confirms the importance of chlorfenapyr as an LLIN treatment to control malaria in areas with pyrethroid-resistant vectors. However, an arsenal of new active ingredients is required for successful long-term resistance management, and additional innovations, including pyriproxyfen, need to be further investigated for effective vector control strategies.

Malar J. 2023 Jan 12;22(1):15.

doi: 10.1186/s12936-022-04429-7.

**[Durable wall lining for malaria control in Liberia: results of a cluster randomized trial](#)**

[David Giesbrecht](#)<sup>1</sup>, [Tuwuyor G Belleh](#)<sup>2</sup>, [Julie Pontarollo](#)<sup>3</sup>, [Victor S Hinneh](#)<sup>4</sup>, [Oliver Pratt](#)<sup>4</sup>, [Sajid Kamal](#)<sup>3</sup>, [Richard Allan](#)<sup>5</sup>

**Abstract**

**Background:** Malaria control in Liberia depends upon universal coverage with pyrethroid-impregnated long-lasting insecticidal nets (LLINs). Despite regular mass distribution, LLIN coverage and usage is patchy. Pyrethroid resistance in malaria vectors may further reduce LLIN efficacy. Durable Wall Lining (DWL), a novel material treated with two non-pyrethroid class insecticides, was designed to be installed onto the surface of inner walls, and cover openings and ceiling surfaces of rural houses.

**Objectives:** AIM: To determine the malaria control efficacy of DWL.

**Primary objective:** To determine if DWL has an additional protective effect in an area of pyrethroid resistance.

**Secondary objectives:** To compare surface bio-availability of insecticides and entomological effectiveness over the study duration.

**Design:** A cluster randomized trial.

**Participants:** Children aged 2-59 months.

**Control arm:** 50 houses per 20 clusters, all of which received LLIN within the previous 12 months.

**Active arm:** 50 houses per 20 experimental clusters, all of which received LLINs with the previous 12 months, and had internal walls and ceilings lined with DWL.

**Randomisation:** Cluster villages were randomly allocated to control or active arms, and paired on 4 covariates.

**Main outcome measures:** PRIMARY MEASURE: Prevalence of infection with *P. falciparum* in children aged 2 to 59 months.

**Secondary measure:** Surface bioavailability and entomological effectiveness of DWL active ingredients.

**Results:** Plasmodium falciparum prevalence in active clusters after 12 months was 34.6% compared to 40.1% in control clusters ( $p = 0.052$ ). The effect varied with elevation and was significant ( $RR = 1.3$ ,  $p = 0.022$ ) in 14 pairs of upland villages. It was not significant ( $RR = 1.3$ ,  $p = 0.344$ ) in 6 pairs of coastal villages. Pooled risk ratio (RR) was calculated in SAS (Cary, NC, USA) using the Cochran-Mantel-Haenszel (CMH) test for upland and coastal cluster pairs. DWL efficacy was sustained at almost 100% for 12 months.

**Conclusions:** Findings indicate that DWL is a scalable and effective malaria control intervention in stable transmission areas with pyrethroid-resistant vectors, where LLIN usage is difficult to achieve, and where local housing designs include large gable and eave openings.

Malar J. 2022 Dec 17;21(1):387.

doi: 10.1186/s12936-022-04405-1.

**Ideational factors and their association with insecticide treated net use in Magoe District, Mozambique**

[Joshua O Yukich<sup>1</sup>](#), [Paul Hutchinson<sup>2</sup>](#), [Baltazar Candrinho<sup>3</sup>](#), [Jessica Butts<sup>4</sup>](#), [Filipe Murimirigua<sup>5</sup>](#), [Thomas P Eisele<sup>6</sup>](#), [Rose Zulliger<sup>7</sup>](#)

**Abstract**

**Background:** Insecticide treated bed nets (ITN) are considered a core malaria vector control tool by the WHO and are the main contributor to the large decline in malaria burden in sub-Saharan Africa over the past 20 years, but they are less effective if they are not broadly and regularly used. ITN use may depend on factors including temperature, relative humidity, mosquito density, seasonality, as well as ideational or psychosocial factors including perceptions of nets and perceptions of net use behaviours.

**Methods:** A cross-sectional household survey was conducted as part of a planned randomized controlled trial in Magoe District, Mozambique. Interviewers captured data on general malaria and ITN perceptions including ideational factors related to perceived ITN response efficacy, self-efficacy to use an ITN, and community norms around ITN using a standardized questionnaire. Only households with sufficient ITNs present for all children to sleep under (at least one ITN for every two children under the age of five years) were eligible for inclusion in the study. Additional questions were added about seasonality and frequency of ITN use.

**Results:** One-thousand six hundred sixteen mother-child dyads were interviewed. Responses indicated gaps in use of existing nets and net use was largely independent of ideational factors related to ITNs. Self-reported ITN use varied little by season nor meaningfully when different methods were used to solicit responses on net use behaviour. Mothers' perceived response efficacy of ITNs was negatively associated with net use (high perceived response efficacy reduced the log-odds of net use by 0.27 (95% CI - 0.04 to - 0.51), implying that stronger beliefs in the effectiveness of ITNs might result in reduced net use among their children.

**Conclusions:** In this context, ITN use among children was not clearly related to mothers' ideational factors measured in the study. Scales used in solicitation of ideation around ITN use and beliefs need careful design and testing across a broader range of populations in order to identify ideational factors related to ITN use among those with access.

Malar J. 2023 Feb 1;22(1):35.

doi: 10.1186/s12936-023-04458-w.

[\*\*Prevalence and predictors of adverse events following exposure to long-lasting insecticidal nets used for malaria prevention: a community based cross-sectional study in the Democratic Republic of the Congo\*\*](#)

[Gillon Ilombe<sup>1,2,3</sup>](#), [Thérèse Mpiempie<sup>4</sup>](#), [Gauthier Mesia<sup>4</sup>](#), [Junior R Matangila<sup>5</sup>](#), [Aimée M Lulebo<sup>6</sup>](#), [Vivi Maketa<sup>5</sup>](#), [Baby Mabanzila<sup>5</sup>](#), [Nicole M Muela<sup>7</sup>](#), [Flory T Muanda<sup>4,8,9</sup>](#), [Sylvie Linsuke<sup>10,11</sup>](#), [Jean-Pierre van Geertruyden<sup>10</sup>](#), [Pascal Lutumba<sup>5</sup>](#)

Affiliations expand

**Abstract**

**Background:** Malaria morbidity and mortality increase in the Democratic Republic of the Congo (DRC) may be the consequence of the low utilization rate of long-lasting insecticidal nets (LLINs) resulting from poor compliance due to adverse events (AEs). This study aimed at determining the prevalence and predictors of AEs following the mass distribution of LLINs in the Kisantu Health Zone (KHZ), a high malaria-endemic region in the DRC.

**Methods:** A community-based cross-sectional study embedded was conducted within a randomized controlled trial (RCT) after the mass distribution of LLINs in 30 villages located in DRC KHZ. A three-stage sampling method was used without replacement to select 1790 children. Data was collected on adverse events (AEs) using a reporting form and information on demographics, nutritional status, and house characteristics. This was done using a structured questionnaire administered to household heads. Logistic regression models were used to identify predictors of AEs following the mass distribution of LLINs.

**Result:** In a total of 1790 children enrolled, 17.8% (95% CI 16.1-19.7) experienced AEs. The most common AEs were respiratory-related (61%). Around 60% of AEs occurred within 24 h of use, and 51% were resolved without treatment. Sleeping under deltamethrin LLINs (Adjusted OR, 95% CI 5.5 [3.8-8.0]) and zinc roofing (Adjusted OR, 95% CI 1.98 [1.1-3.57]) were associated with the risk of reporting an AE following the mass distribution of LLINs.

**Conclusion:** Approximately 1 out of 5 children had an AE within 24 h following LLIN use. These adverse events were often respiratory-related. LLINs and roofing types were associated with a higher risk of reporting AEs. However, further research using a robust study design is needed to confirm these findings. Future studies should design and implement interventions aiming to reduce AEs and improve compliance with LLINs.

## Environmental prevention of malaria

Cochrane Database Syst Rev. 2022 Oct 6;10(10):CD013398.

doi: 10.1002/14651858.CD013398.pub4.

[\*\*House modifications for preventing malaria\*\*](#)

[Tilly Fox<sup>1</sup>](#), [Joanna Furnival-Adams<sup>2</sup>](#), [Marty Chaplin<sup>1</sup>](#), [Mark Napier<sup>3,4</sup>](#), [Evelyn A Olanga<sup>5</sup>](#)

**Abstract**

**Background:** Malaria remains an important public health problem. Research in 1900 suggested house modifications may reduce malaria transmission. A previous version of this review concluded that house screening may be effective in reducing malaria. This update includes data from five new studies.

**Objectives:** To assess the effects of house modifications that aim to reduce exposure to mosquitoes on malaria disease and transmission.

**Search methods:** We searched the Cochrane Infectious Diseases Group Specialized Register; Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE (PubMed); Embase (OVID); Centre for Agriculture and Bioscience International (CAB) Abstracts (Web of Science); and the Latin American and Caribbean Health Science Information database (LILACS) up to 25 May 2022. We also searched the World Health Organization International Clinical Trials Registry Platform, ClinicalTrials.gov, and the ISRCTN registry to identify ongoing trials up to 25 May 2022.

**Selection criteria:** Randomized controlled trials, including cluster-randomized controlled trials (cRCTs), cross-over studies, and stepped-wedge designs were eligible, as were quasi-experimental trials, including controlled before-and-after studies, controlled interrupted time series, and non-randomized cross-over studies. We sought studies investigating primary construction and house modifications to existing homes reporting epidemiological outcomes (malaria case incidence, malaria infection incidence or parasite prevalence). We extracted any entomological outcomes that were also reported in these studies.

**Data collection and analysis:** Two review authors independently selected eligible studies, extracted data, and assessed the risk of bias. We used risk ratios (RR) to compare the effect of the intervention with the control for dichotomous data. For continuous data, we presented the mean difference; and for count and rate data, we used rate ratios. We presented all results with 95% confidence intervals (CIs). We assessed the certainty of evidence using the GRADE approach.

**Main results:** One RCT and six cRCTs met our inclusion criteria, with an additional six ongoing RCTs. We did not identify any eligible non-randomized studies. All included trials were conducted in sub-Saharan Africa since 2009; two randomized by household and four at the block or village level. All trials assessed screening of windows, doors, eaves, ceilings, or any combination of these; this was either alone, or in combination with roof modification or eave tube installation (an insecticidal "lure and kill" device that reduces mosquito entry whilst maintaining some airflow). In one trial, the screening material was treated with 2% permethrin insecticide. In five trials, the researchers implemented the interventions. A community-based approach was adopted in the other trial. Overall, the implementation of house modifications probably reduced malaria parasite prevalence (RR 0.68, 95% CI 0.57 to 0.82; 5 trials, 5183 participants; moderate-certainty evidence), although an inconsistent effect was observed in a subpopulation of children in one study. House modifications reduced moderate to severe anaemia prevalence (RR 0.70, 95% CI 0.55 to 0.89; 3 trials, 3643 participants; high-certainty evidence). There was no consistent effect on clinical malaria incidence, with rate ratios ranging from 0.38 to 1.62 (3 trials, 3365 participants, 4126.6 person-years). House modifications may reduce indoor mosquito density (rate ratio 0.63, 95% CI 0.30 to 1.30; 4 trials, 9894 household-nights; low-certainty evidence), although two studies showed little effect on this parameter.

**Authors' conclusions:** House modifications - largely screening, sometimes combined with insecticide and lure and kill devices - were associated with a reduction in malaria parasite prevalence and a reduction in people with anaemia. Findings on malaria incidence were



mixed. Modifications were also associated with lower indoor adult mosquito density, but this effect was not present in some studies.

Soc Sci Med. 2023 Feb 19;321:115778.

doi: 10.1016/j.socscimed.2023.115778. Online ahead of print.

**[The economic impacts of house screening against malaria transmission: Experimental evidence from eastern Zambia](#)**

[Brian Chisanga](#)<sup>1</sup>, [Erwin Bulte](#)<sup>2</sup>, [Menale Kassie](#)<sup>3</sup>, [Clifford Mutero](#)<sup>3</sup>, [Freddie Masaninga](#)<sup>4</sup>, [Onyango Peter Sangoro](#)<sup>5</sup>

**Abstract**

Malaria imposes an economic burden for human populations in many African countries, and this burden may be reduced through house screening initiatives. We use a randomized controlled trial to measure the economic impacts of house screening against malaria infection. We use a sample of 800 households from 89 villages in rural and peri-urban Zambia to collect baseline data in August 2019 and endline data in August 2020. The main outcome variables are (self-reported) malaria prevalence rates, labor supply, and income, and consider individual and household-level outcomes. House screening reduces malaria prevalence, the number of sick days due to malaria, and the number of malaria episodes. Impacts on adults are more pronounced than on children. In terms of economic impacts, house screening increases labor supply and (household) income. We find particularly large effects on labor supply for women household members. A cost-benefit analysis, based on estimated benefits and measured costs, suggests that the private benefits of house screening exceed the costs. While not all houses are suitable for house screening, we conclude that screening is a promising and cost-effective approach to reduce malaria infections.

BMC Infect Dis. 2023 Feb 6;23(1):72.

doi: 10.1186/s12879-023-07991-w.

**[Impact of population based indoor residual spraying with and without mass drug administration with dihydroartemisinin-piperaquine on malaria prevalence in a high transmission setting: a quasi-experimental controlled before-and-after trial in northeastern Uganda](#)**

[Dorothy C Echodu](#)<sup>1</sup>, [Adoke Yeka](#)<sup>2</sup>, [Thomas Eganyu](#)<sup>3</sup>, [Wycliff Odude](#)<sup>3</sup>, [Fred Bukenya](#)<sup>3</sup>, [Benjamin Amoah](#)<sup>4</sup>, [Humphrey Wanzira](#)<sup>3</sup>, [Kathryn Colborn](#)<sup>5</sup>, [Richard C Elliott](#)<sup>6,7</sup>, [Suzanne E Powell](#)<sup>6</sup>, [Maxwell Kilama](#)<sup>3</sup>, [Ronald Mulebeke](#)<sup>2</sup>, [Joaniter Nankabirwa](#)<sup>8</sup>, [Emanuele Giorgi](#)<sup>9</sup>, [Mellisa Roskosky](#)<sup>6,10</sup>, [Osborn Omoding](#)<sup>3</sup>, [Samuel Gonahasa](#)<sup>8</sup>, [Jimmy Opigo](#)<sup>11</sup>

**Abstract**

**Background:** Declines in malaria burden in Uganda have slowed. Modelling predicts that indoor residual spraying (IRS) and mass drug administration (MDA), when co-timed, have synergistic impact. This study investigated additional protective impact of population-based MDA on malaria prevalence, if any, when added to IRS, as compared with IRS alone and with standard of care (SOC).

**Methods:** The 32-month quasi-experimental controlled before-and-after trial enrolled an open cohort of residents (46,765 individuals, 1st enumeration and 52,133, 4th enumeration) of Katakwi District in northeastern Uganda. Consented participants were assigned to three arms based on residential subcounty at study start: MDA+IRS, IRS, SOC. IRS with pirimiphos methyl and MDA with dihydroartemisinin- piperazine were delivered in 4 co-timed campaign-style rounds 8 months apart. The primary endpoint was population prevalence of malaria, estimated by 6 cross-sectional surveys, starting at baseline and preceding each subsequent round.

**Results:** Comparing malaria prevalence in MDA+IRS and IRS only arms over all 6 surveys (intention-to-treat analysis), roughly every 6 months post-interventions, a geostatistical model found a significant additional 15.5% (95% confidence interval (CI): [13.7%, 17.5%],  $Z = 9.6$ ,  $p = 5e-20$ ) decrease in the adjusted odds ratio (aOR) due to MDA for all ages, a 13.3% reduction in under 5's (95% CI: [10.5%, 16.8%],  $Z = 4.02$ ,  $p = 5e-5$ ), and a 10.1% reduction in children 5-15 (95% CI: [8.5%, 11.8%],  $Z = 4.7$ ,  $p = 2e-5$ ). All ages residents of the MDA + IRS arm enjoyed an overall 80.1% reduction (95% CI: [80.0%, 83.0%],  $p = 0.0001$ ) in odds of qPCR confirmed malaria compared with SOC residents. Secondary difference-in-difference analyses comparing surveys at different timepoints to baseline showed aOR (MDA + IRS vs IRS) of qPCR positivity between 0.28 and 0.66 ( $p < 0.001$ ). Of three serious adverse events, one (nonfatal) was considered related to study medications. Limitations include the initial non-random assignment of study arms, the single large cluster per arm, and the lack of an MDA-only arm, considered to violate equipoise.

**Conclusions:** Despite being assessed at long time points 5-7 months post-round, MDA plus IRS provided significant additional protection from malaria infection over IRS alone. Randomized trials of MDA in large areas undergoing IRS recommended as well as cohort studies of impact on incidence.

Malar J. 2023 Mar 23;22(1):106.

doi: 10.1186/s12936-022-04431-z.

### **Association between malaria and household air pollution interventions in a predominantly rural area of Ghana**

[Kwaku Poku Asante<sup>#1</sup>](#), [Blair J Wylie<sup>#2</sup>](#), [Felix B Oppong<sup>3</sup>](#), [Ashlinn Quinn<sup>4</sup>](#), [Stephaney Gyaase<sup>3</sup>](#), [Alison G Lee<sup>5</sup>](#), [Kenneth Ayuurebobi Ae-Ngibise<sup>3</sup>](#), [Katrin Burkart<sup>6</sup>](#), [Ellen Abrafi Boamah-Kaali<sup>3</sup>](#), [Seyram Kaali<sup>3</sup>](#), [Steven Chillrud<sup>7</sup>](#), [Patrick L Kinney<sup>#8</sup>](#), [Seth Owusu-Agyei<sup>9</sup>](#), [Darby Jack<sup>#10</sup>](#)

#### **Abstract**

**Background:** Though anecdotal evidence suggests that smoke from HAP has a repellent effect on mosquitoes, very little work has been done to assess the effect of biomass smoke on malaria infection. The study, therefore, sought to investigate the hypothesis that interventions to reduce household biomass smoke may have an unintended consequence of increasing placental malaria or increase malaria infection in the first year of life.

**Methods:** This provides evidence from a randomized controlled trial among 1414 maternal-infant pairs in the Kintampo North and Kintampo South administrative areas of Ghana. Logistic regression was used to assess the association between study intervention assignment (LPG, Biolite or control) and placental malaria. Finally, an extended Cox model

was used to assess the association between study interventions and all episodes of malaria parasitaemia in the first year of infant's life.

**Results:** The prevalence of placental malaria was 24.6%. Out of this, 20.8% were acute infections, 18.7% chronic infections and 60.5% past infections. The study found no statistical significant association between the study interventions and all types of placental malaria (OR = 0.88; 95% CI 0.59-1.30). Of the 1165 infants, 44.6% experienced at least one episode of malaria parasitaemia in the first year of life. The incidence of first and/or only episode of malaria parasitaemia was however found to be similar among the study arms.

**Conclusion:** The findings suggest that cookstove interventions for pregnant women and infants, when combined with additional malaria prevention strategies, do not lead to an increased risk of malaria among pregnant women and infants.

## Intermittent preventative treatment and seasonal malaria prophylaxis

Am J Trop Med Hyg. 2022 Aug 22;107(4):796-803.

doi: 10.4269/ajtmh.21-1218. Print 2022 Oct 12.

### [Overall and Gender-Specific Effects of Intermittent Preventive Treatment of Malaria with Artemisinin-Based Combination Therapies among Schoolchildren in Mali: A Three-Group Open Label Randomized Controlled Trial](#)

[Hamma Maiga<sup>1,2</sup>](#), [Charles Opondo<sup>3</sup>](#), [R Matthew Chico<sup>4</sup>](#), [Lauren M Cohee<sup>5</sup>](#), [Issaka Sagara<sup>2</sup>](#), [Oumar B Traore<sup>2</sup>](#), [Mamadou Tekete<sup>2</sup>](#), [Antoine Dara<sup>2</sup>](#), [Zoumana I Traore<sup>2</sup>](#), [Modibo Diarra<sup>2</sup>](#), [Samba Coumare<sup>2</sup>](#), [Aly Kodio<sup>2</sup>](#), [Amadou Bamadio<sup>2</sup>](#), [Bouran Sidibe<sup>2</sup>](#), [Ogobara K Doumbo<sup>2</sup>](#), [Abdoulaye A Djimde<sup>2</sup>](#)

#### **Abstract**

Intermittent preventive treatment of malaria among schoolchildren (IPTsc) reduces clinical malaria, asymptomatic parasitemia, and anemia. The effects of IPTsc by gender have not been studied longitudinally. We investigated overall IPTsc efficacy and conducted a secondary analysis to explore gender-specific differences. We enrolled schoolchildren aged 6-13 years in an open-label, rolling-cohort randomized controlled trial between September 2007 and February 2013 in Kollo, Mali. Annually, schoolchildren received two full-treatment courses of sulfadoxine-pyrimethamine (SP) plus artesunate, or amodiaquine (AQ) plus artesunate, or no malaria treatment as control. We used mixed-effects generalized linear models to estimate differences in treatment outcomes across groups with interaction terms to explore gender-specific differences associated with *Plasmodium falciparum* infection, hemoglobin, and grade point averages (GPA) based on standardized testing. Overall, 305 students contributed 4,564 observations. Compared with the control, SP plus artesunate and AQ plus artesunate reduced the odds of *P. falciparum* infection (odds ratio [OR]: 0.33, 95% CI: 0.26-0.43; OR: 0.46, 95% CI: 0.36-0.59). We found strong evidence of increased mean hemoglobin concentrations (g/dL) in the SP plus artesunate group versus control (difference +0.37, 95% CI: 0.13-0.58). Collectively, schoolchildren given AQ plus artesunate had higher mean GPA (difference +0.36, 95% CI: 0.02-0.69) relative to control. Schoolgirls, compared with schoolboys, given SP plus artesunate had greater improvement in GPA (+0.50, 95% CI: -

0.02 to 1.02 versus -0.27, 95% CI: -0.71 to 0.16); interaction P = 0.048, respectively. The IPTsc decreases *P. falciparum* infections in schoolchildren. Treatment regimens that include longer-acting drugs may be more effective at decreasing malaria-related anemia and improving educational outcomes as observed among girls in this setting.

Malar J. 2023 Jan 6;22(1):7.

doi: 10.1186/s12936-022-04428-8.

**[Implementation research of a cluster randomized trial evaluating the implementation and effectiveness of intermittent preventive treatment for malaria using dihydroartemisinin-piperazine on reducing malaria burden in school-aged children in Tanzania: methodology, challenges, and mitigation](#)**

[Geoffrey Makenga](#)<sup>1,2</sup>, [Misago D Seth](#)<sup>3</sup>, [Vito Baraka](#)<sup>3</sup>, [Bruno P Mmbando](#)<sup>3</sup>, [Daniel P Challe](#)<sup>3</sup>, [Filbert Francis](#)<sup>3</sup>, [Athanas Mhina](#)<sup>3</sup>, [Daniel T R Minja](#)<sup>3</sup>, [Mercy Chiduo](#)<sup>3</sup>, [Celine Mandara](#)<sup>3</sup>, [Edwin Liheluka](#)<sup>3</sup>, [Samwel Gesase](#)<sup>3</sup>, [Method Segeja](#)<sup>3</sup>, [George Mtove](#)<sup>3</sup>, [Mathias Kamugisha](#)<sup>3</sup>, [Abdallah Lusasi](#)<sup>4</sup>, [Frank Chacky](#)<sup>4,5</sup>, [Anna David](#)<sup>4</sup>, [Sumaiyya Thawer](#)<sup>6,7</sup>, [Ally Mohamed](#)<sup>4</sup>, [Samwel Lazaro](#)<sup>4</sup>, [Fabrizio Molteni](#)<sup>6,7</sup>, [Alex Nkayamba](#)<sup>8</sup>, [Jean-Pierre Van Geertruyden](#)<sup>5</sup>, [John P A Lusingu](#)<sup>3,9</sup>

**Abstract**

**Background:** It has been more than 20 years since the malaria epidemiologic shift to school-aged children was noted. In the meantime, school-aged children (5-15 years) have become increasingly more vulnerable with asymptomatic malaria prevalence reaching up to 70%, making them reservoirs for subsequent transmission of malaria in the endemic communities. Intermittent Preventive Treatment of malaria in schoolchildren (IPTsc) has proven to be an effective tool to shrink this reservoir. As of 3<sup>rd</sup> June 2022, the World Health Organization recommends IPTsc in moderate and high endemic areas. Even so, for decision-makers, the adoption of scientific research recommendations has been stifled by real-world implementation challenges. This study presents methodology, challenges faced, and mitigations used in the evaluation of the implementation of IPTsc using dihydroartemisinin-piperazine (DP) in three councils (Handeni District Council (DC), Handeni Town Council (TC) and Kilindi DC) of Tanga Region, Tanzania so as to understand the operational feasibility and effectiveness of IPTsc on malaria parasitaemia and clinical malaria incidence.

**Methods:** The study deployed an effectiveness-implementation hybrid design to assess feasibility and effectiveness of IPTsc using DP, the interventional drug, against standard of care (control). Wards in the three study councils were the randomization unit (clusters). Each ward was randomized to implement IPTsc or not (control). In all wards in the IPTsc arm, DP was given to schoolchildren three times a year in four-month intervals. In each council, 24 randomly selected wards (12 per study arm, one school per ward) were chosen as representatives for intervention impact evaluation. Mixed design methods were used to assess the feasibility and acceptability of implementing IPTsc as part of a more comprehensive health package for schoolchildren. The study reimaged an existing school health programme for Neglected Tropical Diseases (NTD) control include IPTsc implementation.

**Results:** The study shows IPTsc can feasibly be implemented by integrating it into existing school health and education systems, paving the way for sustainable programme adoption in a cost-effective manner.

**Conclusions:** Through this article other interested countries may realise a feasible plan for IPTsc implementation. Mitigation to any challenge can be customized based on local circumstances without jeopardising the gains expected from an IPTsc programme.

PLoS One. 2023 Feb 22;18(2):e0277789.

doi: 10.1371/journal.pone.0277789. eCollection 2023.

**Effects of anti-malarial prophylaxes on maternal transfer of Immunoglobulin-G (IgG) and association to immunity against Plasmodium falciparum infections among children in a Ugandan birth cohort**

Erick Jacob Okek<sup>1,2</sup>, Moses Ocan<sup>2,3</sup>, Sande James Obondo<sup>1</sup>, Anthony Kiyimba<sup>4</sup>, Emmanuel Arinaitwe<sup>2,4</sup>, Joaniter Nankabirwa<sup>2,4</sup>, Isaac Ssewanyana<sup>4,5</sup>, Moses Robert Kamywa<sup>2,4</sup>

**Abstract**

**Background:** The in-utero transfer of malaria specific IgG to the fetus in Plasmodium falciparum infected pregnant women potentially plays a role in provision of immune protection against malaria in the first birth year. However, the effect of Intermittent Prophylactic Treatment in Pregnancy (IPTp) and placental malaria on the extent of in-utero antibody transfer in malaria endemic regions like Uganda remain unknown. The aim of this study was thus to establish the effect of IPTp on in-utero transfer of malaria specific IgG to the fetus and the associated immune protection against malaria in the first birth year of children born to mothers who had P. falciparum infection during pregnancy in Uganda.

**Methods:** We screened a total of 637 cord blood samples from a double blinded randomized clinical trial on Sulfadoxine-Pyrimethamine (SP) and Dihydroartemisinin-Piperaquine (DP) IPTp in a Ugandan birth cohort; study conducted from Busia, Eastern Uganda. Luminex assay was used to measure the cord levels of IgG sub-types (IgG1, IgG2, IgG3 and IgG4) against 15 different P. falciparum specific antigens, with tetanus toxoid (t.t) as a control antigen. Mann-Whitney U test (non-parametric) in STATA (ver15) was used in statistical analysis of the samples. In addition, Multivariate cox regression analysis was used to determine the effect of maternal transfer of IgG on the incidence of malaria in the first birth year of children under study.

**Results:** Mothers on SP expressed higher levels of cord IgG4 against erythrocyte binding antigens (EBA140, EBA175 and EBA181) ( $p < 0.05$ ). Placental malaria did not affect cord levels of IgG sub-types against selected P. falciparum specific antigens ( $p > 0.05$ ). Children who expressed higher levels (75th percentile) of total IgG against the six key P. falciparum antigens (Pf SEA, Rh4.2, AMA1, GLURP, Etramp5Ag1 and EBA 175) had higher risk of malaria in the first birth year; AHRs: 1.092, 95% CI: 1.02-1.17 (Rh4.2); 1.32, 95% CI: 1.00-1.74 (PfSEA); 1.21, 95%CI: 0.97-1.52 (Etramp5Ag1); 1.25, 95%CI: 0.98-1.60 (AMA1); 1.83, 95%CI: 1.15-2.93 (GLURP) (GLURP), and 1.35,; 95%CI: 1.03-1.78 (EBA175). Children born to mothers categorized as poorest had the highest risk of malaria infections in the first birth year (AHR: 1.79, 95% CI: 1.31-2.4). Children born to mothers who had malaria infections during gestation had higher risk of getting malaria in the first birth year (AHR 1.30; 95%CI: 0.97-1.7).

**Conclusion:** Malaria prophylaxis in pregnant mothers using either DP or SP does not affect expression of antibodies against P. falciparum specific antigens in the cord blood. Poverty and malaria infections during pregnancy are key risk factors of malaria infections in the first birth year of growth of children. Antibodies against P. falciparum specific antigens does not protect against parasitemia and malaria infections in the first birth year of children born in malaria endemic areas.

Malar J. 2023 Feb 22;22(1):63.

doi: 10.1186/s12936-023-04488-4.

**[A non-randomized controlled trial to assess the protective effect of SMC in the context of high parasite resistance in Uganda](#)**

[Anthony Nuwa](#)<sup>1</sup>, [Kevin Baker](#)<sup>2,3</sup>, [Craig Bonnington](#)<sup>2</sup>, [Musa Odongo](#)<sup>4</sup>, [Tonny Kyagulanyi](#)<sup>4</sup>, [John Baptist Bwanika](#)<sup>4</sup>, [Sol Richardson](#)<sup>2,5</sup>, [Jane Nabakooza](#)<sup>6</sup>, [Jane Achan](#)<sup>2</sup>, [Richard Kajubi](#)<sup>4</sup>, [David Salandini Odong](#)<sup>4</sup>, [Maureen Nakirunda](#)<sup>4</sup>, [Godfrey Magumba](#)<sup>4</sup>, [Geofrey Beinomugisha](#)<sup>4</sup>, [Madeleine Marasciulo-Rice](#)<sup>2</sup>, [Hilda Abio](#)<sup>4</sup>, [Christian Rassi](#)<sup>2</sup>, [Damian Rutazaana](#)<sup>6</sup>, [Denis Rubahika](#)<sup>6</sup>, [James Tibenderana](#)<sup>2</sup>, [Jimmy Opigo](#)<sup>6</sup>

**Abstract**

**Background:** Until recently, due to widespread prevalence of molecular markers associated with sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) resistance in east and southern Africa, seasonal malaria chemoprevention (SMC) has not been used at scale in this region. This study assessed the protective effectiveness of monthly administration of SP + AQ (SPAQ) to children aged 3-59 months in Karamoja sub-region, Uganda, where parasite resistance is assumed to be high and malaria transmission is seasonal.

**Methods:** A two-arm quasi-experimental, open-label prospective non-randomized control trial (nRCT) was conducted in three districts. In two intervention districts, 85,000 children aged 3-59 months were targeted to receive monthly courses of SMC using SPAQ during the peak transmission season (May to September) 2021. A third district served as a control, where SMC was not implemented. Communities with comparable malaria attack rates were selected from the three districts, and households with at least one SMC-eligible child were purposively selected. A total cohort of 600 children (200 children per district) were selected and followed using passive surveillance for breakthrough confirmed malaria episodes during the five-month peak transmission season. Malaria incidence rate per person-months and number of malaria episodes among children in the two arms were compared. Kaplan-Meier failure estimates were used to compare the probability of a positive malaria test. Other factors that may influence malaria transmission and infection among children in the two arms were also assessed using multivariable cox proportional hazards regression model.

**Results:** The malaria incidence rate was 3.0 and 38.8 per 100 person-months in the intervention and control groups, respectively. In the intervention areas 90.0% (361/400) of children did not experience any malaria episodes during the study period, compared to 15% (29/200) in the control area. The incidence rate ratio was 0.078 (95% CI 0.063-0.096), which corresponds to a protective effectiveness of 92% (95% CI 90.0-94.0) among children in the intervention area.

**Conclusion:** SMC using SPAQ provided high protective effect against malaria during the peak transmission season in children aged 3-59 months in the Karamoja sub-region of Uganda.

CPT Pharmacometrics Syst Pharmacol. 2023 May;12(5):656-667.

doi: 10.1002/psp4.12892. Epub 2023 Mar 14.

**[Interplay among malnutrition, chemoprevention, and the risk of malaria in young Ugandan children: Longitudinal pharmacodynamic and growth analysis](#)**

[Ali Mohamed Ali](#)<sup>1,2</sup>, [Erika Wallender](#)<sup>3</sup>, [Emma Hughes](#)<sup>1</sup>, [Grant Dorsey](#)<sup>4</sup>, [Radojka M Savic](#)<sup>1</sup>



## Abstract

African children are at risk of malaria and malnutrition. We quantified relationships between malaria and malnutrition among young Ugandan children in a high malaria transmission region. Data were used from a randomized controlled trial where Ugandan HIV-unexposed (n = 393) and HIV-exposed (n = 186) children were randomized to receive no malaria chemoprevention, monthly sulfadoxine-pyrimethamine, daily trimethoprim-sulfamethoxazole, or monthly dihydroartemisinin-piperaquine (DP) from age 6-24 months, and then were followed off chemoprevention until age 36 months. Monthly height and weight, and time of incident malaria episodes were obtained; 89 children who received DP contributed piperaquine (PQ) concentrations. Malaria hazard was modeled using parametric survival analysis adjusted for repeated events, and height and weight were modeled using a Brody growth model. Among 579 children, stunting (height-for-age z-score [ZHA] < -2) was associated with a 17% increased malaria hazard (95% confidence interval [CI] 10-23%) compared with children with a ZHA of zero. DP was associated with a 35% lower malaria hazard (hazard ratio [HR] [95% CI], 0.65 [0.41-0.97]), compared to no chemoprevention. After accounting for PQ levels, stunted children who received DP had 2.1 times the hazard of malaria (HR [95% CI] 2.1 [1.6-3.0]) compared with children with a ZHA of zero who received DP. Each additional malaria episode was associated with a 0.4% reduced growth rate for height. Better dosing regimens are needed to optimize malaria prevention in malnourished populations, but, importantly, malaria chemoprevention may reduce the burden of malnutrition in early childhood.

## Treatment of uncomplicated malaria

Lancet Infect Dis. 2023 Apr;23(4):471-483.

doi: 10.1016/S1473-3099(22)00658-2. Epub 2022 Nov 30.

[Safety of age-dosed, single low-dose primaquine in children with glucose-6-phosphate dehydrogenase deficiency who are infected with Plasmodium falciparum in Uganda and the Democratic Republic of the Congo: a randomised, double-blind, placebo-controlled, non-inferiority trial](#)

[Walter R Taylor<sup>1</sup>](#), [Peter Olupot-Olupot<sup>2</sup>](#), [Marie A Onyamboko<sup>3</sup>](#), [Pimnara Peerawaranun<sup>4</sup>](#), [Winifred Weere<sup>5</sup>](#), [Cate Namayanja<sup>5</sup>](#), [Peter Onyas<sup>5</sup>](#), [Harriet Titin<sup>5</sup>](#), [Joy Baseke<sup>6</sup>](#), [Rita Muhindo<sup>5</sup>](#), [Daddy K Kayembe<sup>3</sup>](#), [Pauline O Ndjowo<sup>3</sup>](#), [Benjamin B Basara<sup>3</sup>](#), [Georgette S Bongo<sup>3</sup>](#), [Charles B Okalebo<sup>5</sup>](#), [Grace Abongo<sup>5</sup>](#), [Sophie Uyoga<sup>7</sup>](#), [Thomas N Williams<sup>8</sup>](#), [Chiraporn Taya<sup>4</sup>](#), [Mehul Dhorda<sup>9</sup>](#), [Joel Tarning<sup>9</sup>](#), [Arjen M Dondorp<sup>9</sup>](#), [Naomi Waithira<sup>9</sup>](#), [Caterina Fanello<sup>9</sup>](#), [Kathryn Maitland<sup>8</sup>](#), [Mavuto Mukaka<sup>9</sup>](#), [Nicholas J P Day<sup>9</sup>](#)

## Abstract

**Background:** WHO recommends gametocytocidal, single low-dose primaquine for blocking the transmission of Plasmodium falciparum; however, safety concerns have hampered the implementation of this strategy in sub-Saharan Africa. We aimed to investigate the safety of age-dosed, single low-dose primaquine in children from Uganda and the Democratic Republic of the Congo.

**Methods:** We conducted this randomised, double-blind, placebo-controlled, non-inferiority trial at the Mbale Regional Referral Hospital, Mbale, Uganda, and the Kinshasa Mahidol

Oxford Research Unit, Kinshasa, Democratic Republic of the Congo. Children aged between 6 months and 11 years with acute uncomplicated *P falciparum* infection and haemoglobin concentrations of at least 6 g/dL were enrolled. Patients were excluded if they had a comorbid illness requiring inpatient treatment, were taking haemolysing drugs for glucose-6-phosphate dehydrogenase (G6PD) deficiency, were allergic to the study drugs, or were enrolled in another clinical trial. G6PD status was defined by genotyping for the G6PD c.202T allele, the cause of the G6PD-deficient A- variant. Participants were randomly assigned (1:1) to receive single low-dose primaquine combined with either artemether-lumefantrine or dihydroartemisinin-piperaquine, dosed by bodyweight. Randomisation was stratified by age and G6PD status. The primary endpoint was the development of profound (haemoglobin <4 g/dL) or severe (haemoglobin <5 g/dL) anaemia with severity features, within 21 days of treatment. Analysis was by intention to treat. The sample size assumed an incidence of 1.5% in the placebo group and a 3% non-inferiority margin. The trial is registered at ISRCTN, 11594437, and is closed to new participants.

**Findings:** Participants were recruited at the Mbale Regional Referral Hospital between Dec 18, 2017, and Oct 7, 2019, and at the Kinshasa Mahidol Oxford Research Unit between July 17, 2017, and Oct 5, 2019. 4620 patients were assessed for eligibility. 3483 participants were excluded, most owing to negative rapid diagnostic test or negative malaria slide (n=2982). 1137 children with a median age of 5 years were enrolled and randomly assigned (286 to the artemether-lumefantrine plus single low-dose primaquine group, 286 to the artemether-lumefantrine plus placebo group, 283 to the dihydroartemisinin-piperaquine plus single low-dose primaquine group, and 282 to the dihydroartemisinin-piperaquine plus placebo group). Genotyping of G6PD identified 239 G6PD-c.202T hemizygous males and 45 G6PD-c.202T homozygous females (defining the G6PD-deficient group), 119 heterozygous females, 418 G6PD-c.202C normal males and 299 G6PD-c.202C normal females (defining the non-G6PD-deficient group), and 17 children of unknown status. 67 patients were lost to follow-up and four patients withdrew during the study-these numbers were similar between groups. No participants developed profound anaemia and three developed severe anaemia: from the G6PD-deficient group, none (0%) of 133 patients who received placebo and one (0.66%) of 151 patients who received primaquine (difference -0.66%, 95% CI -1.96 to 0.63; p=0.35); and from the non-G6PD-deficient group, one (0.23%) of 430 patients who received placebo and one (0.25%) of 407 patients who received primaquine (-0.014%, -0.68 to 0.65; p=0.97).

**Interpretation:** Gametocytocidal, age-dosed, single low-dose primaquine was well tolerated in children from Uganda and the Democratic Republic of the Congo who were infected with *P falciparum*, and the safety profile of this treatment was similar to that of the placebo. These data support the wider implementation of single low-dose primaquine in Africa.

Malar J. 2023 May 13;22(1):154.

doi: 10.1186/s12936-023-04574-7.

[Efficacy and safety of pyronaridine-artesunate versus artemether-lumefantrine in the treatment of acute uncomplicated malaria in children in South-West Nigeria: an open-labelled randomized controlled trial](#)

[Catherine O Falade](#)<sup>1,2</sup>, [Adebola E Orimadegun](#)<sup>3</sup>, [Fiyinfoluwa I Olusola](#)<sup>4</sup>, [Obaro S Michael](#)<sup>4</sup>, [Oluwafunmibi E Anjorin](#)<sup>5</sup>, [Roland I Funwei](#)<sup>6</sup>, [Aduragbenro D Adedapo](#)<sup>4</sup>, [Abiola L Olusanya](#)<sup>7</sup>, [Bose E Orimadegun](#)<sup>8</sup>, [Olugbenga A Mokuolu](#)<sup>9</sup>

**Abstract**

**Background:** In Nigeria, declining responsiveness to artemether-lumefantrine (AL), the artemisinin-based combination therapy (ACT) of choice since 2005, has been reported. Pyronaridine-artesunate (PA) is a newer fixed-dose ACT recently prequalified by the WHO for the treatment of uncomplicated falciparum malaria. However, PA data from the Nigerian pediatric population is scarce. Therefore, the efficacy and safety of PA and AL using the WHO 28-day anti-malarial therapeutic efficacy study protocol in Ibadan, southwest Nigeria, were compared.

**Methods:** In an open-labelled, randomized, controlled clinical trial, 172 children aged 3-144 months with a history of fever and microscopically confirmed uncomplicated *Plasmodium falciparum* malaria were enrolled in southwest Nigeria. Enrollees were randomly assigned to receive PA or AL at standard dosages according to body weight for 3 days. Venous blood was obtained for hematology, blood chemistry, and liver function tests on days 0, 3, 7, and 28 as part of the safety evaluation.

**Results:** 165 (95.9%) of the enrolled individuals completed the study. About half (52.3%; 90/172) of enrollees were male. Eighty-seven (50.6%) received AL, while 85 (49.4%) received PA. Day 28, adequate clinical and parasitological response for PA was 92.7% [(76/82) 95% CI 83.1, 95.9] and 71.1% [(59/83) 95% CI 60.4, 79.9] for AL (0.001). Fever and parasite clearance were similar in both groups. Two of six and eight of 24 parasite recurrences were observed among PA- and AL-treated children, respectively. PCR-corrected Day-28 cure rates for PA were 97.4% (76/78) and 88.1% (59/67) for AL (= 0.04) in the per-protocol population after new infections were censored. Hematological recovery at day 28 was significantly better among PA-treated patients (34.9% 2.8) compared to those treated with AL (33.1% 3.0) (0.002). Adverse events in both treatment arms were mild and similar to the symptoms of malaria infection. Blood chemistry and liver function tests were mostly within normal limits, with an occasional marginal rise.

**Conclusion:** PA and AL were well-tolerated. PA was significantly more efficacious than AL in both the PCR-uncorrected and PCR-corrected per-protocol populations during this study. The results of this study support the inclusion of PA in the anti-malarial treatment guidelines in Nigeria.

Clin Infect Dis. 2023 Feb 8;76(3):443-452.

doi: 10.1093/cid/ciac783.

**[The Impact of Extended Treatment With Artemether-lumefantrine on Antimalarial Exposure and Reinfection Risks in Ugandan Children With Uncomplicated Malaria: A Randomized Controlled Trial](#)**

[Meghan E Whalen](#)<sup>1</sup>, [Richard Kajubi](#)<sup>2</sup>, [Justin Goodwin](#)<sup>3</sup>, [Francis Orukan](#)<sup>2</sup>, [McKenzie Colt](#)<sup>3</sup>, [Liusheng Huang](#)<sup>1</sup>, [Kacey Richards](#)<sup>3</sup>, [Kaicheng Wang](#)<sup>3</sup>, [Fangyong Li](#)<sup>3</sup>, [Norah Mwebaza](#)<sup>2,4</sup>, [Francesca T Aweeka](#)<sup>1</sup>, [Sunil Parikh](#)<sup>3</sup>

**Abstract**

**Background:** Artemether-lumefantrine (AL) is the most widely used artemisinin-based combination therapy in Sub-Saharan Africa and is threatened by the emergence of artemisinin resistance. Dosing is suboptimal in young children. We hypothesized that extending AL duration will improve exposure and reduce reinfection risks.

**Methods:** We conducted a prospective, randomized, open-label pharmacokinetic/pharmacodynamic study of extended duration AL in children with malaria

in high-transmission rural Uganda. Children received 3-day (standard 6-dose) or 5-day (10-dose) AL with sampling for artemether, dihydroartemisinin, and lumefantrine over 42-day clinical follow-up. Primary outcomes were (1) comparative pharmacokinetic parameters between regimens and (2) recurrent parasitemia analyzed as intention-to-treat.

**Results:** A total of 177 children aged 16 months to 16 years were randomized, contributing 227 total episodes. Terminal median lumefantrine concentrations were significantly increased in the 5-day versus 3-day regimen on days 7, 14, and 21 ( $P < .001$ ). A predefined day 7 lumefantrine threshold of 280 ng/mL was strongly predictive of recurrence risk at 28 and 42 days ( $P < .001$ ). Kaplan-Meier estimated 28-day (51% vs 40%) and 42-day risk (75% vs 68%) did not significantly differ between 3- and 5-day regimens. No significant toxicity was seen with the extended regimen.

**Conclusions:** Extending the duration of AL was safe and significantly enhanced overall drug exposure in young children but did not lead to significant reductions in recurrent parasitemia risk in our high-transmission setting. However, day 7 levels were strongly predictive of recurrent parasitemia risk, and those in the lowest weight-band were at higher risk of underdosing with the standard 3-day regimen.

Malar J. 2022 Nov 14;21(1):331.

doi: 10.1186/s12936-022-04369-2.

**[Comparative effect of artemether-lumefantrine and artesunate-amodiaquine on gametocyte clearance in children with uncomplicated Plasmodium falciparum malaria in Madagascar](#)**

[Malalanandrianina A Rakotoarisoa](#)<sup>1</sup>, [Jocia Fenomanana](#)<sup>2</sup>, [Bronislaw Tchesterico Dodoson](#)<sup>3</sup>, [Voahangy Hanitriniaina I Andrianaranjaka](#)<sup>4</sup>, [Arsène Ratsimbaoa](#)<sup>3</sup>

**Abstract**

**Background:** Gametocytes are the sexual stages ensuring continuity of the development cycle of the parasite, as well as its transmission to humans. The efficacy of artemisinin-based anti-malarials against asexual stages of Plasmodium has been reported in Madagascar, but their effects on gametocytes are not well documented. The present study aims to determine the emergence of gametocyte and gametocyte clearance after artesunate-amodiaquine (ASAQ) or artemether-lumefantrine (AL) treatment in children with uncomplicated Plasmodium falciparum malaria in 5 regions of Madagascar.

**Methods:** 558 children with uncomplicated P. falciparum malaria, aged between 1 and 15 years, were assigned randomly to AL or ASAQ treatment. They come from 5 regions of Madagascar with different epidemiological facies related to malaria: Ankilivalo, Benenitra, Ampanihy, Ankazomborona and Matanga. Gametocytes were identified by microscopy, from t blood smears at day 1, day 2, day 3, day 7, day 14, day 21 and day 28 after treatment.

**Results:** At baseline, 9.7% (54/558) children [95% CI: 7.4-12.5%] had detectable gametocyte by microscopy. Among the 54 enrolled children, gametocytes emergence rate was high during the first days of treatment in both treatment arms (AL and ASAQ), especially on day 1. Gametocytes were undetectable from day 14 for AL arm while for ASAQ arm, gametocyte carriage was gradually decreased but persisted until day 21.

**Conclusion:** This study demonstrates that AL has a more rapid effect on gametocyte clearance compared to ASAQ in children with uncomplicated Plasmodium falciparum malaria.

Int J Infect Dis. 2023 May;130:189-195.

doi: 10.1016/j.ijid.2023.03.010. Epub 2023 Mar 9.

**Ultra-short course, high-dose primaquine to prevent Plasmodium vivax infection following uncomplicated pediatric malaria: A randomized, open-label, non-inferiority trial of early versus delayed treatment**

[Sze-Ann Woon<sup>1</sup>](#), [Brioni R Moore<sup>2</sup>](#), [Moses Laman<sup>3</sup>](#), [Paula Tesine<sup>3</sup>](#), [Lina Lorry<sup>3</sup>](#), [Bernadine Kasian<sup>3</sup>](#), [Phantica Yambo<sup>3</sup>](#), [Gumul Yadi<sup>3</sup>](#), [William Pomat<sup>3</sup>](#), [Kevin T Batty<sup>4</sup>](#), [Sam Salman<sup>5</sup>](#), [Leanne J Robinson<sup>6</sup>](#), [Timothy M E Davis<sup>7</sup>](#), [Laurens Manning<sup>8</sup>](#)

**Abstract**

**Objectives:** We aimed to assess safety, tolerability, and Plasmodium vivax relapse rates of ultra-short course (3.5 days) high-dose (1 mg/kg twice daily) primaquine (PQ) for uncomplicated malaria because of any Plasmodium species in children randomized to early- or delayed treatment.

**Methods:** Children aged 0.5 to 12 years with normal glucose-6-phosphate-dehydrogenase (G6PD) activity were enrolled. After artemether-lumefantrine (AL) treatment, children were randomized to receive PQ immediately after (early) or 21 days later (delayed). Primary and secondary endpoints were the appearance of any P. vivax parasitemia within 42 or 84 days, respectively. A non-inferiority margin of 15% was applied (ACTRN12620000855921).

**Results:** A total of 219 children were recruited, 70% with Plasmodium falciparum and 24% with P. vivax. Abdominal pain (3.7% vs 20.9%, P <0.0001) and vomiting (0.9% vs 9.1%, P = 0.01) were more common in the early group. At day 42, P. vivax parasitemia was observed in 14 (13.2%) and 8 (7.8%) in the early and delayed groups, respectively (difference, -5.4%; 95% confidence interval -13.7 to 2.8). At day 84, P. vivax parasitemia was observed in 36 (34.3%) and 17 (17.5%; difference -16.8%, -28.6 to -6.1).

**Conclusion:** Ultra-short high-dose PQ was safe and tolerated without severe adverse events. Early treatment was non-inferior to delayed treatment in preventing P. vivax infection at day 42.

## Community based malaria testing and management

BMC Med. 2022 Oct 4;20(1):322.

doi: 10.1186/s12916-022-02530-x.

**Proactive community case management decreased malaria prevalence in rural Madagascar: results from a cluster randomized trial**

[Rila Ratovoson<sup>#1</sup>](#), [Andres Garchitorena<sup>#2,3</sup>](#), [Daouda Kassie<sup>2,4</sup>](#), [Jemima A Ravelonarivo<sup>5,6</sup>](#), [Voahangy Andrianaranjaka<sup>5,7</sup>](#), [Seheno Razanatsiorimalala<sup>5</sup>](#), [Avotra Razafimandimby<sup>2</sup>](#), [Fanjasoa Rakotomanana<sup>2</sup>](#), [Laurie Ohlstein<sup>8</sup>](#), [Reziky Mangahasimbola<sup>2</sup>](#), [Sandro A N Randrianirisoa<sup>2</sup>](#), [Jocelyn Razafindrakoto<sup>9</sup>](#), [Catherine M Dentinger<sup>10,11</sup>](#), [John Williamson<sup>10</sup>](#), [Laurent Kapesa<sup>9</sup>](#), [Patrice Piola<sup>12</sup>](#), [Milijaona Randrianariveojosia<sup>5,13</sup>](#), [Julie Thwing<sup>10</sup>](#), [Laura C Steinhardt<sup>10</sup>](#), [Laurence Baril<sup>2</sup>](#)

**Abstract**

**Background:** Malaria remains a leading cause of morbidity and mortality worldwide, with progress in malaria control stalling in recent years. Proactive community case management (pro-CCM) has been shown to increase access to diagnosis and treatment and reduce malaria



burden. However, lack of experimental evidence may hinder the wider adoption of this intervention. We conducted a cluster randomized community intervention trial to assess the efficacy of pro-CCM at decreasing malaria prevalence in rural endemic areas of Madagascar.

**Methods:** Twenty-two fokontany (smallest administrative unit) of the Mananjary district in southeast Madagascar were selected and randomized 1:1 to pro-CCM (intervention) or conventional integrated community case management (iCCM). Residents of all ages in the intervention arm were visited by a community health worker every 2 weeks from March to October 2017 and screened for fever; those with fever were tested by a rapid diagnostic test (RDT) and treated if positive. Malaria prevalence was assessed using RDTs on all consenting study area residents prior to and following the intervention. Hemoglobin was measured among women of reproductive age. Intervention impact was assessed via difference-in-differences analyses using logistic regressions in generalized estimating equations.

**Results:** A total of 27,087 and 20,475 individuals participated at baseline and endline, respectively. Malaria prevalence decreased from 8.0 to 5.4% in the intervention arm for individuals of all ages and from 6.8 to 5.7% in the control arm. Pro-CCM was associated with a significant reduction in the odds of malaria positivity in children less than 15 years (OR = 0.59; 95% CI [0.38-0.91]), but not in older age groups. There was no impact on anemia among women of reproductive age.

**Conclusion:** This trial suggests that pro-CCM approaches could help reduce malaria burden in rural endemic areas of low- and middle-income countries, but their impact may be limited to younger age groups with the highest malaria burden.

BMJ Open. 2023 Jun 26;13(6):e070482.

doi: 10.1136/bmjopen-2022-070482.

[\*\*Supply-side and demand-side factors influencing uptake of malaria testing services in the community: lessons for scale-up from a post-hoc analysis of a cluster randomised, community-based trial in western Kenya\*\*](#)

[Joseph Kirui<sup>1</sup>](#), [Josephine Malinga<sup>2</sup>](#), [Edna Sang<sup>3</sup>](#), [George Ambani<sup>4</sup>](#), [Lucy Abel<sup>4</sup>](#), [Erick Nalianya<sup>3</sup>](#), [Jane Namae<sup>5</sup>](#), [Matthew Boyce<sup>6</sup>](#), [Jeremiah Laktabai<sup>4,5</sup>](#), [Diana Menya<sup>7</sup>](#), [Wendy O'Meara<sup>2,7</sup>](#)

**Abstract**

**Objectives:** Maximising the impact of community-based programmes requires understanding how supply of, and demand for, the intervention interact at the point of delivery.

**Design:** Post-hoc analysis from a large-scale community health worker (CHW) study designed to increase the uptake of malaria diagnostic testing.

**Setting:** Respondents were identified during a household survey in western Kenya between July 2016 and April 2017.

**Participants:** Household members with fever in the last 4 weeks were interviewed at 12 and 18 months post-implementation. We collected monthly testing data from 244 participating CHWs and conducted semistructured interviews with a random sample of 70 CHWs.

**Primary and secondary outcome measures:** The primary outcome measure was diagnostic testing before treatment for a recent fever. The secondary outcomes were receiving a test from a CHW and tests done per month by each CHW.

**Results:** 55% (n=948 of 1738) reported having a malaria diagnostic test for their recent illness, of which 38.4% were tested by a CHW. Being aware of a local CHW (adjusted OR=1.50,



95% CI: 1.10 to 2.04) and belonging to the wealthiest households (vs least wealthy) were associated with higher testing (adjusted OR=1.53, 95% CI: 1.14 to 2.06). Wealthier households were *less* likely to receive their test from a CHW compared with poorer households (adjusted OR=0.32, 95% CI: 0.17 to 0.62). Confidence in artemether-lumefantrine to cure malaria (adjusted OR=2.75, 95% CI: 1.54 to 4.92) and perceived accuracy of a malaria rapid diagnostic test (adjusted OR=2.43, 95% CI: 1.12 to 5.27) were positively associated with testing by a CHW. Specific CHW attributes were associated with performing a higher monthly number of tests including formal employment, serving more than 50 households (vs <50) and serving areas with a higher test positivity. On demand side, confidence of the respondent in a test performed by a CHW was strongly associated with seeking a test from a CHW.

**Conclusion:** Scale-up of community-based malaria testing is feasible and effective in increasing uptake among the poorest households. To maximise impact, it is important to recognise factors that may restrict delivery and demand for such services.

## Treatment of severe malaria

Malar J. 2022 Sep 7;21(1):259.

doi: 10.1186/s12936-022-04279-3.

### [Efficacy of three anti-malarial regimens for uncomplicated Plasmodium falciparum malaria in Cambodia, 2009-2011: a randomized controlled trial and brief review](#)

[Dysoley Lek](#)<sup>1</sup>, [Agus Rachmat](#)<sup>2</sup>, [Dustin Harrison](#)<sup>2</sup>, [Geoffrey Chin](#)<sup>3</sup>, [Suwanna Chaoratanakawee](#)<sup>4</sup>, [David Saunders](#)<sup>3</sup>, [Didier Menard](#)<sup>5</sup>, [William O Rogers](#)<sup>2</sup>

#### Abstract

**Background:** Anti-malarial resistance remains an important public health challenge in Cambodia. The effectiveness of three therapies for uncomplicated falciparum malaria was evaluated in Oddar Meanchey province in Northern Cambodia from 2009 to 2011.

**Methods:** In this randomized, open-label, parallel group-controlled trial, 211 subjects at least 5 years old with uncomplicated falciparum malaria were treated with 3 days of directly observed therapy: 63 received artesunate-mefloquine (AS/MQ), 77 received dihydroartemisinin-piperaquine (DHA/PPQ), and 71 received atovaquone-proguanil (ATQ/PG). The subjects were followed for 42 days or until recurrent parasitaemia.

Genotyping of msp1, msp2, and glurp among individual parasite isolates distinguished recrudescence from reinfection. Pfmdr1 copy number was measured by real-time PCR and half-maximal parasite inhibitory concentrations (IC<sub>50</sub>) were measured in vitro by 48-h isotopic hypoxanthine incorporation assay.

**Results:** The per-protocol PCR-adjusted efficacy (95% confidence interval) at 42 days was 80.6% (70.8-90.5%) for AS/MQ, 97.2% (93.3-100%) for DHA/PPQ, and 92.9% (86.1-99.6%) for ATQ/PG. On day 3, 57.9% remained parasitaemic in the AS/MQ and DHA/PPQ arms. At baseline, 46.9% had microscopic Plasmodium falciparum gametocytaemia. Both recurrences in the DHA/PPQ arm lost Pfmdr1 copy number amplification at recrudescence. All four recurrences in the ATQ/PG arm were wild-type for cytochrome bc<sub>1</sub>. One subject withdrew from the ATQ/PG arm due to drug allergy.

**Conclusions:** This study was conducted at the epicentre of substantial multi-drug resistance that emerged soon thereafter. Occurring early in the national transition from AS/MQ to DHA/PPQ, both DHA/PPQ and ATQ/PG had acceptable efficacy against uncomplicated

falciparum malaria. However, efficacy of AS/MQ was only 80% with apparent mefloquine resistance based on elevated Pfmdr1 copy number and IC<sub>50</sub>. By 2009, there was already significant evidence of artemisinin resistance not previously reported at the Northern Cambodia–Thai border. This study suggests the basis for early development of significant DHA/PPQ failures within 3 years of introduction. Artemisinin resistance likely occurred on the Northern border concurrently with that reported along the Western border in Pailin. Trial registration This legacy trial was conducted prior to International Committee of Medical Journal Editors' requirements for preregistration on ClinicalTrials.gov. The full protocol has been provided.

## Malaria and comorbidities

Am J Trop Med Hyg. 2023 Jan 9;108(3):561-568.

doi: 10.4269/ajtmh.22-0573. Print 2023 Mar 1.

### [The Association between Malnutrition and Malaria Infection in Children under 5 Years in Burkina Faso: A Longitudinal Study](#)

[Elisabeth Gebreegziabher](#)<sup>1</sup>, [Clarisse Dah](#)<sup>2</sup>, [Boubacar Coulibaly](#)<sup>2</sup>, [Ali Sie](#)<sup>2</sup>, [Mamadou Bountogo](#)<sup>2</sup>, [Mamadou Ouattara](#)<sup>2</sup>, [Adama Compaoré](#)<sup>2</sup>, [Moustapha Nikiema](#)<sup>2</sup>, [Jérôme Tiansi](#)<sup>2</sup>, [Nestor Dembélé](#)<sup>2</sup>, [Elodie Lebas](#)<sup>1</sup>, [Michelle Roh](#)<sup>3</sup>, [David V Glidden](#)<sup>3</sup>, [Benjamin F Arnold](#)<sup>1,4</sup>, [Thomas M Lietman](#)<sup>1,4</sup>, [Catherine E Oldenburg](#)<sup>1,3,4</sup>

#### **Abstract**

The relationship between malaria infection and malnutrition is complex. Using data from a randomized controlled trial of 450 children 0-5 years of age in Burkina Faso, we examined the effect of malaria infection on short-term changes in anthropometric measures, the effect of malnutrition on malaria infection, and whether age modified the effect of baseline anthropometric measures on malaria infection. Malaria infection, assessed by blood smear microscopy and weight, height, mid-upper arm circumference, height-for-age z-score, weight-for-age z-score, and weight-for-height z-score were measured at three time points: baseline, 2 weeks, and 6 months. We used generalized estimating equations adjusted for sex, age, breastfeeding, maternal education, and study treatment (azithromycin versus placebo) for all analyses. Interaction terms were used to assess effect modification by age. Among the 366 children with no malaria infection at baseline, 43 (11.6%) had malaria infection within 6 months. There were no important differences in anthropometric measures at 2 weeks and 6 months between those with and without malaria infection at baseline. There were no significant differences in prevalence of malaria infection by baseline anthropometric measures. Age (0-30 months versus 30-60 months) modified the effect of baseline weight and height on malaria infection. Among those aged 0-30 months, for each kilogram increase in weight, malaria infection increased by 27% (95% CI: 6-53%), and for each centimeter increase in height, it increased by 9% (95% CI: 1-17%), but there were no differences for those aged 30-60 months.

## 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)

EClinicalMedicine. 2023 Feb 28;58:101878.

doi: 10.1016/j.eclinm.2023.101878. eCollection 2023 Apr.

### [Optimising the dosage of ready-to-use therapeutic food in children with uncomplicated severe acute malnutrition in the Democratic Republic of the Congo: a non-inferiority, randomised controlled trial](#)

[Cécile Cazes](#)<sup>1</sup>, [Kevin Phelan](#)<sup>2</sup>, [Victoire Hubert](#)<sup>3</sup>, [Harouna Boubacar](#)<sup>3</sup>, [Liévin Izie Bozama](#)<sup>4</sup>, [Gilbert Tshibangu Sakubu](#)<sup>5</sup>, [Bruno Bindamba Senge](#)<sup>4</sup>, [Norbert Baya](#)<sup>4</sup>, [Rodrigue Alitanou](#)<sup>3</sup>, [Antoine Kouamé](#)<sup>6</sup>, [Cyrille Yao](#)<sup>6</sup>, [Delphine Gabillard](#)<sup>1</sup>, [Maguy Daures](#)<sup>1</sup>, [Augustin Augier](#)<sup>2</sup>, [Xavier Anglaret](#)<sup>1</sup>, [Moumouni Kinda](#)<sup>7</sup>, [Susan Shepherd](#)<sup>7</sup>, [Renaud Becquet](#)<sup>1</sup>

#### Abstract

**Background:** Current standard management of severe acute malnutrition uses ready-to-use therapeutic food (RUTF) at a single weight-based calculation resulting in an increasing amount of RUTF provided to the family as the child's weight increases during recovery. Using RUTF at a gradually reduced dosage as the child recovers could reduce costs while achieving similar growth response.

**Methods:** We conducted an open-label, non-inferiority, randomised controlled trial in the Democratic Republic of the Congo. Children aged 6-59 months with a mid-upper-arm circumference (MUAC) of less than 115 mm or a weight-for-height z-score (WHZ) of less than -3 or bipedal oedema and without medical complication were randomly assigned (1:1 ratio) using a specially developed software and random blocks (size was kept confidential), to either the current standard treatment (increasing the RUTF amount with increasing weight) or the OptiMA strategy (decreasing the RUTF dose with increasing weight and MUAC). The main endpoint was proportion of children who achieved recovery over the 6 months follow up period, as defined as meeting the following criteria for two consecutive weeks after a minimum of 4 weeks' treatment: axillary temperature less than 37.5 °C, no bipedal oedema, and anthropometric improvement (either MUAC 125 mm or greater or WHZ -1.5 or higher). We performed analyses on the intention-to-treat (ITT) (all children) and per-protocol populations (participants who had a minimum prescription of 4 weeks' RUTF, received at least 90% of the total amount of RUTF they were supposed to receive as per the protocol, and had a maximum interval of 6 weeks between any two visits in the 6-month follow-up). The non-inferiority margin was 10%. This trial is registered at ClinicalTrials.gov, and is now closed [NCT03751475](#).

**Findings:** Between July 22, 2019, and January 20, 2020, 491 children were randomly assigned, of whom 482 were analysed (240 in the standard group and 242 in the OptiMA group). In the ITT analysis, 234 (98%) children in the standard group and 231 (96%) children in OptiMA recovered (difference 2.0%, 95% CI -2.0% to 6.4%). In the PP analysis, 234 (98%) children in the standard group and 228 (97%) in OptiMA recovered (difference 1.3%, 95% CI -2.3% to 5.1%). Sensitivity analyses applying the same anthropometric recovery criteria to each group also showed non-inferiority of the OptiMA strategy in ITT and PP analysis.

**Interpretation:** This non-inferiority trial treating uncomplicated children with MUAC of less than 115 mm or a WHZ of less than -3 or bipedal oedema with decreasing RUTF dose as MUAC and weight increase demonstrated non-inferiority compared to the standard protocol in a highly food-insecure context in the Democratic Republic of the Congo. These findings add evidence on the safety of RUTF dose reduction with significant RUTF cost savings.

Indian J Pediatr. 2022 Nov;89(11):1066-1072.

doi: 10.1007/s12098-022-04079-2. Epub 2022 Feb 1.

**[Acceptability of Locally Produced Ready to Use Therapeutic Food \(RUTF\) in Malnourished Children: A Randomized, Double-Blind, Crossover Study](#)**

[Kiruthika Selvaraj](#)<sup>1</sup>, [Raja Sriswan Mamidi](#)<sup>1</sup>, [Rajini Peter](#)<sup>1</sup>, [Bharati Kulkarni](#)<sup>2</sup>

**Abstract**

**Objective:** To compare the acceptability of a locally produced ready-to-use therapeutic food (L-RUTF) with the standard ready-to-use therapeutic food (S-RUTF).

**Methods:** It was a single-center, randomized, double-blind, two-way crossover study. The participants were 6-59-month-old children residing in an urban slum, with weight-for-height z score (WHZ) < -2SD. The study had two intervention periods of feeding with two types of RUTF- L-RUTF and S-RUTF-for a period of 24 h, separated by a wash-out period of 7 d. The outcome measures were the acceptability measured as consumption of more than two-thirds of the total calories offered (150 kcal/kg/24 h) and the degree of liking of the food measured by organoleptic evaluation.

**Result:** Both types of RUTF did not qualify as acceptable. L-RUTF was preferred over S-RUTF in organoleptic evaluation.

**Conclusion:** The study suggests that RUTF products are not suitable for use as a single therapeutic food during nutrition rehabilitation of children with acute malnutrition.

Nutrients. 2022 Jul 29;14(15):3116.

doi: 10.3390/nu14153116.

**[Increased vs. Standard Dose of Iron in Ready-to-Use Therapeutic Foods for the Treatment of Severe Acute Malnutrition in a Community Setting: A Systematic Review and Meta-Analysis](#)**

[Aamer Imdad](#)<sup>1</sup>, [Jaimie L Rogner](#)<sup>2</sup>, [Melissa François](#)<sup>3</sup>, [Shehzad Ahmed](#)<sup>4</sup>, [Abigail Smith](#)<sup>5</sup>, [Olivia J Tsistinas](#)<sup>5</sup>, [Emily Tanner-Smith](#)<sup>6</sup>, [Jai K Das](#)<sup>7</sup>, [Fanny F Chen](#)<sup>3</sup>, [Zulfiqar Ahmed Bhutta](#)<sup>8,9</sup>

**Abstract**

The optimal dose of iron in ready-to-use therapeutic foods (RUTF) used to treat uncomplicated severe acute malnutrition (SAM) in community settings is not well established. The objective of this systematic review was to assess if an increased iron dose in RUTF, compared with the standard iron dose in the World Health Organization (WHO)-recommended peanut-based RUTF, improved outcomes in children aged six months or older. We searched multiple electronic databases and only included randomized controlled trials. We pooled the data in a meta-analysis to obtain relative risk (RR) and reported it with a 95% confidence interval (CI). Three studies, one each from Zambia, the Democratic Republic of Congo, and Malawi, were included. In all studies, the RUTF used in the intervention group was milk-free soya-maize-sorghum-based RUTF. The pooled results showed that, compared

to the control group, a high iron content in RUTF may lead to increase in hemoglobin concentration (mean difference 0.33 g/dL, 95% CI: 0.02, 0.64, two studies, certainty of evidence: low) and a decrease in any anemia (RR 0.66, 95% CI: 0.48, 0.91, two studies, certainty of evidence: low), but also decrease recovery rates (RR 0.91, 95% CI: 0.84, 0.99, three studies, certainty of evidence: low) and increase mortality (RR 1.30, 95% CI: 0.87, 1.95, three studies, certainty of evidence: moderate). However, the CIs were imprecise for the latter outcome. Future studies with large sample sizes are needed to confirm the beneficial versus harmful effects of high iron content in RUTF in treating uncomplicated SAM in children aged 6-59 months in community settings.

PLoS Med. 2023 May 23;20(5):e1004227.

doi: 10.1371/journal.pmed.1004227. eCollection 2023 May.

**[Effect of milk protein and whey permeate in large quantity lipid-based nutrient supplement on linear growth and body composition among stunted children: A randomized 2 × 2 factorial trial in Uganda](#)**

[Joseph Mbabazi<sup>1,2</sup>](#), [Hannah Pesu<sup>1</sup>](#), [Rolland Mutumba<sup>1,2</sup>](#), [Suzanne Filteau<sup>3</sup>](#), [Jack I Lewis<sup>1</sup>](#), [Jonathan C Wells<sup>4</sup>](#), [Mette F Olsen<sup>1,5</sup>](#), [André Briend<sup>1,6</sup>](#), [Kim F Michaelsen<sup>1</sup>](#), [Christian Mølgaard<sup>1</sup>](#), [Christian Ritz<sup>7</sup>](#), [Nicolette Nabukeera-Barungi<sup>2</sup>](#), [Ezekiel Mupere<sup>2</sup>](#), [Henrik Friis<sup>1</sup>](#), [Benedikte Grenov<sup>1</sup>](#)

**Abstract**

**Background:** Despite possible benefits for growth, milk is costly to include in foods for undernourished children. Furthermore, the relative effects of different milk components, milk protein (MP), and whey permeate (WP) are unclear. We aimed to assess the effects of MP and WP in lipid-based nutrient supplement (LNS), and of LNS itself, on linear growth and body composition among stunted children.

**Methods and findings:** We performed a randomized, double-blind, 2 × 2 factorial trial among 12 to 59 months old stunted children in Uganda. Children were randomized to 4 formulations of LNS with MP or soy protein isolate and WP or maltodextrin (100 g/day for 12 weeks) or no supplementation. Investigators and outcome assessors were blinded; however, participants were only blinded to the ingredients in LNS. Data were analyzed based on intention-to-treat (ITT) using linear mixed-effects models adjusted for age, sex, season, and site. Primary outcomes were change in height and knee-heel length, and secondary outcomes included body composition by bioimpedance analysis (ISRCTN13093195). Between February and September 2020, we enrolled 750 children with a median age of 30 (interquartile range 23 to 41) months, with mean ( $\pm$  standard deviation) height-for-age z-score (HAZ)  $-3.02 \pm 0.74$  and 12.7% (95) were breastfed. The 750 children were randomized to LNS (n = 600) with or without MP (n = 299 versus n = 301) and WP (n = 301 versus n = 299), or no supplementation (n = 150); 736 (98.1%), evenly distributed between groups, completed 12-week follow-up. Eleven serious adverse events occurred in 10 (1.3%) children, mainly hospitalization with malaria and anemia, all deemed unrelated to the intervention. Unsupplemented children had 0.06 (95% confidence interval, CI [0.02, 0.10]; p = 0.015) decline in HAZ, accompanied by 0.29 (95% CI [0.20, 0.39]; p < 0.001) kg/m<sup>2</sup> increase in fat mass index (FMI), but 0.06 (95% CI [-0.002, 0.12]; p = 0.057) kg/m<sup>2</sup> decline in fat-free mass index (FFMI). There were no interactions between MP and WP. The main effects of MP were 0.03 (95% CI [-0.10, 0.16]; p = 0.662) cm in height and 0.2 (95% CI [-0.3, 0.7]; p = 0.389) mm in knee-heel length. The main effects of WP were -0.08 (95% CI [-0.21, 0.05]; p = 0.220) cm and -0.2

(95% CI [-0.7; 0.3];  $p = 0.403$ ) mm, respectively. Interactions were found between WP and breastfeeding with respect to linear growth ( $p < 0.02$ ), due to positive effects among breastfed and negative effects among non-breastfed children. Overall, LNS resulted in 0.56 (95% CI [0.42, 0.70];  $p < 0.001$ ) cm height increase, corresponding to 0.17 (95% CI [0.13, 0.21];  $p < 0.001$ ) HAZ increase, and 0.21 (95% CI [0.14, 0.28];  $p < 0.001$ ) kg weight increase, of which 76.5% (95% CI [61.9; 91.1]) was fat-free mass. Using height-adjusted indicators, LNS increased FFMI (0.07 kg/m<sup>2</sup>, 95% CI [0.0001; 0.13];  $p = 0.049$ ), but not FMI (0.01 kg/m<sup>2</sup>, 95% CI [-0.10, 0.12];  $p = 0.800$ ). Main limitations were lack of blinding of caregivers and short study duration.

**Conclusions:** Adding dairy to LNS has no additional effects on linear growth or body composition in stunted children aged 12 to 59 months. However, supplementation with LNS, irrespective of milk, supports linear catch-up growth and accretion of fat-free mass, but not fat mass. If left untreated, children already on a stunting trajectory gain fat at the expense of fat-free mass, thus nutrition programs to treat such children should be considered.

Matern Child Nutr. 2022 Oct;18(4):e13400.

doi: 10.1111/mcn.13400. Epub 2022 Jul 21.

**[Burden and risk factors for relapse following successful treatment of uncomplicated severe acute malnutrition in young children: Secondary analysis from a randomised trial in Niger](#)**

[Lilia Bliznashka](#)<sup>1</sup>, [Kyra H Grantz](#)<sup>2</sup>, [J r mie Botton](#)<sup>3</sup>, [Fatou Berth ](#)<sup>4</sup>, [Souna Garba](#)<sup>4</sup>, [Kerstin E Hanson](#)<sup>4</sup>, [Rebecca F Grais](#)<sup>5</sup>, [Sheila Isanaka](#)<sup>5,6,7</sup>

**Abstract**

This study aimed to quantify the burden of relapse following successful treatment for uncomplicated severe acute malnutrition (SAM) and to identify associated risk factors in rural Niger. We used data from 1490 children aged 6-59 months discharged as recovered from an outpatient nutritional programme for SAM and followed for up to 12 weeks after admission. Postdischarge SAM relapse was defined as weight-for-height Z-score  $< -3$ , mid-upper arm circumference (MUAC)  $< 115$  mm or bipedal oedema after having been discharged as recovered. Postdischarge hospitalisation was defined as admission to inpatient SAM treatment or hospitalisation for any cause after having been discharged as recovered. We used multivariate log-binomial models to identify independent risk factors. After programmatic discharge, 114 (8%) children relapsed to SAM and 89 (6%) were hospitalised. Factors associated with SAM relapse were discharge during the lean season (relative risk [RR] = 1.80 [95% confidence interval [CI] = 1.22-2.67]) and larger household size (RR = 1.56 [95% CI = 1.01-2.41]), whereas older child age (RR = 0.94 [95% CI = 0.88-1.00]), higher child MUAC at discharge (RR = 0.93 [95% CI = 0.87-1.00]) and maternal literacy (RR = 0.54 [95% CI = 0.29-0.98]) were protective factors. Discharge during the lean season (RR = 2.27 [95% CI = 1.46-3.51]) was independently associated with postdischarge hospitalisation. Future nutritional programmes in the context of Niger may consider modification of anthropometric discharge criteria or the provision of additional home support or follow-up during the lean season as potential interventions to prevent relapse. More research including postdischarge follow-up is needed to better understand the sustainability of treatment outcomes after discharge and the type of intervention that may best sustain recovery over time.



Indian J Pediatr. 2023 Jun 1.

doi: 10.1007/s12098-023-04614-9. Online ahead of print.

**[A Randomized Controlled Trial on Comparison of Clinical Outcome in Uncomplicated SAM Managed with and without Antibiotics](#)**

[Yashwant Kumar Rao](#)<sup>1</sup>, [Vaishnavi Baranwal](#)<sup>2</sup>, [Tanu Midha](#)<sup>3</sup>, [Arij Javed](#)<sup>2</sup>, [Pragati Kumari](#)<sup>2</sup>

**Abstract**

**Objectives:** To assess the clinical outcome of management of uncomplicated severe acute malnutrition (SAM) at community level with antibiotics vs. without antibiotics.

**Methods:** A randomized controlled trial was conducted on children aged 6 to 59 mo with uncomplicated SAM, selected randomly from rural areas of Kanpur. A total of 100 children were enrolled and were randomized into two groups, the intervention group who were given antibiotics for a week and the control group who were not given antibiotics. Rest of the management was same. Demographic, clinical and anthropometric details of each child were taken.

**Results:** Gender and socio-economic status was comparable in both the groups. Anthropometric parameters (mean weight for age, height for age and weight for height) in both the groups were not significantly different at the time of enrolment and also at two weeks follow-up. At 2 wk follow-up, weight/height Z score in the intervention and control group were  $-1.29 \pm 0.84$  and  $-1.45 \pm 0.93$ , respectively (p value = 0.436).

**Conclusions:** It was concluded that whether antibiotics were given or not in the management of children with uncomplicated SAM, improvement in clinical and anthropometric parameters was seen without any significant difference.

Sci Rep. 2023 Jun 30;13(1):10636.

doi: 10.1038/s41598-023-36841-7.

**[Effect of nutrition intervention on cognitive development among malnourished preschool children: randomized controlled trial](#)**

[Ansuya](#)<sup>1</sup>, [Baby S Nayak](#)<sup>2</sup>, [B Unnikrishnan](#)<sup>3</sup>, [Y N Shashidhara](#)<sup>1</sup>, [Suneel C Mundkur](#)<sup>4</sup>

**Abstract**

Childhood malnutrition impairs health, development, and productivity in adulthood. Underweight children have been found to have a variety of cognitive abnormalities. The present study examined the effect of a nutrition-focused intervention on cognitive development among malnourished preschool children between 3 and 5 years of age residing in selected villages of Udipi district, Karnataka. A cluster of 12 villages was chosen randomly. The trial had enrolled preschool children (n = 253) from randomly assigned selected villages to intervention (n = 127) and control arms (n = 126). The mothers in the intervention arm received nutrition-focused intervention and reinforcement of health teaching for 12 months. The post-intervention outcome on the cognitive development of malnourished children was measured at 6 months and 12 months. Statistical analyses indicated that 52% of children in the intervention group had average cognitive development scores on the pre-test, whereas on the post-test, only 5.5% were in the average level of cognitive development. In the control group, the average cognitive development status of the children decreased from 44.4% in the pretest to 26.2% in the post-test. The cognitive development of malnourished children in the intervention group improved compared to the control group (p < 0.001). This study

revealed that home-based nutrition-focused food helps to enhance children's cognitive development

## Environmental enteric dysfunction

Am J Clin Nutr. 2023 May;117(5):976-984.

doi: 10.1016/j.ajcnut.2023.01.019. Epub 2023 Apr 19.

### [Probiotics for children with uncomplicated severe acute malnutrition \(PruSAM study\): A randomized controlled trial in the Democratic Republic of Congo](#)

[Richard Mbusa Kambale](#)<sup>1</sup>, [Joseph Ntagerwa Ntagazibwa](#)<sup>2</sup>, [Joe Bwija Kasengi](#)<sup>2</sup>, [Adrien Burume Zigashane](#)<sup>2</sup>, [Isia Nancy Francisca](#)<sup>2</sup>, [Benjamin Ntaligeza Mashukano](#)<sup>2</sup>, [Gaylord Amani Ngaboyeka](#)<sup>3</sup>, [Esto Bahizire](#)<sup>4</sup>, [Francis Zech](#)<sup>5</sup>, [Laure B Bindels](#)<sup>6</sup>, [Dimitri Van der Linden](#)<sup>7</sup>

#### Abstract

**Background:** Severe acute malnutrition (SAM) contributes to nearly 1 million deaths annually worldwide, with diarrhea and pneumonia being the common morbidity associated with mortality.

**Objectives:** To assess the effect of probiotics on diarrhea, pneumonia, and nutritional recovery in children with uncomplicated SAM.

**Methods:** A randomized, double-blind, placebo-controlled study was conducted involving 400 children with uncomplicated SAM randomly assigned to ready-to-use therapeutic food (RUTF) either with (n = 200) or without (n = 200) probiotics. Patients received 1 mL daily dose of a blend of *Lactobacillus rhamnosus* GG and *Limosilactobacillus reuteri* DSM 17938 (dosage, 2 billion colony-forming units; 50:50) or placebo during 1 mo. They were simultaneously fed with the RUTF for 6 to 12 wk, depending on patients' recovery rates. The primary outcome was the duration of diarrhea. Secondary outcomes included diarrheal and pneumonic incidence, nutritional recovery, and transfer to inpatient care rate.

**Results:** For children with diarrhea, the number of days of disease was lower in the probiotic group (4.11; 95% CI: 3.37, 4.51) than that in the placebo group (6.68; 95% CI: 6.26, 7.13; P < 0.001). For children aged 16 mo or older, the risk of diarrhea was lower in the probiotic group (75.6%; 95% CI: 66.2, 82.9) than that in the placebo group (95.0%; 95% CI: 88.2, 97.9; P < 0.001), but no significant difference of the risk for the youngest. In the probiotic group, nutritional recovery happened earlier: at the 6th wk, 40.6% of the infants were waiting for nutritional recovery, contrasting with 68.7% of infants in the placebo group; but the nutritional recovery rate at the 12th wk was similar between the groups. Probiotics had no effect on pneumonic incidence and transfer to inpatient care.

**Conclusions:** This trial supports using probiotics for the treatment of children with uncomplicated SAM. Its effect on diarrhea could positively affect nutritional programs in resource-limited settings.

Int J Environ Res Public Health. 2022 Sep 1;19(17):10891.

doi: 10.3390/ijerph191710891.

### **Lack of Associations between Environmental Exposures and Environmental Enteric Dysfunction among 18-Month-Old Children in Rural Malawi**

[Zhifei Liu<sup>1</sup>](#), [Yue-Mei Fan<sup>1</sup>](#), [Per Ashorn<sup>1,2</sup>](#), [Chilungamo Chingwanda<sup>3</sup>](#), [Kenneth Maleta<sup>3</sup>](#), [Lotta Hallamaa<sup>1</sup>](#), [Heikki Hyöty<sup>1,4</sup>](#), [David Chaima<sup>3</sup>](#), [Ulla Ashorn<sup>1</sup>](#)

#### **Abstract**

Environmental enteric dysfunction (EED) is common and contributes to linear growth faltering (stunting) and mortality among children in low-resource settings. A few studies on the environmental causes of EED have been conducted but the exact exposures that cause or predispose children to EED are context-specific and not clear. This study aimed to assess associations between selected environmental exposures and EED markers among 620 18-month-old children. This was a secondary analysis of data from Malawian children who participated in a randomized controlled trial (iLiNS-DYAD, registered at [clinicaltrials.gov](https://clinicaltrials.gov) as [NCT01239693](https://clinicaltrials.gov/ct2/show/study/NCT01239693)) from birth to 18 months of age. Data on environmental exposures, including drinking water source, sanitation, exposure to animals, housing materials, season, residential area, and food insecurity were collected at enrolment. Biomarkers of EED included concentrations of calprotectin, regenerating 1B protein (REG1B), and alpha-1-antitrypsin from stool samples to assess intestinal inflammation, repair, and permeability, respectively. We performed bivariate and multivariable analyses to assess associations between environmental exposures and EED biomarkers. Adjusting for possible confounders, we did not find associations between the selected environmental exposures and the three biomarkers. These results do not provide support for our hypothesis that the studied adverse environmental exposures are associated with increased concentrations of children's EED markers in rural Malawi.

J Nutr. 2023 Jan 14;152(12):2744-2753.

doi: 10.1093/jn/nxac207.

### **An Alternative Oat-Containing, Ready-To-Use, Therapeutic Food Does Not Alter Intestinal Permeability or the 16S Ribosomal RNA Fecal Microbiome Configuration Among Children With Severe Malnutrition in Sierra Leone: A Randomized Controlled Trial**

[D Taylor Hendrixson<sup>1</sup>](#), [Nino Naskidashvili<sup>2</sup>](#), [Kevin B Stephenson<sup>3</sup>](#), [Marie L Laury<sup>4</sup>](#), [Aminata Shamit Koroma<sup>5</sup>](#), [Mark J Manary<sup>2,6,7</sup>](#)

#### **Abstract**

**Background:** Previously, a novel oat ready-to-use therapeutic food (o-RUTF) resulted in improved recovery from severe acute malnutrition (SAM) when compared to a standard RUTF (s-RUTF). The o-RUTF contained 18% oat, while the s-RUTF has no cereal ingredients.

**Objectives:** We determined the effects of o-RUTF on intestinal permeability, as measured by lactulose permeability, and the 16S ribosomal RNA (rRNA) fecal microbiome configuration of children with SAM.

**Methods:** This was a prospective, randomized, double-blinded, controlled clinical trial. Sierra Leonean children aged 6-59 mo with SAM, defined by a midupper arm circumference < 11.5 cm, were randomized to receive o-RUTF or s-RUTF. All children received 7 d of amoxicillin per guidelines. Lactulose permeability testing and fecal 16S rRNA sequencing were performed at baseline and after 4 wk of therapy. The change in lactulose permeability was the primary outcome, while the fecal 16S rRNA configuration at 4 wk was a secondary outcome.

**Results:** Of the 129 children enrolled, lactulose permeability testing was completed by 100 at baseline and 82 at week 4. After 4 wk of therapeutic feeding, there were no differences in lactulose permeability between the o-RUTF and s-RUTF groups ( $P = 0.84$ ), and over half of children had increased lactulose permeability (50% s-RUTF compared with 58% o-RUTF, mean difference = -7.5%; 95% CI: -29.2, 15.2;  $P = 0.50$ ). After 4 wk of feeding, there were no differences in the 16S rRNA configurations between the o-RUTF and s-RUTF groups (Permanova, 999 permutations;  $P = 0.648$ ; pseudo- $F = 0.581$ ), nor were there differences in  $\alpha$  or  $\beta$  diversity.

**Conclusions:** Despite remarkably different compositions of o-RUTF and s-RUTF, no differences were identified in lactulose permeability or the fecal 16S rRNA configuration among children with SAM receiving these foods. These results suggest that the o-RUTF exerts its beneficial effects through mechanisms other than reducing intestinal permeability or altering the fecal 16S configuration.

Nat Commun. 2023 Feb 14;14(1):654.

doi: 10.1038/s41467-023-36135-6.

**[The gut microbiome and early-life growth in a population with high prevalence of stunting](#)**

[Ruairi C Robertson](#)<sup>#1,2</sup>, [Thaddeus J Edens](#)<sup>#3</sup>, [Lynnea Carr](#)<sup>#4</sup>, [Kuda Mutasa](#)<sup>5</sup>, [Ethan K Gough](#)<sup>6</sup>, [Ceri Evans](#)<sup>1,5</sup>, [Hyun Min Geum](#)<sup>7</sup>, [Iman Baharmand](#)<sup>7</sup>, [Sandeep K Gill](#)<sup>7</sup>, [Robert Ntozini](#)<sup>5</sup>, [Laura E Smith](#)<sup>5,8</sup>, [Bernard Chasekwa](#)<sup>5</sup>, [Florence D Majo](#)<sup>5</sup>, [Naume V Tavengwa](#)<sup>5</sup>, [Batsirai Mutasa](#)<sup>5</sup>, [Freddy Francis](#)<sup>9</sup>, [Joice Tome](#)<sup>5</sup>, [Rebecca J Stoltzfus](#)<sup>10</sup>, [Jean H Humphrey](#)<sup>6</sup>, [Andrew J Prendergast](#)<sup>1,5,6</sup>, [Ame R Manges](#)<sup>11,12</sup>

**Abstract**

Stunting affects one-in-five children globally and is associated with greater infectious morbidity, mortality and neurodevelopmental deficits. Recent evidence suggests that the early-life gut microbiome affects child growth through immune, metabolic and endocrine pathways. Using whole metagenomic sequencing, we map the assembly of the gut microbiome in 335 children from rural Zimbabwe from 1-18 months of age who were enrolled in the Sanitation, Hygiene, Infant Nutrition Efficacy Trial (SHINE; [NCT01824940](#)), a randomized trial of improved water, sanitation and hygiene (WASH) and infant and young child feeding (IYCF). Here, we show that the early-life gut microbiome undergoes programmed assembly that is unresponsive to the randomized interventions intended to improve linear growth. However, maternal HIV infection is associated with over-diversification and over-maturity of the early-life gut microbiome in their uninfected children, in addition to reduced abundance of Bifidobacterium species. Using machine learning models (XGBoost), we show that taxonomic microbiome features are poorly predictive of child growth, however functional metagenomic features, particularly B-vitamin and nucleotide biosynthesis pathways, moderately predict both attained linear and ponderal growth and growth velocity. New approaches targeting the gut microbiome in early childhood may complement efforts to combat child undernutrition.

## Maternal health

(see also Malaria)

### Antenatal and maternal care during pregnancy

J Glob Health. 2023 Feb 3;13:04022.

doi: 10.7189/jogh.13.04022.

#### [Effectiveness of the maternal and child health handbook for improving continuum of care and other maternal and child health indicators: A cluster randomized controlled trial in Angola](#)

[Olukunmi Omobolanle Balogun](#)<sup>1</sup>, [Ai Aoki](#)<sup>1</sup>, [Caroline Kaori Tomo](#)<sup>1</sup>, [Keiji Mochida](#)<sup>2,3</sup>, [Sachi Fukushima](#)<sup>2</sup>, [Masashi Mikami](#)<sup>4</sup>, [Toru Sadamori](#)<sup>5</sup>, [Michiru Kuramata](#)<sup>5</sup>, [Helga Reis Freitas](#)<sup>6</sup>, [Pedro Sapalalo](#)<sup>7</sup>, [Lino Tchicondingosse](#)<sup>7</sup>, [Rintaro Mori](#)<sup>8</sup>, [Hirotugu Aiga](#)<sup>9,10</sup>, [Ketha Rubuz Francisco](#)<sup>6</sup>, [Kenji Takehara](#)<sup>1</sup>

#### Abstract

**Background:** The maternal and child health (MCH) handbook is promoted as a tool for strengthening continuum of care. We assessed the effect of a MCH handbook intervention package on continuum of maternal and child health care and health outcomes for mother and child.

**Methods:** We conducted an open-label, parallel two-arm cluster randomized controlled trial in Angola. We randomly assigned municipalities in Benguela province through block randomization to a group using a package of enhanced maternity care service (which included the MCH handbook distribution and its supplementary intervention) and another using usual care (two stand-alone home-based records). We included women who were pregnant at the beginning of the trial period and attended a public health care facility for maternity care services. Neither health care providers, study participants nor data assessors were masked, but the statistician was. The primary outcome was a measure of service utilization assessed via achievement of maternal behavior-based continuum of care at three months postpartum. We conducted an intention-to-treat analysis in women with available data.

**Results:** We randomized 10 municipalities to either the intervention (five clusters) or control (five clusters) group. Of the 11 530 women approached between June 8, 2019, and September 30, 2020, 11 006 were recruited and 9039 included in the final analysis (82%; 3774 in the intervention group and 5265 in the control group). The odds for achievement of maternal behavior-based continuum of care in the intervention group was not significantly different from that in the control group (adjusted odds ratio (aOR) = 1.18, 95% confidence interval (CI) = 0.46-2.93) at three months postpartum. However, the odds of initiating antenatal care clinic use were significantly higher in the intervention group (odds ratio (OR) = 5.16, 95% CI = 2.50-10.67). No harms associated with the intervention were reported.

**Conclusions:** Distribution of the MCH handbook and its supplementary interventions promoted initiation of antenatal care service use, but did not increase service utilization sufficiently enough for attainment of study defined maternal behavior-based continuum of care.

Health Policy Plan. 2023 Mar 16;38(3):279-288.

doi: 10.1093/heapol/czac100.

**[The impact of a community health worker intervention on uptake of antenatal care: a cluster-randomized pragmatic trial in Dar es Salaam](#)**

[Mathilda Regan](#)<sup>1</sup>, [Chao Cheng](#)<sup>2</sup>, [Eric Mboggo](#)<sup>3</sup>, [Elysia Larson](#)<sup>4</sup>, [Irene Andrew Lema](#)<sup>5</sup>, [Lucy Magesa](#)<sup>5</sup>, [Lameck Machumi](#)<sup>5</sup>, [Nzovu Ulenga](#)<sup>5</sup>, [David Sando](#)<sup>1</sup>, [Mary Mwanyika-Sando](#)<sup>6</sup>, [Dale A Barnhart](#)<sup>7,8</sup>, [Biling Hong](#)<sup>9</sup>, [Ester Mungure](#)<sup>5</sup>, [Nan Li](#)<sup>1</sup>, [Hellen Siril](#)<sup>5</sup>, [Phares Mujinja](#)<sup>10</sup>, [Helga Naburi](#)<sup>11</sup>, [Charles Kilewo](#)<sup>12</sup>, [Anna Mia Ekström](#)<sup>13,14</sup>, [Pascal Geldsetzer](#)<sup>15,16</sup>, [Wafaie Fawzi](#)<sup>1</sup>, [Till Bärnighausen](#)<sup>16,17</sup>, [Christopher R Sudfeld](#)<sup>1</sup>, [Donna Spiegelman](#)<sup>2</sup>

**Abstract**

The provision of high-quality antenatal care (ANC) is important for preventing maternal and newborn mortality and morbidity, but only around half of pregnant women in Tanzania attended four or more ANC visits in 2019. Although there is emerging evidence on the benefit of community health worker (CHW) interventions on ANC uptake, few large-scale pragmatic trials have been conducted. This pragmatic cluster-randomized trial, implemented directly through the public sector health system, assessed the impact of an intervention that trained public sector CHWs to promote the uptake of ANC. We randomized 60 administrative wards in Dar es Salaam to either a targeted CHW intervention or a standard of care. The impact of the intervention was assessed using generalized estimating equations with an independent working correlation matrix to account for clustering within wards. A total of 243 908 women were included in the analysis of our primary outcome of four or more ANC visits. The intervention significantly increased the likelihood of attending four or more ANC visits [relative risk (RR): 1.42; 95% confidence interval (CI): 1.05, 1.92] and had a modest beneficial effect on the total number of ANC visits (percent change: 7.7%; 95% CI: 0.2%, 15.5%). While slightly more women in the intervention arm attended ANC in their first trimester compared with the standard-of-care arm (19% vs 18.7%), the difference was not significant (RR: 1.02; 95% CI: 0.84, 1.22). Our findings suggest that trained CHWs can increase attendance of ANC visits in Dar es Salaam and similar settings. However, additional interventions appear necessary to promote the early initiation of ANC. This study demonstrates that routine health system data can be leveraged for outcome assessment in trials and programme evaluation and that the results are likely superior, both in terms of bias and precision, to data that are collected specifically for science.

BMC Pregnancy Childbirth. 2022 Dec 30;22(1):981.

doi: 10.1186/s12884-022-05282-x.

**[Antenatal and delivery practices and neonatal mortality amongst women with institutional and non-institutional deliveries in rural Zimbabwe: observational data from a cluster randomized trial](#)**

[Christie Noble](#)<sup>#1</sup>, [Ciaran Mooney](#)<sup>#2</sup>, [Rachel Makasi](#)<sup>3</sup>, [Robert Ntozini](#)<sup>3</sup>, [Florence D Majo](#)<sup>3</sup>, [James A Church](#)<sup>1,3</sup>, [Naume V Tavengwa](#)<sup>3</sup>, [Andrew J Prendergast](#)<sup>1,3,4</sup>, [Jean H Humphrey](#)<sup>3,4</sup>; [Sanitation Hygiene Infant Nutrition Efficacy \(SHINE\) Trial Team](#)

**Abstract**

**Background:** Despite achieving relatively high rates of antenatal care, institutional delivery, and HIV antiretroviral therapy for women during pregnancy, neonatal mortality has



remained stubbornly high in Zimbabwe. Clearer understanding of causal pathways is required to inform effective interventions.

**Methods:** This study was a secondary analysis of data from the Sanitation Hygiene Infant Nutrition Efficacy (SHINE) trial, a cluster-randomized community-based trial among pregnant women and their infants, to examine care during institutional and non-institutional deliveries in rural Zimbabwe and associated birth outcomes.

**Results:** Among 4423 pregnant women, 529 (11.9%) delivered outside a health institution; hygiene practices were poorer and interventions to minimise neonatal hypothermia less commonly utilised for these deliveries compared to institutional deliveries. Among 3441 infants born in institutions, 592 (17.2%) were preterm (< 37 weeks gestation), while 175/462 (37.9%) infants born outside health institutions were preterm (RR: 2.20 (1.92, 2.53)). Similarly, rates of stillbirth [1.2% compared to 3.0% (RR:2.38, 1.36, 4.15)] and neonatal mortality [2.4% compared to 4.8% (RR: 2.01 1.31, 3.10)] were higher among infants born outside institutions. Among mothers delivering at home who reported their reason for having a home delivery, 221/293 (75%) reported that precipitous labor was the primary reason for not having an institutional delivery while 32 (11%), 34 (12%), and 9 (3%), respectively, reported distance to the clinic, financial constraints, and religious/personal preference.

**Conclusions:** Preterm birth is common among all infants in rural Zimbabwe, and extremely high among infants born outside health institutions. Our findings indicate that premature onset of labor, rather than maternal choice, may be the reason for many non-institutional deliveries in low-resource settings, initiating a cascade of events resulting in a two-fold higher risk of stillbirth and neonatal mortality amongst children born outside health institutions. Interventions for primary prevention of preterm delivery will be crucial in reducing neonatal mortality in Zimbabwe.

JMIR Form Res. 2023 Mar 2;7:e36619.

doi: 10.2196/36619.

**[Evaluating the Feasibility, Acceptability, and Preliminary Efficacy of SupportMoms - Uganda, an mHealth-Based Patient-Centered Social Support Intervention to Improve the Use of Maternity Services Among Pregnant Women in Rural Southwestern Uganda: Randomized Controlled Trial](#)**

[Esther C Atukunda](#)<sup>1</sup>, [Mark J Siedner](#)<sup>2</sup>, [Celestino Obua](#)<sup>1</sup>, [Angella Musiimenta](#)<sup>1</sup>, [Norma C Ware](#)<sup>3</sup>, [Samuel Mugisha](#)<sup>1,4</sup>, [Josephine N Najjuma](#)<sup>1</sup>, [Godfrey R Mugenyi](#)<sup>1</sup>, [Lynn T Matthews](#)<sup>5</sup>

**Abstract**

**Background:** SMS text messaging and other mobile health (mHealth) interventions may improve knowledge transfer, strengthen access to social support (SS), and promote positive health behaviors among women in the perinatal period. However, few mHealth apps have been taken to scale in sub-Saharan Africa.

**Objective:** We evaluated the feasibility, acceptability, and preliminary efficacy of a novel, mHealth-based, and patient-centered messaging app designed using behavioral science frameworks to promote maternity service use among pregnant women in Uganda.

**Methods:** We performed a pilot randomized controlled trial between August 2020 and May 2021 at a referral hospital in Southwestern Uganda. We included 120 adult pregnant women enrolled in a 1:1:1 ratio to receive routine antenatal care (ANC; control), scheduled SMS text or audio messages from a novel messaging prototype (scheduled messaging [SM]), and SM

plus SMS text messaging reminders to 2 participant-identified social supporters (SS). Participants completed face-to-face surveys at enrollment and in the postpartum period. The primary outcomes were feasibility and acceptability of the messaging prototype. Other outcomes included ANC attendance, skilled delivery, and SS. We conducted qualitative exit interviews with 15 women from each intervention arm to explore the intervention mechanisms. Quantitative and qualitative data were analyzed using STATA and NVivo, respectively.

**Results:** More than 85% and 75% of participants received  $\geq 85\%$  of the intended SMS text messages or voice calls, respectively. More than 85% of the intended messages were received within 1 hour of the expected time; 18% (7/40) of women experienced network issues for both intervention groups. Over 90% (36/40) of the intervention participants found this app useful, easy to use, engaging, and compatible and strongly recommended it to others; 70% (28/40), 78% (31/40), and 98% (39/40;  $P=.04$ ) of women in the control, SM, and SS arms, respectively, had a skilled delivery. Half (20/40), 83% (33/40), and all (40/40;  $P=.001$ ) of the women in the control, SM, and SS arms attended  $\geq 4$  ANC visits, respectively. Women in the SS arm reported the highest support (median 3.4, IQR 2.8-3.6;  $P=.02$ );  $<20\%$  (8/40;  $P=.002$ ) missed any scheduled ANC visit owing to lack of transportation. Qualitative data showed that women liked the app; they were able to comprehend ANC and skilled delivery benefits and easily share and discuss tailored information with their significant others, who in turn committed to providing them the needed support to prepare and seek help.

**Conclusions:** We demonstrated that developing a novel patient-centered and tailored messaging app that leverages SS networks and relationships is a feasible, acceptable, and useful approach to communicate important targeted health-related information and support pregnant women in rural Southwestern Uganda to use available maternity care services. Further evaluation of maternal-fetal outcomes and integration of this intervention into routine care is needed.

BMC Pregnancy Childbirth. 2023 May 1;23(1):305.

doi: 10.1186/s12884-023-05640-3.

### [\*\*The roles of multi-component interventions in reducing mistreatment of women and enhancing respectful maternity care: a systematic review\*\*](#)

[Habtamu Kasaye<sup>1,2</sup>](#), [Annabel Sheehy<sup>3</sup>](#), [Vanessa Scarf<sup>3</sup>](#), [Kathleen Baird<sup>3</sup>](#)

#### **Abstract**

**Background:** Despite recognition of the adverse impacts of the mistreatment of women during pregnancy, labour and birth, there remains limited evidence on interventions that could reduce mistreatment and build a culture of respectful maternity care (RMC) in health facilities. The sustainability of effective individual interventions and their adaptability to various global contexts remain uncertain. In this systematic review, we aimed to synthesise the best available evidence that has been shown to be effective in reducing the mistreatment of women and/or enhancing RMC during women's maternity care in health facilities.

**Methods:** We searched the online databases PubMed, CINAHL, EBSCO Nursing/Academic Edition, Embase, African Journals Online (AJOL), Scopus, Web of Science, and grey literature using predetermined search strategies. We included cluster randomized controlled trials (RCTs) and pre-and-post observational studies and appraised them using JBI critical appraisal checklists. The findings were synthesised narratively without conducting a meta-analysis. The certainty of evidence was assessed using GRADE criteria.

**Results:** From the 1493 identified records, 11 studies from six sub-Saharan African countries and one study from India were included: three cluster RCTs and nine pre- and post-studies. We identified diverse interventions implemented via various approaches including individual health care providers, health systems, and policy amendments. Moderate certainty evidence from two cluster RCTs and four pre- and post-studies suggests that multi-component interventions can reduce the odds of mistreatment that women may experience in health facilities, with odds of reduction ranging from 18 per cent to 66 per cent. Similarly, women's perceptions of maternity care as respectful increased in moderate certainty evidence from two cluster RCTs and five pre- and post-studies with reported increases ranging from 5 per cent to 50 per cent.

**Conclusions:** Multi-component interventions that address attitudes and behaviors of health care providers, motivate staff, engage the local community, and alleviate health facility and system constraints have been found to effectively reduce mistreatment of women and/or increase respectful maternity care. Such interventions which go beyond a single focus like staff training appear to be more likely to bring about change. Therefore, future interventions should consider diverse approaches that incorporate these components to improve maternal care.

BMJ Open. 2022 Nov 25;12(11):e064673.

doi: 10.1136/bmjopen-2022-064673.

[Impact of conditional cash transfer programmes on antenatal care service uptake in low and middle-income countries: a systematic review](#)

[Ward Jacobs<sup>1</sup>, Laura Emily Downey<sup>2,3</sup>](#)

**Abstract**

**Objective:** Antenatal care (ANC) is crucial to protecting the health of pregnant women and their unborn children; however, the uptake of ANC among pregnant women in low and middle-income countries (LMICs) is suboptimal. One popular strategy to increase the uptake of health services, including ANC visits, are conditional cash transfer (CCT) programmes. CCT programmes require beneficiaries to comply with certain conditionalities in order to receive a financial sum. A systematic review was carried out to determine whether CCT programmes have a positive impact on ANC uptake in LMIC populations.

**Methods:** Electronic databases CENTRAL, MEDLINE, Embase, Maternity and Infant Care and Global Health were searched from database inception to 21 January 2022. Reference checking and grey literature searches were also applied. Eligible study designs were randomised controlled trials, controlled before-after studies and interrupted time series analysis. Risk of bias assessments were undertaken for each study by applying the Risk of Bias 2 tool and the Risk of Bias in Non-randomised Studies of Interventions tool.

**Results:** Out of 1534 screened articles, 18 publications were included for analysis. Eight studies reported statistically non-significant results on all reported outcomes. Seven studies demonstrated statistically significant positive effects ranging from 5.5% to 45% increase in ANC service uptake. A further three studies reported small but statistically significant impact of CCT on the use of ANC services in both positive (2.5% increase) and negative (3.7% decrease) directions. Subanalysis of results disaggregated by socioeconomic status (SES)

indicated that ANC attendance may be more markedly improved by CCT programmes in low SES populations; however, results were inconclusive.

**Conclusion:** Our evidence synthesis presented here demonstrated a highly heterogeneous evidence base pertaining to the impact of CCTs on ANC attendance. More high-powered studies are required to elucidate the true impact of CCT programmes on ANC uptake, with particular focus on the barriers and enablers of such programmes in achieving intended outcomes.

J Perinat Med. 2022 May 27;50(9):1264-1270.

doi: 10.1515/jpm-2021-0668. Print 2022 Nov 25.

**[The effect of 150 and 80 mg doses of aspirin on preventing preterm birth in high-risk pregnant women](#)**

[Maryam Kasraeian<sup>1</sup>](#), [Nasrin Asadi<sup>1</sup>](#), [Homeira Vafaei<sup>1</sup>](#), [Mahin Tazang<sup>1</sup>](#), [Azam Faraji<sup>1</sup>](#), [Neda Rahimirad<sup>2</sup>](#), [Sedighe Yousofi<sup>1</sup>](#), [Seyedeh Fatemeh Khaleghi<sup>1</sup>](#), [Marjan Zare<sup>2</sup>](#)

**Abstract**

**Objectives:** Preterm birth (PTB) is the common cause of neonatal mortality nationwide. The present study aimed to evaluate the efficacy of different doses of aspirin in preventing PTB in high-risk pregnant women. As secondary outcomes, other perinatal complications were compared.

**Methods:** This double-blind randomized clinical trial was conducted on high-risk pregnant women with impaired placental perfusion diagnosed in the first trimester of pregnancy referring to the perinatal centers affiliated to Shiraz university of Medical Sciences between February 2020 and March 2021. The subjects were randomly divided in two groups administered with 150 or 80 mg aspirin every night from 11 to 13+6 weeks until 36 weeks or delivery. This study is registered in the Iranian Registry of Clinical Trials (IRCT20140317017035N6; <http://www.irct.ir/>). Univariate and multiple logistic regressions were applied using SPSS 22.

**Results:** A total of 101 subjects received 80 mg aspirin and 89 ones received 150 mg aspirin. The results of multiple analysis revealed a significantly lower odds of PTB (OR 0.4 (0.19, 0.99)) in the 150 mg group compared to the 80 mg group. As secondary outcomes, preeclampsia (PEC) and PEC with severe features (PECsf) were lower (OR 0.2 (0.06, 0.82) and 0.1 (0.01, 0.92), respectively); however, fetal age and neonatal weight were higher in the 150 mg group (OR 1.2 (1.04, 1.33) and 1.001 (1-1.001), respectively).

**Conclusions:** The study findings indicated that, compared with 80 mg of aspirin, taking 150 mg of aspirin reduced PTB and perinatal complications in high risk pregnant women.

J Nutr Sci. 2022 Jul 13;11:e58.

doi: 10.1017/jns.2022.51. eCollection 2022.

**[Effect of Picture-based health education and counselling on knowledge and adherence to preconception Iron-folic acid supplementation among women planning to be pregnant in Eastern Ethiopia: a randomized controlled trial](#)**

[Anteneh Berhane<sup>1,2</sup>](#), [Tefera Belachew<sup>2</sup>](#)

**Abstract**

The present study examined the effect of picture-based nutrition education on knowledge and adherence to pre-conception iron-folic acid supplement (IFAS) in Ethiopia, a country where there is a high burden of neural tube defects (NTDs) and anaemia. In eastern Ethiopia, a parallel randomised controlled trial design was employed among women planning to get pregnant. The interventional arm ( $n$  122) received a preconception picture-based nutrition education and counselling along with an IFAS and the control arm ( $n$  122) received only a preconception IFAS. The effects of the intervention between-group differences were assessed using a  $\chi^2$  and independent sample  $t$ -test. Bivariate and multivariable linear regression model was fitted to detect independent variables affecting the outcome. The outcome measures regarding the knowledge and adherence to the IFAS intake during the three months of the intervention period were determined. It was observed that large proportion of women in the intervention group (42.6 %) had an adherence to IFAS compared to the control group (3.3 %); ( $P < 0.0001$ ). Based on bivariate and multivariable linear regression analyses, among NTDs affecting pregnancy, the history of spontaneous abortion and knowledge were independently associated with adherence to the IFAS ( $P < 0.05$ ). Preconception nutrition education with regular follow-ups could be effective in improving knowledge and adherence to the IFAS intake. This intervention is very short, simple, cost-effective and has the potential for adaptation development to a large-scale implementation in the existing healthcare system in Ethiopia to prevent NTDs and adverse birth outcomes among women who plan to get pregnant.

## Maternal malaria prevention

Lancet. 2023 Mar 25;401(10381):1020-1036.

doi: 10.1016/S0140-6736(22)02535-1. Epub 2023 Mar 10.

### [Effect of monthly intermittent preventive treatment with dihydroartemisinin-piperazine with and without azithromycin versus monthly sulfadoxine-pyrimethamine on adverse pregnancy outcomes in Africa: a double-blind randomised, partly placebo-controlled trial](#)

[Mwayiwawo Madanitsa<sup>1</sup>](#), [Hellen C Barsosio<sup>2</sup>](#), [Daniel T R Minja<sup>3</sup>](#), [George Mtove<sup>3</sup>](#), [Reginald A Kavishe<sup>4</sup>](#), [James Dodd<sup>5</sup>](#), [Queen Saidi<sup>4</sup>](#), [Eric D Onyango<sup>2</sup>](#), [Kephas Otieno<sup>2</sup>](#), [Duolao Wang<sup>5</sup>](#), [Ulla Ashorn<sup>6</sup>](#), [Jenny Hill<sup>5</sup>](#), [Crispin Mukerebe<sup>7</sup>](#), [Samwel Gesase<sup>3</sup>](#), [Omari A Msemu<sup>3</sup>](#), [Victor Mwapasa<sup>8</sup>](#), [Kamija S Phiri<sup>8</sup>](#), [Kenneth Maleta<sup>8</sup>](#), [Nigel Klein<sup>9</sup>](#), [Pascal Magnussen<sup>10</sup>](#), [John P A Lusingu<sup>3</sup>](#), [Simon Kariuki<sup>8</sup>](#), [Jacklin F Moshia<sup>4</sup>](#), [Michael Alifrangis<sup>10</sup>](#), [Helle Hansson<sup>10</sup>](#), [Christentze Schmiegelow<sup>10</sup>](#), [Julie R Gutman<sup>11</sup>](#), [R Matthew Chico<sup>12</sup>](#), [Feiko O Ter Kuile<sup>13</sup>](#)

#### Abstract

**Background:** Intermittent preventive treatment in pregnancy (IPTp) with dihydroartemisinin-piperazine is more effective than IPTp with sulfadoxine-pyrimethamine at reducing malaria infection during pregnancy in areas with high-grade resistance to sulfadoxine-pyrimethamine by *Plasmodium falciparum* in east Africa. We aimed to assess whether IPTp with dihydroartemisinin-piperazine, alone or combined with azithromycin, can reduce adverse pregnancy outcomes compared with IPTp with sulfadoxine-pyrimethamine.

**Methods:** We did an individually randomised, double-blind, three-arm, partly placebo-controlled trial in areas of high sulfadoxine-pyrimethamine resistance in Kenya, Malawi, and

Tanzania. HIV-negative women with a viable singleton pregnancy were randomly assigned (1:1:1) by computer-generated block randomisation, stratified by site and gravidity, to receive monthly IPTp with sulfadoxine-pyrimethamine (500 mg of sulfadoxine and 25 mg of pyrimethamine for 1 day), monthly IPTp with dihydroartemisinin-piperaquine (dosed by weight; three to five tablets containing 40 mg of dihydroartemisinin and 320 mg of piperaquine once daily for 3 consecutive days) plus a single treatment course of placebo, or monthly IPTp with dihydroartemisinin-piperaquine plus a single treatment course of azithromycin (two tablets containing 500 mg once daily for 2 consecutive days). Outcome assessors in the delivery units were masked to treatment group. The composite primary endpoint was adverse pregnancy outcome, defined as fetal loss, adverse newborn baby outcomes (small for gestational age, low birthweight, or preterm), or neonatal death. The primary analysis was by modified intention to treat, consisting of all randomised participants with primary endpoint data. Women who received at least one dose of study drug were included in the safety analyses. This trial is registered with ClinicalTrials.gov, [NCT03208179](https://clinicaltrials.gov/ct2/show/study/NCT03208179).

**Findings:** From March-29, 2018, to July 5, 2019, 4680 women (mean age 25.0 years [SD 6.0]) were enrolled and randomly assigned: 1561 (33%; mean age 24.9 years [SD 6.1]) to the sulfadoxine-pyrimethamine group, 1561 (33%; mean age 25.1 years [6.1]) to the dihydroartemisinin-piperaquine group, and 1558 (33%; mean age 24.9 years [6.0]) to the dihydroartemisinin-piperaquine plus azithromycin group. Compared with 335 (23.3%) of 1435 women in the sulfadoxine-pyrimethamine group, the primary composite endpoint of adverse pregnancy outcomes was reported more frequently in the dihydroartemisinin-piperaquine group (403 [27.9%] of 1442; risk ratio 1.20, 95% CI 1.06-1.36;  $p=0.0040$ ) and in the dihydroartemisinin-piperaquine plus azithromycin group (396 [27.6%] of 1433; 1.16, 1.03-1.32;  $p=0.017$ ). The incidence of serious adverse events was similar in mothers (sulfadoxine-pyrimethamine group 17.7 per 100 person-years, dihydroartemisinin-piperaquine group 14.8 per 100 person-years, and dihydroartemisinin-piperaquine plus azithromycin group 16.9 per 100 person-years) and infants (sulfadoxine-pyrimethamine group 49.2 per 100 person-years, dihydroartemisinin-piperaquine group 42.4 per 100 person-years, and dihydroartemisinin-piperaquine plus azithromycin group 47.8 per 100 person-years) across treatment groups. 12 (0.2%) of 6685 sulfadoxine-pyrimethamine, 19 (0.3%) of 7014 dihydroartemisinin-piperaquine, and 23 (0.3%) of 6849 dihydroartemisinin-piperaquine plus azithromycin treatment courses were vomited within 30 min.

**Interpretation:** Monthly IPTp with dihydroartemisinin-piperaquine did not improve pregnancy outcomes, and the addition of a single course of azithromycin did not enhance the effect of monthly IPTp with dihydroartemisinin-piperaquine. Trials that combine sulfadoxine-pyrimethamine and dihydroartemisinin-piperaquine for IPTp should be considered.

Clin Infect Dis. 2022 Aug 31;75(3):406-415.

doi: 10.1093/cid/ciab965.

**[Piperaquine-Induced QTc Prolongation Decreases With Repeated Monthly Dihydroartemisinin-Piperaquine Dosing in Pregnant Ugandan Women](#)**

[Emma Hughes](#)<sup>1</sup>, [Erika Wallender](#)<sup>2</sup>, [Richard Kajubi](#)<sup>3</sup>, [Prasanna Jagannathan](#)<sup>4</sup>, [Teddy Ochieng](#)<sup>3</sup>, [Abel Kakuru](#)<sup>3</sup>, [Moses R Kamya](#)<sup>3,5</sup>, [Tamara D Clark](#)<sup>6</sup>, [Philip J Rosenthal](#)<sup>6</sup>, [Grant Dorsey](#)<sup>6</sup>, [Francesca Aweeka](#)<sup>2</sup>, [Radojka M Savic](#)<sup>1</sup>



## Abstract

**Background:** Intermittent preventive treatment with monthly dihydroartemisinin-piperaquine (DHA-PQ) is highly effective at preventing both malaria during pregnancy and placental malaria. Piperaquine prolongs the corrected QT interval (QTc), and it is possible that repeated monthly dosing could lead to progressive QTc prolongation. Intensive characterization of the relationship between piperaquine concentration and QTc interval throughout pregnancy can inform effective, safe prevention guidelines.

**Methods:** Data were collected from a randomized controlled trial, where pregnant Ugandan women received malaria chemoprevention with monthly DHA-PQ (120/960 mg DHA/PQ; n = 373) or sulfadoxine-pyrimethamine (SP; 1500/75 mg; n = 375) during the second and third trimesters of pregnancy. Monthly trough piperaquine samples were collected throughout pregnancy, and pre- and postdose electrocardiograms were recorded at 20, 28, and 36 weeks' gestation in each woman. The pharmacokinetics-QTc relationship for piperaquine and QTc for SP were assessed using nonlinear mixed-effects modeling.

**Results:** A positive linear relationship between piperaquine concentration and Fridericia corrected QTc interval was identified. This relationship progressively decreased from a 4.42 to 3.28 to 2.13 millisecond increase per 100 ng/mL increase in piperaquine concentration at 20, 28, and 36 weeks' gestation, respectively. Furthermore, 61% (n = 183) of women had a smaller change in QTc at week 36 than week 20. Nine women given DHA-PQ had grade 3-4 cardiac adverse events. SP was not associated with any change in QTc.

**Conclusions:** Repeated DHA-PQ dosing did not result in increased risk of QTc prolongation and the postdose QTc intervals progressively decreased. Monthly dosing of DHA-PQ in pregnant women carries minimal risk of QTc prolongation.

Rev Epidemiol Sante Publique. 2022 Oct;70(5):209-214.

doi: 10.1016/j.respe.2022.07.002. Epub 2022 Aug 19.

### [Impact of mobile phone intervention on intermittent preventive treatment of malaria during pregnancy in Burkina Faso : A pragmatic randomized trial](#)

[Smaïla Ouédraogo](#)<sup>1</sup>, [Manfred Accrombessi](#)<sup>2</sup>, [Adama Ouattara](#)<sup>3</sup>, [Achille Massougbojji](#)<sup>4</sup>, [Edgard D Dabira](#)<sup>5</sup>, [Maurice Sarigda](#)<sup>6</sup>, [Ismaël Diallo](#)<sup>7</sup>, [Adama Zida](#)<sup>7</sup>, [Méda Nicolas](#)<sup>8</sup>, [Laurent Ouédraogo](#)<sup>8</sup>, [Michel Cot](#)<sup>9</sup>, [Blaise Sondo](#)<sup>10</sup>

## Abstract

**Purpose:** Intermittent preventive treatment of malaria with sulphadoxine-pyrimethamine for pregnant women (IPTp-SP) coverage remains far below the desirable goal of at least three doses before delivery. This study evaluates an innovative intervention using mobile phones as a means of increasing coverage for the third dose of IPTp-SP.

**Methods:** This study in Burkina Faso was designed as an open-label, pragmatic, two-arm, randomised trial. Pregnant women who attended antenatal clinic (ANC) visits were included at their first ANC visit and followed until delivery. The intervention was built around the use of mobile phones as means ensuring direct tracking of pregnant women.

**Results:** Two hundred and forty-eight (248) pregnant women were included in the study. The proportion of women who received at least three doses of IPTp-SP was 54.6%. In the intervention group, 54.1% of women received at least three doses of IPTp-SP versus 55.1% in the control group, a non-significant difference (adjusted odds ratio "aOR", 0.86; 95% confidence interval "95% CI", 0.49-1.51). Women in the intervention group were more likely

to carry out their ANC visits in a timely manner than those in the control group (aOR, 3.21 ; 95 % CI, 1.91-5.39).

**Conclusion:** While mobile phone intervention did not increase the proportion of women receiving three doses of IPTp-SP, it did help to increase the proportion of timely ANC visits.

## Obstetric care and delivery

Glob Health Action. 2022 Dec 31;15(1):2058170.

doi: 10.1080/16549716.2022.2058170.

### [Strategies to increase rural maternal utilization of skilled health personnel for childbirth delivery in low- and middle-income countries: a narrative review](#)

[Jeanette R Nelson](#)<sup>1</sup>, [Rebekah H Ess](#)<sup>2</sup>, [Ty T Dickerson](#)<sup>2,3</sup>, [Lisa H Gren](#)<sup>2</sup>, [L Scott Benson](#)<sup>2,4</sup>, [Stephen O Manortey](#)<sup>5</sup>, [Stephen C Alder](#)<sup>1,2,4,5,6</sup>

#### Abstract

**Background:** Skilled attendance at birth is considered key to accomplishing Sustainable Development Goal (SDG) 3.1 aimed at reducing maternal mortality. Many maternal deaths can be prevented if a woman receives care by skilled health personnel. Maternal utilization of skilled health delivery services in rural areas in low- and middle-income countries is 70% compared to 90% in urban areas. Previous studies have found community-based interventions may increase rural maternal uptake of skilled health delivery services, but evidence is lacking on which strategies are most effective.

**Objective:** To review the effectiveness of community-based strategies to increase rural maternal utilization of skilled health personnel for childbirth delivery in low- and middle-income countries.

**Methods:** We conducted a narrative review. PubMed, CINAHL, Cochrane Library, and PsycINFO databases were searched for articles from database inception through 13 November 2019. Key search terms were pre-determined. Information was extracted on studies meeting our inclusion criteria: cluster and randomized trials, rural setting, reproductive aged women, community engagement, low- and middle-income countries. Studies were considered effective if statistically significant ( $p < 0.05$ ). A narrative synthesis was conducted.

**Results:** Ten cluster randomized trials out of 5,895 candidate citations met the inclusion criteria. Strategies included home-based visits, women's groups, and combined approaches. Out of the ten articles, only three studies were found to significantly increase maternal uptake of skilled health personnel for delivery, and each used a different strategy. The results are inconclusive as to which strategies are most effective. Limitations of this review include heterogeneity and generalizability of studies.

**Conclusions:** This research suggests that different strategies may be effective at improving maternal utilization of skilled health personnel for delivery in certain rural settings while ineffective in others. More research is warranted to better understand the context in which strategies may be effective and under what conditions.

doi: 10.1186/s12884-022-05199-5.

## **Effect of implementing a birth plan on maternal and neonatal outcomes: a randomized controlled trial**

[Parivash Ahmadpour<sup>1</sup>](#), [Sanaz Moosavi<sup>2</sup>](#), [Sakineh Mohammad-Alizadeh-Charandabi<sup>3</sup>](#), [Shayesteh Jahanfar<sup>4</sup>](#), [Mojgan Mirghafourvand<sup>5</sup>](#)

### **Abstract**

**Background:** The birth plan is an approach for pregnant women to offering their expectations of labor and birth. The purpose of this study was to investigate the effect of birth plan on maternal and neonatal outcomes.

**Methods:** This study was a randomized controlled clinical trial performed on 106 pregnant women, 32-36 weeks of pregnancy, referring to Taleghani educational hospital in Tabriz city-Iran. Participants were randomly assigned to the two groups of birth plan and control using a randomized block method. Participants in the birth plan group received the interventions based on the mother's requested birth plan. The birth plan included items of the mother's preferences in labor, mobility, eating and drinking, monitoring, pain relief, drug options, labor augmentation, pushing, amniotomy, episiotomy, infant care, and caesarean section. The control group received routine hospital care. The primary outcomes were childbirth experience and duration of the active phase of labor and the secondary outcomes were support and control in labor, fear of labor, post-traumatic stress disorder (PTSD), postpartum depression, duration of the second and third phases of labor, frequency of vaginal delivery, frequency of admission of newborn in NICU (Neonatal Intensive Care Unit), the mean first and fifth minute Apgar scores. The socio-demographic and obstetrics characteristics questionnaire, Wijma Delivery Expectancy/Experience Questionnaire (W-DEQ-versions A), and Edinburgh Postnatal Depression Scale (EPDS) were completed at the beginning of the study (at the gestational age of 32-36 weeks). The questionnaire of delivery information, neonatal information, and Delivery Fear Scale (DFS) was completed during and after the delivery. Also, a partogram was completed for all participants by the researcher. The participants in both groups followed up until 4-6 weeks post-delivery, whereby the instruments of Childbirth Experience Questionnaire 2.0 (CEQ2.0), Support and Control In Birth (SCIB) scale, EPDS, and PTSD Symptom Scale 1 (PSS-I) were completed by the researcher through an interview. The independent t-test, the chi-square test, and ANCOVA was used to analyze.

**Results:** The mean (SD) of CEQ score was significantly higher in the birth plan group ( $3.2 \pm 0.2$ ) compared to the control ( $2.1 \pm 0.2$ ) (MD = 1.0; 95% CI: 1.1 to 0.9;  $P < 0.001$ ). Also, the mean (SD) SCIB score in the birth plan group was significantly higher than that of those in the control group ( $P < 0.001$ ). The mean scores of DFS ( $P = 0.015$ ), EPDS ( $P < 0.001$ ), and PTSD ( $P < 0.001$ ) as well as the frequency of emergency caesarean section ( $P = 0.007$ ) in the birth plan group were significantly lower than those in the control group.

**Conclusion:** This was the first study to assess the implementation of a birth plan in Iran. Based on the findings, a birth plan improves childbirth experiences; increases perceived support and control in labor; reduces fear of delivery; suppresses psychological symptoms of depression and PTSD, and increases the frequency of vaginal delivery.

Birth. 2023 Feb 12.

doi: 10.1111/birt.12709. Online ahead of print.

**[Improved obstetric management after implementation of a scaled-up quality improvement intervention: A nested before-after study in three public hospitals in Nepal](#)**

[Helena Litorp](#)<sup>1,2</sup>, [Mats Målvqvist](#)<sup>1</sup>, [Avinash K Sunny](#)<sup>3</sup>, [Abhishek Gurung](#)<sup>3</sup>, [Rejina Gurung](#)<sup>3</sup>, [Ashish Kc](#)<sup>1,4</sup>

**Abstract**

**Background:** We assessed the change in obstetric management after implementation of a quality improvement intervention, the Nepal Perinatal Quality Improvement Package (NePeriQIP).

**Methods:** The Nepal Perinatal Quality Improvement Package was a stepped-wedge cluster-randomized controlled trial conducted in 12 public hospitals in Nepal between April 2017 and October 2018. In this study, three hospitals allocated at different time points to the intervention were selected for a nested before-after analysis. We used bivariate and multivariate analyses to compare obstetric management in the control vs intervention group.

**Results:** There were 25 977 deliveries in the three hospitals during the study period: 10 207 (39%) in the control and 15 770 (61%) in the intervention group. After adjusting for maternal age, ethnicity, education, gestational age, stage of labor at admission, complications during labor, and birthweight, the intervention group had a higher proportion of fetal heart rate monitoring performed as per protocol (adjusted odds ratio [aOR] 1.19, 95% confidence interval [CI] 1.12-1.27), shorter time intervals between each fetal heart rate monitoring (aOR 2.09, 95% CI 1.96-2.23), a higher likelihood of abnormal fetal heart rate being detected (aOR 1.53, 95% CI 1.25-1.68), progress of labor more often being recorded immediately after per vaginal examination (aOR 2.73, 95% CI 2.55-2.93), and partograph filled as per standards (aOR 3.18, 95% CI 2.98-3.50). The cesarean birth rate was 2.5% in the control group and 8.2% in the intervention group (aOR 3.12, 95% CI 2.64-3.68).

**Conclusions:** The NePeriQIP intervention has potential to improve obstetric care, especially intrapartum fetal surveillance, in similar low-resource settings.

Int J Gynaecol Obstet. 2023 Apr;161(1):17-25.

doi: 10.1002/ijgo.14483. Epub 2022 Oct 12.

**[Breech delivery in low-income settings: A systematic review of perinatal and maternal outcomes in vaginal versus cesarean breech deliveries](#)**

[Herman A Sorensen](#)<sup>1</sup>, [Josephine Obel](#)<sup>2</sup>, [Jeppe B Schroll](#)<sup>3,4</sup>, [Lone Krebs](#)<sup>3,4</sup>

**Abstract**

Most studies comparing vaginal breech delivery (VBD) with cesarean breech delivery (CBD) have been conducted in high-income settings. It is uncertain whether these results are applicable in a low-income setting. To assess the neonatal and maternal mortality and morbidity for singleton VBD compared to CBD in low- and lower-middle-income settings, the PubMed database was searched from January 1, 2000, to January 23, 2020 (updated April 21, 2021). Randomized controlled trials (RCTs) and non-RCTs comparing singleton VBD with singleton CBD in low- and lower-middle-income settings reporting infant mortality were selected. Two authors independently assessed papers for eligibility and risk of bias. The primary outcome was relative risk of perinatal mortality. Meta-analysis was conducted on applicable outcomes. Eight studies (one RCT, seven observational) (12 510 deliveries) were included. VBD increased perinatal mortality (relative risk [RR] 2.67, 95% confidence interval

[CI] 1.82-3.91; one RCT, five observational studies, 3289 women) and risk of 5-minute Apgar score below 7 (RR 3.91, 95% CI 1.90-8.04; three observational studies, 430 women) compared to CBD. There was a higher risk of hospitalization and postpartum bleeding in CBD. Most of the studies were deemed to have moderate or serious risk of bias. CBD decreases risk of perinatal mortality but increases risk of bleeding and hospitalization.

J Matern Fetal Neonatal Med. 2022 Dec;35(25):6320-6328.

doi: 10.1080/14767058.2021.1911995. Epub 2021 Apr 26.

**Efficacy and safety of intravenous paracetamol in management of labour pains in a low resource setting: a randomized clinical trial**

[Mohamed Elsibai Anter<sup>1</sup>](#), [Said Abdel Attey Saleh<sup>1</sup>](#), [Sara Shawkey Allam<sup>1</sup>](#), [Ahmed Mohamed Nofal<sup>1</sup>](#)

**Abstract**

**Objective:** To assess the use of single dose of paracetamol intravenously in management of labour pains.

**Background:** Pain during labour is a complex, subjective and multi-faceted physiological phenomenon that varies in intensity among women and is subjected to many social and cultural modifiers.

**Subjects and methods:** This randomized clinical study was conducted in Obstetrics and gynecology department from March 2019 to March 2020 including 96 primiparous women randomized into paracetamol group ( $n = 48$ ) received 1000 mg of paracetamol IV infusion and pethidine group ( $n = 48$ ) received 50 mg of pethidine given slowly IV. Primary outcome is the change of the intensity of perceived labor pain. Pain score was followed and recorded by visual analogue scale (VAS). Our study protocol was registered at ClinicalTrials.gov; [NCT04744727](#).

**Results:** VAS score was highly significant improved gradually after 30 min, 1, 2 and 3 h of paracetamol and pethidine taken compared at start study, but participants in paracetamol group had lower pain after 2 and 3 h ( $3.92 \pm 1.42$  and  $5.69 \pm 1.07$ ) than those of the pethidine groups ( $4.42 \pm 1.87$  and  $5.38 \pm 1.34$ ). Also, 2.1% of paracetamol group developed dizziness and 4.2% developed nausea and vomiting, while there was 29.2% of pethidine group developed dizziness and 37.5% developed nausea and vomiting.

**Conclusions:** Intravenous paracetamol as labour analgesia is effective, safe, inexpensive, available and with no maternal or fetal side effects as compared to Pethidine. Paracetamol needs to have more chance in comparison to other forms as a labour pain analgesia, especially in our communities.

Int J Gynaecol Obstet. 2022 Jul;158(1):79-85.

doi: 10.1002/ijgo.13963. Epub 2021 Oct 26.

**"Suction Tube Uterine Tamponade" for treatment of refractory postpartum hemorrhage: Internal feasibility and acceptability pilot of a randomized clinical trial**

[Sylvia N Cebekhulu<sup>1</sup>](#), [Hazmath Abdul<sup>2</sup>](#), [Joanne Batting<sup>3</sup>](#), [Lawrence Chauke<sup>4</sup>](#), [Fuziwe Dlakavu<sup>5</sup>](#), [Sue Fawcus<sup>6</sup>](#), [Logie Govender<sup>2</sup>](#), [Busiwe Majeke<sup>7</sup>](#), [Xolani Mbongozi<sup>8</sup>](#), [Mandisa](#)

[Singata-Madliki<sup>3</sup>](#), [Katrin Middleton<sup>9</sup>](#), [Philiswa Mlandu<sup>10</sup>](#), [Poovangela Naidoo<sup>10</sup>](#), [Sanele Ndaba<sup>11</sup>](#), [Priya Soma-Pillay<sup>12</sup>](#), [Trevi Spence<sup>13</sup>](#), [Symphorien C Ntambua<sup>14</sup>](#), [Justus Hofmeyr<sup>3,15</sup>](#)

## Abstract

**Objective:** To assess feasibility and acceptability of a novel, low-cost "Suction Tube Uterine Tamponade" (STUT) treatment for refractory postpartum hemorrhage (PPH).

**Methods:** We allocated patients with refractory PPH by randomly ordered envelopes to STUT or routine uterine balloon tamponade (UBT, Ellavi free-flow system) in 10 hospitals in South Africa. In the STUT group, a 24FG Levin stomach tube was inserted into the uterine cavity and vacuum created with a vacuum pump or manual vacuum aspiration syringe.

**Results:** For this internal pilot study, 12 participants were allocated to STUT and 12 to UBT. Insertion failed in one of each group and was recorded as difficult in 3/10 STUT and 4/9 UBT insertions respectively (five missing data). There were two laparotomies and one intensive care unit admission in the UBT group. Pain during STUT insertion was graded as none/mild in 9/10 and severe in 1/10. The experience of the STUT procedure was graded as fine in 4/11 and "uncomfortable but acceptable" in 7/11.

**Conclusion:** STUT is feasible and acceptable, justifying continuation of our trial. These data will also inform a large World Health Organization trial to test effectiveness of uterine tamponade methods. The numbers are too small to support any clinical recommendation.

Int J Gynaecol Obstet. 2022 Jul;158(1):44-49.

doi: 10.1002/ijgo.13943. Epub 2021 Oct 27.

## [Simultaneous use of high-volume Foley catheter \(60 ml\) and misoprostol for labor induction in nulliparous women: A randomized controlled trial](#)

[Anjali Soni<sup>1</sup>](#), [Aarti Sharma<sup>1</sup>](#), [Chanderdeep Sharma<sup>1</sup>](#), [Suresh Verma<sup>1</sup>](#)

## Abstract

**Objective:** To examine the simultaneous effect of high-volume Foley catheter (HVFC) (60 ml) and vaginal misoprostol on labor induction in nulliparous women.

**Methods:** A randomized, double-blind, controlled trial was conducted among nulliparous post-date (>40 weeks) pregnant women between June and December 2019. At enrollment 100 women were randomized into each group (either HVFC and vaginal misoprostol or low-volume Foley catheter [LVFC] [30 ml] and vaginal misoprostol), for labor induction. Demographic and clinical data were collected at enrollment and delivery.

**Results:** Women in the HVFC group had statistically significantly shorter induction to delivery interval (median 860 min, interquartile range [IQR] 840-940 min vs. 1160 min, IQR 1080-1320 min,  $P < 0.001$ ) and duration of labor (median 615 min, IQR 600-680 min vs. 750, IQR 692.5-800 min,  $P < 0.001$ ). Mode of vaginal delivery ( $n = 94$  vs.  $n = 78$ ,  $P = 0.002$ ), number of doses of misoprostol required (median 2, IQR 1-2 vs. 2, IQR 1-3), and need of oxytocin augmentation ( $n = 22$  vs.  $n = 39$ ,  $P = 0.014$  and  $P < 0.001$ ), was significantly better in the HVFC group. However, there was no significant difference with respect to other maternal or neonatal outcomes.

**Conclusion:** Simultaneous use of HVFC and vaginal misoprostol for labor induction significantly shortens the induction to delivery interval and duration of labor in nulliparous women.

Int J Gynaecol Obstet. 2022 Sep 24.



doi: 10.1002/ijgo.14477. Online ahead of print.

**[Efficacy of combination of transcervical Foley catheter and sublingual misoprostol versus sublingual misoprostol for labor induction in pre-eclampsia at 28-34 weeks](#)**

[Jyotsna Sharma](#)<sup>1</sup>, [Haritha Sagili](#)<sup>1</sup>, [Anish Keepanasseril](#)<sup>1</sup>

**Abstract**

**Objective:** To compare the efficacy of using a combination of transcervical Foley catheter and sublingual misoprostol with sublingual misoprostol alone for induction of labor (IOL) in women with pre-eclampsia between 28 and 34 weeks of pregnancy.

**Methods:** This randomized controlled trial was conducted on women with pre-eclampsia at 28-34 weeks of pregnancy, with unfavorable cervix, admitted to a tertiary hospital in south India. They were randomized to receive either a combination of transcervical Foley catheter and sublingual misoprostol, or sublingual misoprostol alone. Vaginal birth within 24 h of induction, induction to delivery interval, and neonatal morbidity/mortality were the main outcome measures.

**Results:** Vaginal birth within 24 h was higher with the combination of Foley catheter and sublingual misoprostol compared with sublingual misoprostol alone (60% versus 41.4%,  $P = 0.028$ ). Overall vaginal delivery rates were comparable between the groups (90% versus 80%,  $P = 0.051$ ). There was no difference in number of doses of misoprostol, and induction to delivery interval between groups. After excluding those with lower likelihood of neonatal survival, live birth rates, mean birth weight, and neonatal intensive care unit admission rates were similar in both groups.

**Conclusions:** Combination of transcervical Foley catheter and sublingual misoprostol was found to be more effective in achieving vaginal birth within 24 h compared with sublingual misoprostol for IOL in pre-eclampsia between 28 and 34 weeks of pregnancy.

Pregnancy Hypertens. 2022 Aug;29:1-6.

doi: 10.1016/j.preghy.2022.05.001. Epub 2022 May 8.

**[Comparison of intravenous labetalol and hydralazine for severe hypertension in pregnancy in Northeastern Nigeria: A randomized controlled trial](#)**

[Sagir Muhammad](#)<sup>1</sup>, [Hadiza Usman](#)<sup>2</sup>, [Yahaya Musa Dawha](#)<sup>3</sup>, [Anisah Yahya](#)<sup>4</sup>, [Ayoola Yekeen](#)<sup>5</sup>, [Babagana Bako](#)<sup>6</sup>

**Abstract**

**Objectives:** The objectives were to compare the efficacy and safety of intravenous hydralazine and labetalol for acutely lowering severe hypertension in pregnancy.

**Study design:** This was a superiority parallel double-blinded randomized controlled trial conducted from October 2018 to June 2019 in two hospitals in Gombe, Nigeria. Pregnant women with a live singleton fetus at gestational age of at least 28 weeks with severe hypertension were randomized (60 per group) to receive incremental doses of either intravenous labetalol (20 mg; 40 mg; 80 mg; 80 mg; and 80 mg) or 10 mg of intravenous hydralazine - up to a maximum of 5 doses - until the target blood pressure was achieved or the study was terminated.

**Main outcome measures:** The main outcome measures were the mean reduction in mean arterial blood pressure and occurrence of persistent hypertension. Other endpoints were maternal side-effects, perinatal death, Apgar score at birth and SCBU admission.

**Results:** One hundred and thirteen patients' data were analyzed (fifty-six [56] in the hydralazine group and fifty-seven [57] in the labetalol group). There were no significant differences in the fall of the mean arterial blood pressure (labetalol; 24.19 mmHg/hydralazine; 27.68 mmHg) ( $p = 0.192$ ), maternal side effects, perinatal deaths, Apgar scores and SCBU admission between the two groups. Hydralazine, however, produced a more marked reduction in diastolic blood pressure than labetalol ( $p = 0.012$ ).

**Conclusion:** Both labetalol and hydralazine are effective for acute blood pressure control in pregnancy with a similar safety profile

AJOG Glob Rep. 2022 May 19;2(3):100061.

doi: 10.1016/j.xagr.2022.100061. eCollection 2022 Aug.

[\*\*A comparative analysis of neonatal outcomes in pregnancies complicated by preeclampsia and eclampsia in Ghana\*\*](#)

[Emma R Lawrence](#), [Titus K Beyuo](#), [Emily K Kobernik](#), [Cheryl A Moyer](#), [Samuel A Oppong](#)

**Abstract**

**Background:** Worldwide, hypertensive disorders of pregnancy are a serious complication of pregnancy, and contribute to poor maternal and neonatal outcomes. The most significant consequences of hypertensive disorders of pregnancy are observed in sub-Saharan Africa, where neonatal outcomes have not been fully described. Understanding relationships between maternal disease severity and neonatal outcomes can guide patient counseling and allow the targeting of limited resources to the most at-risk neonates.

**Objective:** To describe and compare neonatal outcomes in pregnancies complicated by preeclampsia with severe features and eclampsia.

**Study design:** This study is a secondary analysis of data collected as part of a randomized controlled trial at the Korle-Bu Teaching Hospital in Ghana. Participants were adult pregnant women with preeclampsia with severe features or eclampsia and their neonates. Data include prospectively collected medical and obstetrical history, intrapartum events, and neonatal outcomes. The main outcome of this secondary analysis was a composite of poor neonatal outcomes, defined as 1 or more of the following: stillbirth, very low birthweight (<1500 g), 5-minute Apgar score <7, neonatal intensive care unit admission, or a live birth with a subsequent death before discharge.

**Results:** Median gestational age at delivery was 36.6 weeks (interquartile range, 33.3-38.9). Median birthweight was 2.3 kg (interquartile range, 1.6-3.0), with 227 (19.0%) birthweights <1500 g. There were 162 neonates (15.5%) with an Apgar score <7 at 5 minutes and 144 (11.9%) were stillbirths. Of live births, half ( $n=524$ , 50.3%) were admitted to the neonatal intensive care unit and 7.9% ( $n=91$ ) died before discharge. A composite of poor neonatal outcomes was experienced by 58.2% ( $n=707$ ) of neonates and was twice as likely with a maternal diagnosis of eclampsia (odds ratio, 1.91;  $P=.04$ ). For each additional week of gestational age, the probability of a poor neonatal outcome was reduced by 39% (odds ratio, 0.61;  $P<.0001$ ).

**Conclusion:** Poor neonatal outcomes were experienced by more than half of pregnancies complicated by preeclampsia with severe features or eclampsia. Even after controlling for gestational age, pregnancies complicated by eclampsia were twice as likely to have poor neonatal outcomes.

Int J Gynaecol Obstet. 2022 Sep 30.

doi: 10.1002/ijgo.14483. Online ahead of print.

**[Breech delivery in low-income settings: A systematic review of perinatal and maternal outcomes in vaginal versus cesarean breech deliveries](#)**

[Herman A Sorensen](#)<sup>1</sup>, [Josephine Obel](#)<sup>2</sup>, [Jeppe B Schroll](#)<sup>3,4</sup>, [Lone Krebs](#)<sup>3,4</sup>

**Abstract**

Most studies comparing vaginal breech delivery (VBD) with cesarean breech delivery (CBD) have been conducted in high-income settings. It is uncertain whether these results are applicable in a low-income setting. To assess the neonatal and maternal mortality and morbidity for singleton VBD compared to CBD in low- and lower-middle-income settings, the PubMed database was searched from January 1, 2000, to January 23, 2020 (updated April 21, 2021). Randomized controlled trials (RCTs) and non-RCTs comparing singleton VBD with singleton CBD in low- and lower-middle-income settings reporting infant mortality were selected. Two authors independently assessed papers for eligibility and risk of bias. The primary outcome was relative risk of perinatal mortality. Meta-analysis was conducted on applicable outcomes. Eight studies (one RCT, seven observational) (12 510 deliveries) were included. VBD increased perinatal mortality (relative risk [RR] 2.67, 95% confidence interval [CI] 1.82-3.91; one RCT, five observational studies, 3289 women) and risk of 5-minute Apgar score below 7 (RR 3.91, 95% CI 1.90-8.04; three observational studies, 430 women) compared to CBD. There was a higher risk of hospitalization and postpartum bleeding in CBD. Most of the studies were deemed to have moderate or serious risk of bias. CBD decreases risk of perinatal mortality but increases risk of bleeding and hospitalization.

AJOG Glob Rep. 2022 Jul 20;2(3):100075.

doi: 10.1016/j.xagr.2022.100075. eCollection 2022 Aug.

**[Impact of WHO Labor Care Guide on reducing cesarean sections at a tertiary center: an open-label randomized controlled trial](#)**

[Divya Pandey](#)<sup>1</sup>, [Rekha Bharti](#)<sup>1</sup>, [Anjali Dabral](#)<sup>1</sup>, [Zeba Khanam](#)<sup>1</sup>

**Abstract**

**Background:** The World Health Organization Labor Care Guide was introduced in December 2020 to implement World Health Organization (WHO) guidelines on intrapartum care for a positive childbirth experience.

**Objective:** This study aimed to determine the effect of the WHO Labor Care Guide on labor outcomes, especially in reducing primary cesarean deliveries, and its acceptability by healthcare providers.

**Study design:** This open-label randomized control trial was conducted from September 2021 to December 2021 on 280 low-risk antenatal women admitted for delivery at a busy tertiary care institute in North India. After informed consent, women were allocated into the study and control groups. Labor monitoring was performed using the WHO Labor Care Guide in the study group and the World Health Organization-modified partograph in the control group. Women who had a cesarean delivery in the latent phase of labor were excluded from the study. The primary outcome was mode of delivery, whereas the secondary outcomes were duration of active labor, maternal complications (postpartum hemorrhage and puerperal sepsis), duration of hospital stay, Apgar score at 5 minutes, and neonatal intensive

care unit admission. The labor outcomes in both groups were compared. In the study group, the acceptability, difficulty, and satisfaction levels of the users were assessed using a 5-point Likert scale. The "learning curve" for the use of the Labor Care Guide (LCG) was determined. SPSS software (version 21.0; IBM Corporation, Chicago, IL) was used for statistical analysis.

**Results:** After excluding women who underwent cesarean delivery in the latent phase, 136 women in the study group and 135 women in the control group were observed for labor outcomes. The cesarean delivery rate was 1.5% in the study group vs 17.8% in the control group ( $P=.0001$ ). The duration of the active phase of labor was significantly shorter in the study group than in the control group ( $P<.001$ ). The 2 groups were similar in terms of maternal complications, duration of hospital stay, and Apgar score. The learning curve took average levels of 6.50 and 2.25 Labor Care Guide plots to shift from "very difficult" to "neutral" and "neutral" to "easy," respectively. After an initial learning curve, acceptability and satisfaction levels were found to be high in the WHO Labor Care Guide users.

**Conclusion:** The WHO Labor Care Guide is a simple labor monitoring tool for the reducing primary cesarean delivery rate without increasing the duration of hospital stay and fetomaternal complications.

## Maternal nutrition and micronutrient supplementation

Matern Child Nutr. 2022 Nov 9;e13456.

doi: 10.1111/mcn.13456. Online ahead of print.

### [Supplementary feeding and infection control in pregnant adolescents-A secondary analysis of a randomized trial among malnourished women in Sierra Leone](#)

[Aminata S Koroma](#)<sup>1</sup>, [Mariama Ellie](#)<sup>1</sup>, [Kadiatu Bangura](#)<sup>1</sup>, [Per O Iversen](#)<sup>2,3,4</sup>, [David T Hendrixson](#)<sup>5</sup>, [Kevin Stephenson](#)<sup>6</sup>, [Mark J Manary](#)<sup>7</sup>

#### **Abstract**

Undernutrition during pregnancy in adolescence confers a high risk of maternal morbidity and adverse birth outcomes, particularly in low-resource settings. In a secondary analysis, we hypothesized that younger undernourished pregnant adolescents (<18 years) would benefit more than undernourished pregnant adults (>20 years) from the intervention of supplementary food and anti-infective treatments. The original trial in Sierra Leone enrolled 236 younger adolescents (<18 years), 454 older adolescents (aged 18-19 years), and 741 adults ( $\geq 20$  years), all with a mid-upper arm circumference  $\leq 23$  cm. Younger adolescents had lower final fundal height as well as smaller newborns (-0.3 kg; 95% confidence interval [CI], -0.3, -0.2;  $p < 0.001$ ) and shorter newborns (-1.1 cm; 95% CI, -1.5, -0.7;  $p < 0.001$ ) than adults. The intervention's effect varied significantly between maternal age groups: adults benefited more than younger adolescents with respect to newborn birth weight (difference in difference, 166 g; 95% CI, 26, 306; interaction  $p = 0.02$ ), birth length (difference in difference, 7.4 mm; 95% CI, 0.1, 14.8; interaction  $p = 0.047$ ), and risk for low birth weight (<2.5 kg) (interaction  $p = 0.019$ ). The differences in response persisted despite adjustments for maternal anthropometry, the number of prior pregnancies, and human immunodeficiency virus status. Older adolescents similarly benefited more than younger adolescents, though differences did not reach statistical significance. In conclusion, newborns born to younger

adolescent mothers had worse outcomes than those born to adult mothers, and adults and their newborns benefited more from the intervention than younger adolescents.

J Dev Orig Health Dis. 2023 Jun;14(3):437-448.

doi: 10.1017/S204017442200068X. Epub 2023 Jan 12.

**Differential expression of genes influencing mitotic processes in cord blood mononuclear cells after a pre-conceptual micronutrient-based randomised controlled trial: Pune Rural Intervention in Young Adolescents (PRIYA)**

[Satyajeeet P Khare<sup>#1,2</sup>](#), [Ayush Madhok<sup>#1</sup>](#), [Indumathi Patta<sup>1</sup>](#), [Krishna K Sukla<sup>3</sup>](#), [Vipul V Wagh<sup>2</sup>](#), [Pooja S Kunte<sup>3</sup>](#), [Deepa Raut<sup>3</sup>](#), [Dattatray Bhat<sup>3</sup>](#), [Kalyanaraman Kumaran<sup>4</sup>](#), [Caroline Fall<sup>4</sup>](#), [Utpal Tatu<sup>5</sup>](#), [Giriraj R Chandak<sup>6</sup>](#), [Chittaranjan S Yajnik<sup>3</sup>](#), [Sanjeev Galande<sup>1,7</sup>](#)

**Abstract**

In The Pune Maternal Nutrition Study, vitamin B12 deficiency was seen in 65% of pregnant women, folate deficiency was rare. Maternal total homocysteine concentrations were inversely associated with offspring birthweight, and low vitamin B12 and high folate concentrations predicted higher offspring adiposity and insulin resistance. These findings guided a nested pre-conceptual randomised controlled trial 'Pune Rural Intervention in Young Adolescents'. The interventions included: (1) vitamin B12+multi-micronutrients as per the United Nations International Multiple Micronutrient Antenatal Preparation, and proteins (B12+MMN), (2) vitamin B12 (B12 alone), and (3) placebo. Intervention improved maternal pre-conceptual and in-pregnancy micronutrient nutrition. Gene expression analysis in cord blood mononuclear cells in 88 pregnancies revealed 75 differentially expressed genes between the B12+MMN and placebo groups. The enriched biological processes included G2/M phase transition, chromosome segregation, and nuclear division. Enriched pathways included, mitotic spindle checkpoint and DNA damage response while enriched human phenotypes were sloping forehead and decreased head circumference. Fructose-bisphosphatase 2 (*FBP2*) and Cell Division Cycle Associated 2 (*CDCA2*) genes were under-expressed in the B12 alone group. The latter, involved in chromosome segregation was under-expressed in both intervention groups. Based on the role of B-complex vitamins in the synthesis of nucleotides and S-adenosyl methionine, and the roles of vitamins A and D on gene expression, we propose that the multi-micronutrient intervention epigenetically affected cell cycle dynamics. Neonates in the B12+MMN group had the highest ponderal index. Follow-up studies will reveal if the intervention and the altered biological processes influence offspring diabetes.

m J Clin Nutr. 2022 Dec 19;116(6):1864-1876.

doi: 10.1093/ajcn/nqac259.

**Effects of prenatal nutritional supplements on gestational weight gain in low- and middle-income countries: a meta-analysis of individual participant data**

[Enju Liu<sup>1,2</sup>](#), [Dongqing Wang<sup>3,4</sup>](#), [Anne M Darling<sup>3</sup>](#), [Nandita Perumal<sup>3</sup>](#), [Molin Wang<sup>5,6</sup>](#), [Tahmeed Ahmed<sup>7</sup>](#), [Parul Christian<sup>8</sup>](#), [Kathryn G Dewey<sup>9</sup>](#), [Gilberto Kac<sup>10</sup>](#), [Stephen Kennedy<sup>11</sup>](#), [Vishak Subramoney<sup>12,13</sup>](#), [Brittany Briggs<sup>14</sup>](#), [Wafaie W Fawzi<sup>3,5,15</sup>](#); [members of the GWG Pooling Project Consortium](#)

**Abstract**

**Background:** Gestational weight gain (GWG) below or above the Institute of Medicine (IOM) recommendations has been associated with adverse perinatal outcomes. Few studies have examined the effect of prenatal nutrient supplementations on GWG in low- and middle-income countries (LMICs).

**Objectives:** We aimed to investigate the effects of multiple micronutrient supplements (MMSs) and small-quantity lipid-based nutrient supplements (LNSs) on GWG in LMICs.

**Methods:** A 2-stage meta-analysis of individual participant data was conducted to examine the effects of MMSs (45,507 women from 14 trials) and small-quantity LNSs (6237 women from 4 trials) on GWG compared with iron and folic acid supplements only. Percentage adequacy of GWG and total weight gain at delivery were calculated according to the IOM 2009 guidelines. Binary outcomes included severely inadequate (percentage adequacy <70%), inadequate (<90%), and excessive (>125%) GWG. Results from individual trials were pooled using fixed-effects inverse-variance models. Heterogeneity was examined using I<sup>2</sup>, stratified analysis, and meta-regression.

**Results:** MMSs resulted in a greater percentage adequacy of GWG [weighted mean difference (WMD): 0.86%; 95% CI: 0.28%, 1.44%; P < 0.01] and higher GWG at delivery (WMD: 209 g; 95% CI: 139, 280 g; P < 0.01) than among those in the control arm. Women who received MMSs had a 2.9% reduced risk of severely inadequate GWG (RR: 0.971; 95% CI: 0.956, 0.987; P < 0.01). No association was found between small-quantity LNSs and GWG percentage adequacy (WMD: 1.51%; 95% CI: -0.38%, 3.40%; P = 0.21). Neither MMSs nor small-quantity LNSs were associated with excessive GWG.

**Conclusions:** Maternal MMSs were associated with greater GWG percentage adequacy and total GWG at delivery than was iron and folic acid only. This finding is consistent with previous results on birth outcomes and will inform policy development and local recommendations of switching routine prenatal iron and folic acid supplements to MMSs.

Arch Dis Child. 2023 May 4;archdischild-2023-325352.

doi: 10.1136/archdischild-2023-325352. Online ahead of print.

**[Neurodevelopment, vision and auditory outcomes at age 2 years in offspring of participants in the 'Women First' maternal preconception nutrition randomised controlled trial](#)**

[Michelle Fernandes](#)<sup>1,2,3</sup>, [Nancy F Krebs](#)<sup>4</sup>, [Jamie Westcott](#)<sup>4</sup>, [Antoinette Tshetu](#)<sup>5</sup>, [Adrien Lokangaka](#)<sup>5</sup>, [Melissa Bauserman](#)<sup>6</sup>, [Ana L Garcés](#)<sup>7</sup>, [Lester Figueroa](#)<sup>7</sup>, [Sarah Saleem](#)<sup>8</sup>, [Sumera A Aziz](#)<sup>8</sup>, [Robert L Goldenberg](#)<sup>9</sup>, [Shivaprasad S Goudar](#)<sup>10</sup>, [Sangappa M Dhaded](#)<sup>10</sup>, [Richard J Derman](#)<sup>11</sup>, [Jennifer F Kemp](#)<sup>4</sup>, [Marion Koso-Thomas](#)<sup>12</sup>, [Amaanti Sridhar](#)<sup>13</sup>, [Elizabeth M McClure](#)<sup>13</sup>, [K Michael Hambidge](#)<sup>4</sup>; [Women First Preconception Nutrition Trial Study Group](#)

**Abstract**

**Background:** Maternal nutrition in preconception and early pregnancy influences fetal growth. Evidence for effects of prenatal maternal nutrition on early child development (ECD) in low-income and middle-income countries is limited.

**Objectives:** To examine impact of maternal nutrition supplementation initiated prior to or during pregnancy on ECD, and to examine potential association of postnatal growth with ECD domains.

**Design:** Secondary analysis regarding the offspring of participants of a maternal multicountry, individually randomised trial.



**Setting:** Rural Democratic Republic of the Congo, Guatemala, India and Pakistan.

**Participants:** 667 offspring of Women First trial participants, aged 24 months.

**Intervention:** Maternal lipid-based nutrient supplement initiated preconceptionally (arm 1, n=217), 12 weeks gestation (arm 2, n=230) or not (arm 3, n=220); intervention stopped at delivery.

**Main outcome measures:** The INTERGROWTH-21st Neurodevelopment Assessment (INTER-NDA) cognitive, language, gross motor, fine motor, positive and negative behaviour scores; visual acuity and contrast sensitivity scores and auditory evoked response potentials (ERP). Anthropometric z-scores, family care indicators (FCI) and sociodemographic variables were examined as covariates.

**Results:** No significant differences were detected among the intervention arms for any INTER-NDA scores across domains, vision scores or ERP potentials. After adjusting for covariates, length-for-age z-score at 24 months (LAZ<sub>24</sub>), socio-economic status, maternal education and FCI significantly predicted vision and INTER-NDA scores ( $R^2=0.11-0.38$ ,  $p<0.01$ ).

**Conclusions:** Prenatal maternal nutrition supplementation was not associated with any neurodevelopmental outcomes at age 2 years. Maternal education, family environment and LAZ<sub>24</sub> predicted ECD. Interventions addressing multiple components of the nurturing care model may offer greatest impact on children's developmental potential.

J Nutr. 2022 Oct 6;152(10):2277-2286.

doi: 10.1093/jn/nxac171.

**[Fortified Balanced Energy-Protein Supplementation, Maternal Anemia, and Gestational Weight Gain: A Randomized Controlled Efficacy Trial among Pregnant Women in Rural Burkina Faso](#)**

[Giles Hanley-Cook](#)<sup>1</sup>, [Laeticia C Toe](#)<sup>1,2</sup>, [Kokeb Tesfamariam](#)<sup>1</sup>, [Brenda de Kok](#)<sup>1</sup>, [Alemayehu Argaw](#)<sup>1</sup>, [Anderson Compaoré](#)<sup>3</sup>, [Moctar Ouédraogo](#)<sup>3</sup>, [Trenton Dailey-Chwalibóg](#)<sup>1</sup>, [Patrick Kolsteren](#)<sup>1</sup>, [Carl Lachat](#)<sup>1</sup>, [Lieven Huybregts](#)<sup>1,4</sup>

**Abstract**

**Background:** Anemia and suboptimal gestational weight gain (GWG) are associated with adverse maternal and birth outcomes. Limited research indicates that balanced energy-protein (BEP) supplements reduce the incidence of inadequate GWG.

**Objectives:** We assessed the efficacy of a micronutrient-fortified BEP supplement on the secondary outcomes of anemia, GWG, GWG rate, and GWG in relation to the Institute of Medicine (IOM)'s recommendations, as compared with an iron-folic acid (IFA) tablet.

**Methods:** We conducted a randomized controlled trial in Burkina Faso, among pregnant women (15-40 y old) enrolled at <21 weeks of gestation. Women received either BEP and IFA (intervention) or IFA (control). Hemoglobin (g/dL) concentrations were measured at baseline and the third antenatal care visit (ANC), whereas maternal weight was measured at baseline and all subsequent ~7-weekly ANCs. GWG (kg) was calculated as a woman's last weight measurement (at ~36 weeks of gestation) minus weight at enrollment, whereas GWG rate (kg/wk) was GWG divided by the time between the first and last weight measurements. GWG adequacy (%) was computed as GWG divided by the IOM's recommendation. Binary outcomes included severely inadequate, inadequate, and excessive GWG. Statistical analyses followed the intention-to-treat principle. Linear regression and probability models were fitted for the continuous and binary outcomes, respectively, adjusting for baseline measurements.

**Results:** Women in the BEP group tended to have higher, but nonsignificantly different, GWG (0.28 kg; 95% CI: -0.05, 0.58 kg; P = 0.099). Furthermore, there were no significant differences in prenatal anemia prevalence, GWG rate, GWG adequacy, or incidence of inadequate or excessive GWG. Findings were robust to model adjustments and complete case and per protocol analyses.

**Conclusions:** This trial does not provide evidence that fortified BEP supplementation reduces maternal anemia or increases GWG, as compared with IFA. In conjunction with the small, but positive, effects of maternal BEP supplementation on birth outcomes, our findings warrant the investigation of additional biochemical and postnatal outcomes

Lancet. 2023 May 13;401(10388):1595-1609.

doi: 10.1016/S0140-6736(23)00278-7. Epub 2023 Apr 21.

**Ferric carboxymaltose versus standard-of-care oral iron to treat second-trimester anaemia in Malawian pregnant women: a randomised controlled trial**

[Sant-Rayn Pasricha<sup>1</sup>](#), [Martin N Mwangi<sup>2</sup>](#), [Ernest Moya<sup>3</sup>](#), [Ricardo Ataide<sup>4</sup>](#), [Glory Mzembe<sup>3</sup>](#), [Rebecca Harding<sup>5</sup>](#), [Truwah Zinenani<sup>3</sup>](#), [Leila M Larson<sup>6</sup>](#), [Ayse Y Demir<sup>7</sup>](#), [William Nkhono<sup>3</sup>](#), [Jobiba Chinkhumba<sup>3</sup>](#), [Julie A Simpson<sup>8</sup>](#), [Danielle Clucas<sup>9</sup>](#), [William Stones<sup>10</sup>](#), [Sabine Braat<sup>4</sup>](#), [Kamija S Phiri<sup>11</sup>](#)

**Abstract**

**Background:** Anaemia affects 46% of pregnancies in Africa; oral iron is recommended by WHO but uptake and adherence are suboptimal. We tested a single dose of a modern intravenous iron formulation, ferric carboxymaltose, for anaemia treatment in Malawian pregnant women.

**Methods:** In this open-label, individually randomised controlled trial, we enrolled women with a singleton pregnancy of 13-26 weeks' gestation in primary care and outpatient settings across two regions in southern Malawi. Women were eligible if they had capillary haemoglobin of less than 10.0 g/dL and negative malaria rapid diagnostic test. Participants were randomised by sealed envelope 1:1. Assessors for efficacy outcomes (laboratory parameters and birthweight) were masked to intervention; participants and study nurses were not masked. Participants were given ferric carboxymaltose up to 1000 mg (given once at enrolment in an outpatient primary care setting), or standard of care (60 mg elemental iron twice daily for 90 days), along with intermittent preventive malaria treatment. The primary maternal outcome was anaemia at 36 weeks' gestation. The primary neonatal outcome was birthweight. Analyses were performed in the intention-to-treat population for mothers and liveborn neonates, according to their randomisation group. Safety outcomes included incidence of adverse events during infusion and all adverse events from randomisation to 4 weeks' post partum. The trial is registered with ANZCTR, ACTRN12618001268235. The trial has completed follow-up.

**Findings:** Between Nov 12, 2018, and March 2, 2021, 21 258 women were screened, and 862 randomly assigned to ferric carboxymaltose (n=430) or standard of care (n=432). Ferric carboxymaltose did not reduce anaemia prevalence at 36 weeks' gestation compared with standard of care (179 [52%] of 341 in the ferric carboxymaltose group vs 189 [57%] of 333 in the standard of care group; prevalence ratio [PR] 0.92, 95% CI 0.81 to 1.06; p=0.27). Anaemia prevalence was numerically lower in mothers randomly assigned to ferric carboxymaltose

compared with standard of care at all timepoints, although significance was only observed at 4 weeks' post-treatment (PR 0.91 [0.85 to 0.97]). Birthweight did not differ between groups (mean difference -3.1 g [-75.0 to 68.9,  $p=0.93$ ]). There were no infusion-related serious adverse events or differences in adverse events by any organ class (including malaria;  $\geq 1$  adverse event: ferric carboxymaltose 183 [43%] of 430 vs standard of care 170 [39%] of 432; risk ratio 1.08 [0.92 to 1.27];  $p=0.34$ ).

**Interpretation:** In this malaria-endemic sub-Saharan African setting, treatment of anaemic pregnant women with ferric carboxymaltose was safe but did not reduce anaemia prevalence at 36 weeks' gestation or increase birthweight

Lancet. 2023 May 6;401(10387):1508-1517.

doi: 10.1016/S0140-6736(23)00346-X. Epub 2023 Apr 6.

**The effect of vitamin B12 supplementation during pregnancy on infant growth and development in Nepal: a community-based, double-blind, randomised, placebo-controlled trial**

[Ram K Chandyo](#)<sup>1</sup>, [Ingrid Kvestad](#)<sup>2</sup>, [Manjeswori Ulak](#)<sup>3</sup>, [Suman Ranjitkar](#)<sup>4</sup>, [Mari Hysing](#)<sup>5</sup>, [Merina Shrestha](#)<sup>4</sup>, [Catherine Schwinger](#)<sup>6</sup>, [Adrian McCann](#)<sup>7</sup>, [Per M Ueland](#)<sup>8</sup>, [Sudha Basnet](#)<sup>4</sup>, [Laxman Shrestha](#)<sup>4</sup>, [Tor A Strand](#)<sup>9</sup>

**Abstract**

**Background:** Vitamin B12 is required for healthy infant growth and development, but low and marginal vitamin B12 status is endemic in low-income and middle-income countries. We aimed to measure the effect of vitamin B12 supplementation from early pregnancy until 6 months post partum on infant growth and neurodevelopment.

**Methods:** In this community-based, double-blind, placebo-controlled trial, we randomly assigned (1:1) 800 pregnant women (aged 20-40 years) who were up to 15 weeks pregnant-recruited from home visits and outpatient departments at three hospitals in Nepal-to daily supplementation with 50  $\mu$ g oral vitamin B12 or placebo until 6 months postpartum. Independent scientists generated the list that linked allocation to participants' study identification number. Participants were masked to group assignment and all investigators were masked until data cleaning was completed. The primary outcomes were length-for-age Z score (LAZ) at age 12 months and the cognitive composite score of the Bayley Scales of Infant and Toddler Development (3rd edition) at age 6 months and 12 months. The primary and secondary outcomes, including adverse events, were assessed in the intention-to-treat population, for all participants with available outcome data. This trial is registered with ClinicalTrials.gov, [NCT03071666](#).

**Findings:** 800 eligible pregnant women were enrolled in the trial between March 28, 2017, and Oct 15, 2020, with 400 women randomly assigned to each group. Follow-up was completed on May 18, 2022. At baseline, 569 (71%) of 800 women had plasma vitamin B12 indicating low or marginal status ( $<221$  pmol/L). We found no effect of vitamin B12 on the primary outcomes. The mean LAZ at age 12 months were -0.57 (SD 1.03) in the B12 group and -0.55 (1.03) in the placebo group (366 infants in the vitamin B12 group vs 363 infants in the placebo group) with a mean difference of -0.02 (95% CI -0.16 to 0.13). The mean cognitive composite scores were 97.7 (SD 10.5) in the B12 group and 97.1 (10.2) in the placebo group, with a mean difference of 0.5 (95% CI -0.6 to 1.7) measured in 364 and 361 infants. Stillbirths

or infant deaths occurred in three (1%) of 374 women in the vitamin B12 group and nine (2%) of 379 women in the placebo group.

**Interpretation:** Although vitamin B12 deficiency was prevalent in our study population and vitamin B12 supplementation from early pregnancy substantially improved vitamin B12 status, supplementation did not improve infant growth or neurodevelopment. Our findings support the current WHO recommendations of no routine vitamin B12 supplementation during pregnancy.

PLoS Med. 2023 Feb 6;20(2):e1004186.

doi: 10.1371/journal.pmed.1004186. Online ahead of print.

**[Fortified balanced energy-protein supplementation during pregnancy and lactation and infant growth in rural Burkina Faso: A 2 × 2 factorial individually randomized controlled trial](#)**

[Alemayehu Argaw](#)<sup>1,2</sup>, [Brenda de Kok](#)<sup>1</sup>, [Laeticia Celine Toe](#)<sup>1,3</sup>, [Giles Hanley-Cook](#)<sup>1</sup>, [Trenton Dailey-Chwalibóg](#)<sup>1</sup>, [Moctar Ouédraogo](#)<sup>4</sup>, [Anderson Compaoré](#)<sup>4</sup>, [Katrien Vanslambrouck](#)<sup>1</sup>, [Rasmané Ganaba](#)<sup>4</sup>, [Patrick Kolsteren](#)<sup>1</sup>, [Carl Lachat](#)<sup>1</sup>, [Lieven Huybrechts](#)<sup>1,5</sup>

**Abstract**

**Background:** Optimal nutrition is crucial during the critical period of the first 1,000 days from conception to 2 years after birth. Prenatal and postnatal supplementation of mothers with multimicronutrient-fortified balanced energy-protein (BEP) supplements is a potential nutritional intervention. However, evidence on the long-term effects of BEP supplementation on child growth is inconsistent. We evaluated the efficacy of daily fortified BEP supplementation during pregnancy and lactation on infant growth in rural Burkina Faso.

**Methods and findings:** A 2 × 2 factorial individually randomized controlled trial (MISAME-III) was implemented in 6 health center catchment areas in Houndé district under the Hauts-Bassins region. From October 2019 to December 2020, 1,897 pregnant women aged 15 to 40 years with gestational age <21 completed weeks were enrolled. Women were randomly assigned to the prenatal intervention arms receiving either fortified BEP supplements and iron-folic acid (IFA) tablets (i.e., intervention) or IFA alone (i.e., control), which is the standard of care during pregnancy. The same women were concurrently randomized to receive either of the postnatal intervention, which comprised fortified BEP supplementation during the first 6 months postpartum in combination with IFA for the first 6 weeks (i.e., intervention), or the postnatal control, which comprised IFA alone for 6 weeks postpartum (i.e., control). Supplements were provided by trained village-based project workers under direct observation during daily home visits. We previously reported the effect of prenatal BEP supplementation on birth outcomes. The primary postnatal study outcome was length-for-age z-score (LAZ) at 6 months of age. Secondary outcomes were anthropometric indices of growth (weight-for length and weight-for-age z-scores, and arm and head circumferences) and nutritional status (prevalence rates of stunting, wasting, underweight, anemia, and hemoglobin concentration) at 6 months. Additionally, the longitudinal prevalence of common childhood morbidities, incidence of wasting, number of months of exclusive breastfeeding, and trajectories of anthropometric indices from birth to 12 months were evaluated. Prenatal BEP supplementation resulted in a significantly higher LAZ (0.11 standard deviation (SD), 95% confidence interval (CI) [0.01 to 0.21], p = 0.032) and lower

stunting prevalence (-3.18 percentage points (pp), 95% CI [-5.86 to -0.51],  $p = 0.020$ ) at 6 months of age, whereas the postnatal BEP supplementation did not have statistically significant effects on LAZ or stunting at 6 months. On the other hand, postnatal BEP supplementation did modestly improve the rate of monthly LAZ increment during the first 12 months postpartum (0.01 z-score/month, 95% CI [0.00 to 0.02],  $p = 0.030$ ), whereas no differences in growth trajectories were detected between the prenatal study arms. Furthermore, except for the trend towards a lower prevalence of underweight found for the prenatal BEP intervention at 6 months (-2.74 pp, 95% CI [-5.65 to 1.17],  $p = 0.065$ ), no other secondary outcome was significantly affected by the pre- or postnatal BEP supplementation. **Conclusions:** This study provides evidence that the benefits obtained from prenatal BEP supplementation on size at birth are sustained during infancy in terms of linear growth. Maternal BEP supplementation during lactation may lead to a slightly better linear growth towards the second half of infancy. These findings suggest that BEP supplementation during pregnancy can contribute to the efforts to reduce the high burden of child growth faltering in low- and middle-income countries.

Nutrients. 2022 Nov 5;14(21):4687.

doi: 10.3390/nu14214687.

**[The Impact of Antenatal Balanced Plate Nutrition Education for Pregnant Women on Birth Weight: A Cluster Randomised Controlled Trial in Rural Bangladesh](#)**

[Morseda Chowdhury](#)<sup>1,2</sup>, [Camille Raynes-Greenow](#)<sup>2</sup>, [Patrick Kelly](#)<sup>2</sup>, [Neeloy Ashraful Alam](#)<sup>2</sup>, [Kaosar Afsana](#)<sup>3</sup>, [Sk Masum Billah](#)<sup>2,4</sup>, [Michael John Dibley](#)<sup>2</sup>

**Abstract**

Low birth weight (LBW) is a global public health problem with the highest prevalence in South Asia. It is strongly associated with maternal undernutrition. In South Asia, intra-household food distribution is inequitable, with lower dietary adequacy in women. Evidence that nutrition education improves diet during pregnancy and reduces LBW is weak. We assessed the impact of nutrition education for pregnant women on birth weight in rural Bangladesh. We conducted a parallel, two-arm, cluster-randomised controlled trial, with 36 clusters allocated equally to intervention ( $n = 445$ ) or standard care ( $n = 448$ ). From their first trimester until delivery, intervention participants received education about eating balanced meals to meet daily dietary requirements with diverse food groups. The primary outcome of mean birth weight was 127.5 g higher in the intervention compared to control women, and the intervention reduced the risk of LBW by 57%. Post hoc analyses showed a significantly higher birth weight and a greater reduction in LBW amongst adolescent mothers. The mean number of food groups consumed was significantly higher in the intervention from the third month of pregnancy than in the control. A community-based balanced plate nutrition education intervention effectively increased mean birth weight and reduced LBW, and improved dietary diversity in rural Bangladeshi women.

Food Nutr Bull. 2022 Sep;43(3):351-363.

doi: 10.1177/03795721221078351. Epub 2022 Apr 13.



**[Effect of Nutrition Interventions Before and/or During Early Pregnancy on Low Birth Weight in Sub-Saharan Africa: A Systematic Review and Meta-Analysis](#)**

[Melesse Niguse Kuma](#)<sup>1</sup>, [Dessalegn Tamiru](#)<sup>1</sup>, [Girma Beressa](#)<sup>1</sup>, [Tefera Belachew](#)<sup>1,2</sup>

**Abstract**

**Background:** This review aimed at synthesizing evidence on the effectiveness of nutritional interventions that were carried out before and/or during early pregnancy versus the control groups on reducing the risk of low weight at birth in sub-Saharan Africa.

**Methods:** We have searched on MEDLINE, SCOPUS, CINAHL, HINARI, and Cochrane Library of systematic review databases for published articles in English language from 2010 to 2021 years. For unpublished studies, we searched on Google scholar. Randomized controlled trial studies of nutritional interventions carried out before/or during early pregnancy in sub-Saharan Africa to improve low birth weight were considered. The data were extracted and pooled using the Joanna Briggs Institute software. The effect size was calculated using fixed-effect models. Mantel-Haenszel method was used to calculate the relative risk with their respective 95% CI. Heterogeneity was assessed using the standard chi-square and  $I^2$  tests.

**Results:** Seven studies were included in the review with a total of 5934 participants. Three types of nutritional interventions were identified: iron supplementations, lipid-based supplementations, and nutritional education and counseling. We have identified only one intervention started during preconception. The meta-analysis showed that none of the identified nutrition interventions had a statistically significant effect on low birth weight.

**Conclusions:** Based on the review evidence, nutritional interventions before and/or during early pregnancy in sub-Saharan Africa had no significant effect on low birth weight. However, since our evidence was derived from a small number of trials and participants, a large-scale randomized controlled trials review might be required to elucidate the finding.

J Nutr. 2022 Sep 6;152(9):2145-2154.

doi: 10.1093/jn/nxac104.

**[Seasonality and Day-to-Day Variability of Dietary Diversity: Longitudinal Study of Pregnant Women Enrolled in a Randomized Controlled Efficacy Trial in Rural Burkina Faso](#)**

[Giles T Hanley-Cook](#)<sup>1</sup>, [Alemayehu Argaw](#)<sup>1</sup>, [Brenda de Kok](#)<sup>1</sup>, [Laeticia Celine Toe](#)<sup>1,2</sup>, [Trenton Dailey-Chwalibóg](#)<sup>1</sup>, [Moctar Ouédraogo](#)<sup>3</sup>, [Patrick Kolsteren](#)<sup>1</sup>, [Lieven Huybrechts](#)<sup>1,4</sup>, [Carl Lachat](#)<sup>1</sup>

**Abstract**

**Background:** Panel data indicate that nonpregnant women's dietary diversity fluctuates across climatic seasons in low- and middle-income countries. The natural day-to-day variability in food group consumption during gestation is unknown.

**Objectives:** A longitudinal study was conducted among pregnant women enrolled in the Micronutrients pour la Santé de la Mère et de l'Enfant study 3 randomized controlled efficacy trial [i.e., daily fortified balanced energy-protein supplement and an iron-folic acid (IFA) tablet compared with an IFA tablet only] to investigate the number of 24-hour recalls required to estimate usual prenatal food group (FG) diversity and the seasonality of pregnant women's dietary diversity in Houndé, Burkina Faso.

**Methods:** FG consumption was assessed twice weekly by qualitative, list-based, 24-hour recalls among 1757 pregnant women (892 control, 865 intervention). The number of days needed to estimate a woman's usual prenatal 10-point FG diversity score was calculated using the within-subject coefficient of variation. Regression models, including truncated



Fourier series, were fitted to assess seasonal variations in the FG diversity score and the probability of reaching Minimum Dietary Diversity for Women (MDD-W; i.e.,  $\geq 5$  FGs).

**Results:** The monthly mean FG scores ( $< 5$  FGs) and MDD-W prevalence ( $< 45\%$ ) were low. Five list-based recalls allowed observed FG diversity to lie within 15% of the true mean in 90% of the estimations (mean  $\pm$  SD,  $40.4 \pm 20.7$  recalls per woman). Both the FG diversity score and prevalence achieving MDD-W showed responsiveness to seasonal variations, with peaks at the end of the dry season (i.e., April or May) and troughs in the rainy season (i.e., August).

**Conclusions:** Five list-based recalls are sufficient to estimate usual FG diversity during gestation, although intra-annual seasonal patterns did modestly affect the FG diversity score and MDD-W prevalence. Thus, timing of repeated dietary surveys is critical to ensure nonbiased inferences of change and trends in Burkina Faso.

J Obstet Gynaecol India. 2022 Dec;72(6):492-496.

doi: 10.1007/s13224-022-01653-8. Epub 2022 Apr 15.

### [A Randomised Controlled Trial to Compare Injection Ferric Carboxymaltose and Oral Iron in Treating Iron Deficiency Anemia During Pregnancy](#)

[Sushil Chawla](#)<sup>1</sup>, [Akhileshwar Singh](#)<sup>2</sup>, [D Jhamb](#)<sup>3</sup>, [C H Anupama](#)<sup>4</sup>

#### Abstract

**Introduction:** Iron deficiency anemia (IDA) in pregnancy has a prevalence as high as 40-60% in different countries of the world. Oral iron is used to treat his commonest medical disorder in pregnancy. Ferrous sulphate is associated with considerable side effects. Ferric carboxymaltose (FCM) is a newer iron preparation which allows for single and higher dose (up to 1000 mg) of IV iron infusion. This study was conducted to compare the efficacy of FCM and FS in treating IDA during pregnancy.

**Methods:** A randomised control trial was done at a tertiary care centres involving 362 women (181 women each in FS and FCM group). The pregnant anemic women with IDA were enrolled between 18 and 34 weeks of pregnancy. They were given 1000 mg of FCM iv as single dose or were given FS tablets twice daily (120 mg iron daily). The data were collected for rise in the Hb and serum ferritin over a period of 6 weeks.

**Results:** Nine and 18 patients were lost to follow-up in the FCM and FS group, respectively. The data were analysed as per protocol analysis. FCM group women showed 2.6 gm% rise in Hb compared to 1.7 gm% of FS group. One hundred and sixty-six out of 172 women in FS group achieved anemia correction at 6 weeks. No difference was observed in the neonatal outcome. No major side effects were observed in the either group.

**Conclusion:** In our study, FCM was more effective than oral FS in increasing Hb in women with IDA during pregnancy. This clinical benefit with FCM was achieved without the concerns for safety and tolerability of the drug.

Fertil Steril. 2022 Jul;118(1):111-122.

doi: 10.1016/j.fertnstert.2022.04.017. Epub 2022 May 28.

### [Vitamin D and miscarriage: a systematic review and meta-analysis](#)

[Jennifer A Tamblyn<sup>1</sup>](#), [Nicole S P Pilarski<sup>2</sup>](#), [Alexandra D Markland<sup>3</sup>](#), [Ella J Marson<sup>3</sup>](#), [Adam Devall<sup>4</sup>](#), [Martin Hewison<sup>5</sup>](#), [Rachel K Morris<sup>6</sup>](#), [Arri Coomarasamy<sup>7</sup>](#)

## Abstract

**Objective:** To investigate whether a significant association between vitamin D status and the risk of miscarriage or recurrent miscarriage (RM) exists.

**Design:** Systematic review and meta-analysis.

**Setting:** Not applicable.

**Patient(s):** Women with miscarriage and RM.

**Intervention(s):** We searched the Ovid MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature, and Cochrane Central Register of Controlled Trials from database inception to May 2021. Randomized and observational studies investigating the association between maternal vitamin D status and miscarriage and/or vitamin D treatment and miscarriage were included.

**Main outcome measure(s):** The primary outcome was miscarriage or RM, with vitamin D status used as the predictor of risk. Whether vitamin D treatment reduces the risk of miscarriage and RM was also assessed.

**Result(s):** Of 902 studies identified, 10 (n = 7,663 women) were included: 4 randomized controlled trials (n = 666 women) and 6 observational studies (n = 6,997 women). Women diagnosed with vitamin D deficiency (<50 nmol/L) had an increased risk of miscarriage compared with women who were vitamin D replete (>75 nmol/L) (odds ratio, 1.94; 95% confidence interval, 1.25-3.02; 4 studies; n = 3,674; I<sup>2</sup> = 18%). Combined analysis, including women who were vitamin D insufficient (50-75 nmol/L) and deficient (<50 nmol/L) compared with women who were replete (>75 nmol/L), found an association with miscarriage (odds ratio, 1.60; 95% confidence interval, 1.11-2.30; 6 studies; n = 6,338; I<sup>2</sup> = 35%). Although 4 randomized controlled trials assessed the effect of vitamin D treatment on miscarriage, study heterogeneity, data quality, and reporting bias precluded direct comparison and meta-analysis. The overall study quality was "low" or "very low" using the Grading of Recommendations, Assessment, Development and Evaluations approach.

**Conclusion(s):** Vitamin D deficiency and insufficiency are associated with miscarriage. Whether preconception treatment of vitamin D deficiency protects against pregnancy loss in women at risk of miscarriage remains unknown.

Am J Clin Nutr. 2022 Sep 21;nqac259.

doi: 10.1093/ajcn/nqac259. Online ahead of print.

## **Effects of prenatal nutritional supplements on gestational weight gain in low- and middle-income countries: a meta-analysis of individual participant data**

[Enju Liu<sup>1,2</sup>](#), [Dongqing Wang<sup>3,4</sup>](#), [Anne Marie Darling<sup>3</sup>](#), [Nandita Perumal<sup>3</sup>](#), [Molin Wang<sup>5,6</sup>](#), [Tahmeed Ahmed<sup>7</sup>](#), [Parul Christian<sup>8</sup>](#), [Kathryn G Dewey<sup>9</sup>](#), [Gilberto Kac<sup>10</sup>](#), [Stephen Kennedy<sup>11</sup>](#), [Vishak Subramoney<sup>12,13</sup>](#), [Brittany Briggs](#), [Wafaie W Fawzi<sup>3,5,14</sup>](#), [members of the GWG Pooling Project Consortium](#)

## Abstract

**Background:** Gestational weight gain (GWG) below or above the Institute of Medicine (IOM) recommendations has been associated with adverse perinatal outcomes. Few studies have examined the effect of prenatal nutrient supplementations on GWG in low- and middle-income countries (LMICs).

**Objectives:** To investigate the effects of multiple micronutrient supplements (MMS) and small-quantity lipid-based nutrient supplements (LNS) on GWG in LMICs.

**Methods:** A two-stage meta-analysis of individual participant data was conducted to examine the effects of MMS (45,507 women from 14 trials) and small-quantity LNS (6,237 women from 4 trials) on GWG compared to iron and folic acid supplements only. Percent adequacy of GWG and total weight gain at delivery were calculated according to the IOM 2009 guidelines. Binary outcomes included severely inadequate (% adequacy < 70%), inadequate (< 90%), and excessive (>125%) GWG. Results from individual trials were pooled using fixed-effects inverse-variance models. Heterogeneity was examined using I<sup>2</sup>, stratified analysis, and meta-regression.

**Results:** MMS resulted in a greater % adequacy of GWG (weighted mean difference (WMD): 0.86%; 95% CI: 0.28%, 1.44%; P < 0.01) and higher GWG at delivery (WMD: 209 g; 95% CI: 139, 280; P < 0.01) than among those in the control arm. Women who received MMS had a 2.9% reduced risk of severely inadequate GWG (RR: 0.971; 95% CI: 0.956, 0.987; P < 0.01). No association was found between small-quantity LNS and GWG % adequacy (WMD: 1.51%; 95% CI: -0.38%, 3.40%; P = 0.21). Neither MMS nor small-quantity LNS was associated with excessive GWG.

**Conclusions:** Maternal MMS was associated with a greater GWG % adequacy and total GWG at delivery compared to iron and folic acid only. This finding is consistent with previous results on birth outcomes and will inform policy development and local recommendation of switching routine prenatal iron and folic acid supplements to MMS.

Nutrients. 2022 Jul 22;14(15):3003.

doi: 10.3390/nu14153003.

**Differential Effects of Three Nutritional Supplements on the Nutrient Intake of Pregnant Women Enrolled in a Conditional Cash Transfer Program in Mexico: A Cluster Randomized Trial**

[Fabiola Mejía-Rodríguez<sup>1</sup>](#), [Amado D Quezada-Sánchez<sup>2</sup>](#), [Ignacio Méndez Gómez-Humarán<sup>3</sup>](#), [Raquel García-Feregrino<sup>2</sup>](#), [Armando García-Guerra<sup>1</sup>](#), [Ana Cecilia Fernández-Gaxiola<sup>1</sup>](#), [Lynnette M Neufeld<sup>4</sup>](#)

**Abstract**

Supplementation in malnourished pregnant women should not displace natural healthy foods.

**Objective:** To estimate the differential effects of three nutritional supplements on macro- and micronutrient intake of pregnant women beneficiaries of the conditional cash transfer program Prospera (CCT-POP).

**Methods:** Prospective cluster randomized trial. Communities were randomly assigned to receive a fortified beverage (Beverage), micronutrient tablets (Tablets), or micronutrient powder (MNP). Pregnant women (at <math>\geq 25</math> weeks) were recruited. The food frequency questionnaire was applied at 25 and 37 weeks of pregnancy and at one and three months postpartum (mpp). Differential effects of the three supplements on the median change in nutrient intake from baseline to each follow-up stage were estimated.

**Results:** Median change in protein intake from dietary and supplement sources were significantly lower for MNP and Tablets than for Beverages (baseline to 37 w:  $-7.80 \pm 2.90$  and  $-11.54 \pm 3.00$ , respectively; baseline to 1 mpp:  $-7.34 \pm 2.90$  for MNP,  $p < 0.001$ ). Compared to

Beverages, median increases were higher for the MNP for vitamins C ( $31.2 \pm 11.7$ ,  $p < 0.01$ ), E ( $1.67 \pm 0.81$ ,  $p < 0.05$ ), and B12 ( $0.83 \pm 0.27$ ,  $p < 0.01$ ) from baseline to 37 wk; from baseline to 1 mpp, there was a higher median increase in B12 ( $0.55 \pm 0.25$ ,  $p < 0.05$ ) and folate ( $63.4 \pm 24.3$ ,  $p < 0.01$ ); and from baseline to 3 mpp, a higher median increase in iron ( $2.38 \pm 1.06$ ,  $p < 0.05$ ) and folate ( $94.4 \pm 38.1$ ,  $p < 0.05$ ).

**Conclusions:** Intake of micronutrients was higher for MNP and Tablets, likely due to food displacement among Beverage consumers. Although iron bioavailability and absorption inhibitors were not considered for the present analyses, the distribution of Tablets or MNP had several advantages in this context where micronutrient deficiency remains high among pregnant women, but macronutrient intake is generally adequate or even high.

## Post-natal maternal care

J Matern Fetal Neonatal Med. 2023 Dec;36(1):2185754.

doi: 10.1080/14767058.2023.2185754.

[Oral domperidone versus placebo for enhancing exclusive breastfeeding among post-lower segment cesarean section mothers - a double-blind randomized controlled trial](#)  
[Arumugom Archana](#)<sup>1</sup>, [Bethou Adhisivam](#)<sup>2</sup>, [Latha Chaturvedula](#)<sup>3</sup>, [Sadhana Subramanian](#)<sup>4</sup>

### Abstract

**Objective:** To assess whether oral domperidone compared to placebo increases the rate of exclusive breastfeeding for 6 months among post-lower segment cesarean section (LSCS) mothers.

**Methods:** This double-blind Randomized Controlled Trial, conducted in a tertiary care teaching hospital in South India, included 366 post-LSCS mothers with delayed initiation of breastfeeding or with subjective feelings of not having enough milk. They were randomized to two groups - Group A: Standard lactation counseling and oral Domperidone and Group B: Standard lactation counseling and a placebo. The primary outcome was an exclusive breastfeeding rate at 6 months. Exclusive breastfeeding rates at 7 days and 3 months and serial weight gain of an infant were assessed in both groups.

**Results:** Exclusive breastfeeding rate at 7 days was statistically significant in the intervention arm. The exclusive breastfeeding rates at 3 months and 6 months were higher in the domperidone arm compared to placebo but not statistically significant.

**Conclusion:** Oral Domperidone along with effective breastfeeding counseling showed an increasing trend of exclusive breastfeeding rate at 7 days and at six months. Appropriate breastfeeding counseling and postnatal lactation support are important in enhancing exclusive breastfeeding.

BMC Pregnancy Childbirth. 2022 Oct 29;22(1):800.

doi: 10.1186/s12884-022-05138-4.

[Effectiveness of adjunct telephone-based postnatal care on maternal and infant illness in the Greater Accra Region, Ghana: a randomized controlled trial](#)

[Donne Kofi Ameme](#)<sup>1,2</sup>, [Patricia Akweongo](#)<sup>3</sup>, [Edwin Andrew Afari](#)<sup>4</sup>, [Charles Lwanga Noora](#)<sup>5,4</sup>, [Richard Anthony](#)<sup>6</sup>, [Ernest Kenu](#)<sup>5,4</sup>

## Abstract

**Introduction:** Globally, postnatal care (PNC) is fraught with challenges. Despite high PNC coverages in Ghana's Greater Accra Region (GAR), maternal and newborn health outcomes are of great concern. In 2017, neonatal and post-neonatal mortality rates in GAR were 19 and 13 per 1000 live births respectively despite PNC coverages of 93% for at least one PNC and 87.5% for PNC within 48 hours post-delivery. Telephone follow-up has been used to improve health outcomes in some settings, however, its usefulness in improving maternal and infant health during the postnatal period is not well known in Ghana. We assessed effectiveness of telephone-based PNC on infant and maternal illness in selected hospitals in GAR.

**Methods:** An open-label, assessor-blinded, parallel-group, two-arm superiority randomized controlled trial with 1:1 allocation ratio was conducted from September 2020 to March 2021. Mother-baby pairs in intervention arm, in addition to usual PNC, received midwife-led telephone counselling within 48 hours post-discharge plus telephone access to midwife during postnatal period. In control arm, only usual PNC was provided. Descriptive and inferential data analyses were conducted to generate frequencies, relative frequencies, risk ratios and 95% confidence intervals. Primary analysis was by intention-to-treat (ITT), complemented by per-protocol (PP) analysis.

**Results:** Of 608 mother-baby pairs assessed for eligibility, 400 (65.8%) were enrolled. During 3 months follow-up, proportion of infants who fell ill was 62.5% in intervention arm and 77.5% in control arm ( $p = 0.001$ ). Maternal illness occurred in 27.5% of intervention and 38.5% of control participants ( $p = 0.02$ ). Risk of infant illness was 20% less in intervention than control arm in both ITT analysis [RR = 0.8 (95%CI = 0.71-0.92)] and PP analysis [RR = 0.8 (95%CI = 0.67-0.89)]. Compared to controls, risk of maternal illness in intervention arm was 30% lower in both ITT [RR = 0.7 (95%CI = 0.54-0.95)] and PP analysis [RR = 0.7 (95%CI = 0.51-0.94)].

**Conclusion:** Telephone-based PNC significantly reduced risk of maternal and infant illness within first 3 months after delivery. This intervention merits consideration as a tool for adoption and scale up to improve infant and maternal health.

BMJ Open. 2022 Aug 3;12(8):e054148.

doi: 10.1136/bmjopen-2021-054148.

## [Enhanced women's decision-making power after the \*Suchana\* intervention in north-eastern Bangladesh: a cluster randomised pre-post study](#)

[Md Ahshanul Haque](#)<sup>1</sup>, [Nuzhat Choudhury](#)<sup>2</sup>, [S M Tanvir Ahmed](#)<sup>3</sup>, [Fahmida Dil Farzana](#)<sup>1</sup>, [Mohammad Ali](#)<sup>1</sup>, [Farina Naz](#)<sup>1</sup>, [Towfida Jahan Siddiqua](#)<sup>1</sup>, [Mohammad Jyoti Raihan](#)<sup>1</sup>, [Sheikh Shahed Rahman](#)<sup>3</sup>, [A S G Faruque](#)<sup>1</sup>, [Tahmeed Ahmed](#)<sup>1</sup>

## Abstract

**Objectives:** Women's decision-making power is a dimension of empowerment and is crucial for better physical and psychosocial outcomes of mothers. *Suchana*, a large-scale development programme in Bangladesh, actively provided social interventions on behaviour change communication to empower women belonging to the poorest social segment. This paper aims to assess the impact of the *Suchana* intervention on various indicators related to women's decision-making power.

**Design, setting and participants:** The evaluation design was a cluster randomised pre-post design with two cross-sectional surveys conducted among beneficiary women with at least one child aged <23 months from randomly selected poor or very poor beneficiary households in Sylhet division.

**Outcome measure:** Decision-making indicators included food purchases, major household purchases, food preparation, children's healthcare as well as women's own healthcare and visiting family and relatives.

**Results:** Our findings suggest that 45% of women were able to make decisions on food purchases, 25% on major household purchases, 78% on food preparation, 59% on children's healthcare, 51% on their own healthcare and 43% on visiting family and relatives at baseline in the intervention group, whereas the results were almost the same in the control group. In contrast, at the endline survey, the respective proportions were 75%, 56%, 87%, 80%, 77% and 67% in the intervention group, which were significantly improved when compared with the control group. The prevalence of those outcome indicators were 64%, 41%, 80%, 71%, 68% and 56%, respectively, in the control group. As per multiple logistic regression analysis and structural equation modelling, the *Suchana* intervention had a substantial influence on the latent variable of women's decision-making power.

**Conclusion:** In terms of food purchases, major household purchases, children's healthcare, their own healthcare and visiting family and relatives, the *Suchana* intervention favourably influenced the decision-making power of rural women living in a vulnerable region of Bangladesh.

## Maternal mental health

J Int AIDS Soc. 2022 Jul;25(7):e25959.

doi: 10.1002/jia2.25959.

[Interpersonal therapy versus antidepressant medication for treatment of postpartum depression and anxiety among women with HIV in Zambia: a randomized feasibility trial](#)  
[M Bridget Spelke](#)<sup>1,2</sup>, [Ravi Paul](#)<sup>3</sup>, [Bryan S Blette](#)<sup>4</sup>, [Samantha Meltzer-Brody](#)<sup>5</sup>, [Crystal E Schiller](#)<sup>5</sup>, [J M Ncheka](#)<sup>3</sup>, [Margaret P Kasaro](#)<sup>2</sup>, [Joan T Price](#)<sup>1,2</sup>, [Jeffrey S A Stringer](#)<sup>1,2</sup>, [Elizabeth M Stringer](#)<sup>1,2</sup>

### Abstract

**Introduction:** Postpartum depression (PPD) is a prevalent and debilitating disease that may affect medication adherence and thus maternal health and vertical transmission among women with HIV. We assessed the feasibility of a trial of interpersonal psychotherapy (IPT) versus antidepressant medication (ADM) to treat PPD and/or anxiety among postpartum women with HIV in Lusaka, Zambia.

**Methods:** Between 29 October 2019 and 8 September 2020, we pre-screened women 6-8 weeks after delivery with the Edinburgh Postnatal Depression Scale (EPDS) and diagnosed PPD or anxiety with the Mini International Neuropsychiatric Interview. Consenting participants were randomized 1:1 to up to 11 sessions of IPT or daily self-administered sertraline and followed for 24 weeks. We assessed EPDS score, Clinical Global Impression-Severity of Illness (CGI-S) and medication side effects at each visit and measured maternal HIV viral load at baseline and final study visit. Retention, visit adherence, change in EPDS,



CGI-S and log viral load were compared between groups with t-tests and Wilcoxon signed rank tests; we report mean differences, relative risks and 95% confidence intervals. A participant satisfaction survey assessed trial acceptability.

**Results:** 78/80 (98%) participants were retained at the final study visit. In the context of the COVID-19 pandemic, visit adherence was greater among women allocated to ADM (9.9 visits, SD 2.2) versus IPT (8.9 visits, SD 2.4;  $p = 0.06$ ). EPDS scores decreased from baseline to final visit overall, though mean change was greater in the IPT group (-13.8 points, SD 4.7) compared to the ADM group (-11.4 points, SD 5.5;  $p = 0.04$ ). Both groups showed similar changes in mean log viral load from baseline to final study visit (mean difference -0.43, 95% CI -0.32, 1.18;  $p = 0.48$ ). In the IPT group, viral load decreased significantly from baseline (0.9 log copies/ml, SD 1.7) to final visit (0.2 log copies/ml, SD 0.9;  $p = 0.01$ ).

**Conclusions:** This pilot study demonstrates that a trial of two forms of PPD treatment is feasible and acceptable among women with HIV in Zambia. IPT and ADM both improved measures of depression severity; however, a full-scale trial is required to determine whether treatment of PPD and anxiety improves maternal-infant HIV outcomes.

## Family planning and birth spacing

## Meningitis and encephalitis

Indian Pediatr. 2022 Oct 29;S097475591600465.

Online ahead of print.

### [Fourteen Days vs 28 Days of Albendazole Therapy for Neurocysticercosis in Children: An Open Label Randomized Controlled Trial](#)

[Ankit Singla](#)<sup>1</sup>, [Seema Lekhwani](#)<sup>2</sup>, [Narain Das Vaswani](#)<sup>1</sup>, [Jaya Shankar Kaushik](#)<sup>#3</sup>, [Surekha Dabla](#)<sup>4</sup>

#### Abstract

**Background:** There is paucity of literature to support 14-days albendazole therapy for neurocysticercosis (NCC).

**Objective:** To compare the efficacy of 14-day and 28-day albendazole therapy in the management of children with newly diagnosed active NCC.

**Study design:** Open-labelled randomized controlled trial.

**Participants:** Children aged 1-14 years with newly diagnosed active neurocysticercosis.

**Intervention:** Albendazole (15 mg/kg/day) for either of 14 days or 28 days.

**Outcome:** Primary outcome measure was proportion of children with radiological resolution of active lesion at 6-month follow-up. Secondary outcome measures were proportion of children with seizure recurrence, duration to seizure recurrence and calcification on follow-up imaging.

**Results:** A total of 65 children with newly diagnosed NCC were randomized to receive albendazole therapy for 14 days ( $n = 32$ ) or 28 days ( $n = 33$ ). The proportion of children with complete resolution was comparable between the two groups [6(18.8%) vs. 9(27.3%); OR (95%CI):0.61(0.19 to1.98);  $P = 0.56$ ]. Similarly, proportion of children with seizure recurrence [5(15.6%) vs. 2(6.1%); OR (95%CI): 2.87(0.51-16.0);  $P = 0.26$ ] and proportion of children with

calcification on follow-up imaging [26(81.2%) vs. 23(69.7%); OR (95%CI): 1.88(0.59-5.99); P=0.39] were also comparable. There were no major side-effects noted during the study.

**Conclusion:** 14-day treatment with albendazole therapy is as effective as 28-day treatment in achieving radiological resolution at six-month follow-up. However, high rate of calcification in both the groups indicates need for further evaluation with an adequately powered study and longer follow-up.

## Mental health and child psychiatry

Complement Ther Clin Pract. 2023 May;51:101743.

doi: 10.1016/j.ctcp.2023.101743. Epub 2023 Mar 8.

### [Mindfulness group intervention improved self-compassion and resilience of children from single-parent families in Tibetan areas](#)

[Tianyou Guo<sup>1</sup>](#), [Donghong Jiang<sup>1</sup>](#), [Jin Kuang<sup>1</sup>](#), [Meijun Hou<sup>1</sup>](#), [Yanping Gao<sup>1</sup>](#), [Fabian Herold<sup>2</sup>](#), [Alyx Taylor<sup>3</sup>](#), [Yuzhen Huang<sup>1</sup>](#), [Yuming Chen<sup>4</sup>](#)

#### Abstract

**Objective:** The current study aimed to examine the effects of a mindfulness group intervention on self-compassion, psychological resilience, and mental health of children from single-parent families in Tibetan areas.

**Methods:** A total of 64 children from single-parent families in Tibetan areas were randomly allocated to a control group (n = 32) and an intervention group (n = 32). Participants in the control group received conventional education, while participants in the intervention group received 6-week mindfulness intervention in addition to the conventional education. Both groups completed the Five Facet Mindfulness Questionnaire (FFMQ), Self-compassion Scale (SCS), Resilience Scale for Chinese Adolescent (RSCA), and the Mental Health Test (MHT) before and after the intervention.

**Results:** After the intervention, the levels of mindfulness and self-compassion in the intervention group were significantly improved in relative to the control group. The positive cognition in the RSCA was significantly increased in the intervention group, whereas no significant change was observed in the control group. There was a trend towards lower self-blame in the MHT, but no significant impact of the intervention on the overall level of mental health was found.

**Conclusion:** Results suggest that a 6-week mindfulness training effectively improve self-compassion and resilience of single-parent children. Thus, mindfulness training as a cost-effective approach can be arranged in the curriculum, which helps students develop high level of self-compassion and resilience. In addition, there may be a need to improve emotional control in order to improve mental health.

J Behav Ther Exp Psychiatry. 2023 Mar;78:101802.

doi: 10.1016/j.jbtep.2022.101802. Epub 2022 Nov 23.

### [Efficacy of narrative therapy for orphan and abandoned children with anxiety and attention deficit and hyperactivity disorders in Rwanda: A randomized controlled trial](#)

[Françoise Karibwende<sup>1</sup>](#), [Japhet Niyonsenga<sup>2</sup>](#), [Emmanuel Biracyaza<sup>3</sup>](#), [Serge Nyirinkwaya<sup>4</sup>](#), [Innocent Hitayezu<sup>5</sup>](#), [Gitimbwa Simeon Sebatukura<sup>1</sup>](#), [Jeanne Marie Ntete<sup>1</sup>](#), [Jean Mutabaruka<sup>1</sup>](#)

## Abstract

**Background and objective:** Although narrative therapy (NT) is globally practiced for alleviating psychological disorders, studies of its efficacy for vulnerable children are still scarce, especially in African post-conflict settings. Thus, this study was aimed at assessing the efficacy of NT for Rwandan Orphans and abandoned children (OAC) with ADHD and anxiety disorders.

**Method:** This study was a parallel randomized controlled trial in which participants (n = 72) were recruited from SOS Children's Villages. A half of participants (n = 36) were randomly allocated to either the NT group or the waitlist control group (WCG). Outcomes were collected at baseline before randomization and 10 weeks post-randomization.

**Results:** ANOVA results indicated a significant main effect of time for anxiety disorders ( $p < .001$ ,  $\eta^2 = 0.176$ ), and the main effects of group were significant for anxiety disorders ( $p < .001$ ,  $\eta^2 = 0.254$ ) and ADHD disorders ( $p < .001$ ,  $\eta^2 = 0.260$ ). There was a significant time by group interaction effect for anxiety disorders ( $p < .001$ ,  $\eta^2 = 0.328$ ) and for ADHD ( $p < .001$ ,  $\eta^2 = 0.193$ ). Between group analyses showed that the difference in symptoms was significant for anxiety disorders ( $p < .001$ , Cohen's  $d = 1.28$ ) and for ADHD ( $p < .001$ , Cohen's  $d = 1.6$ ) during the posttest, and the effect sizes were large.

**Limitation:** The long-term effects of the intervention for the current sample were not assessed in this study.

**Conclusion:** Despite its limitations, this study provides initial support for the safety, efficacy, and usefulness of NT among Rwandan OAC with ADHD and anxiety disorders. Health professionals must implement the new intervention as an everyday tool.

JAMA Psychiatry. 2023 Jan 1;80(1):22-30.

doi: 10.1001/jamapsychiatry.2022.3989.

## [Effect of General Practitioner Training in a Collaborative Child Mental Health Care Program on Children's Mental Health Outcomes in a Low-Resource Setting: A Cluster Randomized Trial](#)

[Vandad Sharifi<sup>1</sup>](#), [Zahra Shahrivar<sup>1</sup>](#), [Hadi Zarafshan<sup>2</sup>](#), [Sheida Beiky Ashezary<sup>1</sup>](#), [Fariba Arabgol<sup>3</sup>](#), [Mojgan Khademi<sup>4</sup>](#), [Morteza Jafarinia<sup>5,6</sup>](#), [Ahmad Hajebi<sup>7</sup>](#), [Farid Abolhassani<sup>8</sup>](#), [Soheila Emami<sup>9</sup>](#), [Ali Beiki Ashkezari<sup>10</sup>](#), [Elizabeth A Stuart<sup>11</sup>](#), [Ramin Mojtajai<sup>11</sup>](#), [Lawrence Wissow<sup>12</sup>](#)

## Abstract

**Importance:** Integrated care for children is rarely studied, especially in low- and middle-income countries, where generalists often provide mental health care.

**Objectives:** To explore the effect of adding a child and youth component to an existing adult collaborative care program on mental health outcomes and receipt of care.

**Design, setting, and participants:** This cluster randomized trial was conducted within an adult collaborative care program in Tehran, Iran. General practitioners (GPs), their 5- to 15-year-old patients, and patients' parents were included. Children and youths coming for routine medical visits who scored greater than the cutoff on the Strengths and Difficulties Questionnaire (SDQ) were followed up for 6 months. The study was conducted from May 2018 to October 2019, and analysis was conducted from March 2020 to August 2021.

**Interventions:** GPs were randomized to either a 2.5-day training on managing common child mental health problems (intervention) or refresher training on identification and referral (control).

**Main outcomes and measures:** Primary outcome was change in SDQ total problems score; secondary outcomes included discussion of psychosocial issues by the GPs and receipt of mental health care during the follow-up period.

**Results:** Overall, 49 GPs cared for 389 children who scored greater than the cutoff on the SDQ (216 children in intervention group, 173 in control group). Patients' mean (SD) age was 8.9 (2.9) years (range, 5 to 15 years), and 182 (47%) were female patients. At 6 months, children in the intervention group had greater odds of receiving mental health care during the study (odds ratio [OR], 3.0; 95% CI, 1.1 to 7.7), parents were more likely to report that intervention GPs had discussed parent (OR, 2.1; 95% CI, 1.1 to 3.8) and child (OR, 2.0; 95% CI, 0.9 to 4.8) psychosocial issues, and intervention GPs were more likely to say they had provided counseling (OR, 1.8; 95% CI, 1.02 to 3.3). However, there was no greater improvement in SDQ scores among children seen by intervention vs control GPs. Adjusted for clustering within GP, the variables used for balanced allocation (practice size, practice ownership, and study wave), and the other variables associated with change in SDQ scores over time, there was not a significant time-treatment interaction at either the 3- or 6-month follow-up points (linear combination of coefficients for intervention, 0.57 [95% CI, -1.07 to 2.22] and -0.08 [95%CI, -1.76 to 1.56], respectively). In a subgroup of GPs with practices composed of 50% or more children, children seen by intervention GPs improved to a significantly greater extent (-3.6 points; 95% CI, -6.7 to -0.46 points; effect size  $d = 0.66$ ; 95% CI, 0.30 to 1.01) compared with those seen by control GPs.

**Conclusions and relevance:** In this cluster randomized trial, GP training on managing common child mental health problems did not demonstrate greater improvement in child SDQ scores. Child mental health training for GPs in collaborative care can improve children's access to mental health care, but prior experience working with children and their families may be required for GPs to use a brief training in a way that improves child outcomes.

J Adolesc Health. 2023 May;72(5S):S51-S58.

doi: 10.1016/j.jadohealth.2023.01.002.

### [\*\*The Impact of Family Economic Empowerment Intervention on Psychological Difficulties and Prosocial Behavior Among AIDS-Orphaned Children in Southern Uganda\*\*](#)

[Nhial T Tutlam<sup>1</sup>](#), [Lindsey M Filiatreau<sup>1</sup>](#), [William Byansi<sup>2</sup>](#), [Rachel Brathwaite<sup>1</sup>](#), [Proscovia Nabunya<sup>1</sup>](#), [Ozge Sensoy Bahar<sup>1</sup>](#), [Flavia Namuwonge<sup>3</sup>](#), [Fred M Ssewamala<sup>4</sup>](#)

#### **Abstract**

**Purpose:** Children orphaned by AIDS are more likely to have psychological and emotional problems compared to their counterparts. Poverty resulting from orphanhood is linked to the negative psychological outcomes experienced by AIDS-orphaned adolescents. No studies have investigated the impact of an economic empowerment intervention on child psychological and emotional problems and prosocial behavior. Therefore, we aimed to examine the impact of a family economic empowerment intervention on psychological difficulties and prosocial behavior among AIDS-orphaned adolescents.

**Methods:** We analyzed data from a two-arm cluster randomized controlled trial conducted in 10 primary schools in southern Uganda. Schools were randomized to either bolstered

usual care (n = 5 schools; 167 participants) or a family-economic empowerment intervention (Suubi-Maka; n = 5 schools; 179 individuals). We used t-test and multi-level mixed effects models to examine the impact of Suubi-Maka on psychological and behavioral outcomes.

**Results:** No differences were observed between intervention and control groups in almost all the outcomes at baseline, 12 months, and 24 months. Simple main effects comparisons of 12 months versus baseline within each condition indicate modest to significant declines in emotional symptoms, hyperactivity, peer relationships ( $\Delta s = -1.00$  to  $-2.11$ , all  $p < .001$ ), and total difficulties ( $\Delta s = -4.85$  to  $-4.89$ , both  $p < .001$ ) across both groups.

**Discussion:** Our analysis found no meaningful difference between intervention and control groups in child psychological difficulties and prosocial behavior postintervention. However, improvements were observed across both control and treatment groups following the intervention. Future studies should investigate the impact of different components of the intervention.

J Child Psychol Psychiatry. 2022 Nov;63(11):1252-1260.

doi: 10.1111/jcpp.13566. Epub 2022 Jan 6.

[The longitudinal impact of an evidence-based multiple family group intervention \(Amaka Amasanyufu\) on oppositional defiant disorder and impaired functioning among children in Uganda: analysis of a cluster randomized trial from the SMART Africa-Uganda scale-up study \(2016-2022\)](#)

[Rachel Brathwaite<sup>1</sup>](#), [Fred M Ssewamala<sup>1</sup>](#), [Ozge Sensoy Bahar<sup>1</sup>](#), [Mary M McKay<sup>2</sup>](#), [Torsten B Neilands<sup>3</sup>](#), [Phionah Namatovu<sup>1</sup>](#), [Joshua Kiyingi<sup>1</sup>](#), [Lily Zmachinski<sup>1</sup>](#), [Josephine Nabayinda<sup>1</sup>](#), [Keng-Yen Huang<sup>4,5</sup>](#), [Apollo Kivumbi<sup>6</sup>](#), [Arvin Bhana<sup>7,8</sup>](#), [Abel Mwebembezi<sup>6</sup>](#), [Inge Petersen<sup>8</sup>](#), [Kimberly Hoagwood<sup>9</sup>](#), [SMART Africa - Uganda Field Team<sup>10</sup>](#)

**Abstract**

**Background:** Oppositional Defiant Disorders (ODDs) and other Disruptive Behavior Disorders (DBDs) are common among children and adolescents in poverty-impacted communities in sub-Saharan Africa. Without early intervention, its progression into adulthood can result in dire consequences. We examined the impact of a manualized family strengthening intervention called Amaka Amasanyufu designed to reduce ODDs and other DBDs among school-going children residing in low-resource communities in Uganda.

**Methods:** We used longitudinal data from the SMART Africa-Uganda study (2016-2022). Public primary schools were randomized to: (1) Control condition (receiving usual care comprising generalized psychosocial functioning literature), 10 schools; (2) intervention delivered via parent peers (Amaka-parents), 8 schools or; (3) intervention delivered via community healthcare workers (Amaka-community), 8 schools. All the participants were blinded. At baseline, 8- and 16-weeks postintervention initiation, caregivers completed the Iowa Conners Scale, which measured Oppositional Defiant Disorder (ODD) and Impairment Rating Scale to evaluate children's overall impairment and impaired functioning with peers, siblings, and parents; impaired academic progress, self-esteem, and family functioning. Three-level linear mixed-effects models were fitted to each outcome. Pairwise comparisons of postbaseline group means within each time point were performed using Sidak's adjustment for multiple comparisons. Only children positive for ODD and other DBDs were analyzed.

**Results:** Six hundred and thirty-six children screened positive for ODDs and other DBDs (Controls: n = 243; Amaka-parents: n = 194; Amaka-community: n = 199). At 8 weeks, Amaka-

parents' children had significantly lower mean scores for overall impairment compared to controls, (mean difference: -0.71,  $p = .001$ ), while Amaka-community children performed better on ODD (mean difference: -0.84,  $p = .016$ ). At 16 weeks, children in both groups were performing better on ODD and IRS than controls, and there were no significant differences between the two intervention groups.

**Conclusions:** The Amaka Amasanyufu intervention was efficacious in reducing ODD and impaired functioning relative to usual care. Hence, the Amaka Amasanyufu intervention delivered either by Amaka-community or Amaka-parents has the potential to reduce negative behavioral health outcomes among young people in resource-limited settings and improve family functioning.

## Mobile phones, text messages, and Apps

BMJ Glob Health. 2022 Jul;6(Suppl 5):e008838.

doi: 10.1136/bmjgh-2022-008838.

### [The impact of a direct to beneficiary mobile communication program on reproductive and child health outcomes: a randomised controlled trial in India](#)

[Amnesty Elizabeth LeFevre](#)<sup>1,2</sup>, [Neha Shah](#)<sup>2</sup>, [Kerry Scott](#)<sup>2</sup>, [Sara Chamberlain](#)<sup>3,4</sup>, [Osama Ummer](#)<sup>4,5</sup>, [Jean Juste Harrisson Bashingwa](#)<sup>6,7</sup>, [Arpita Chakraborty](#)<sup>8</sup>, [Anna Godfrey](#)<sup>3</sup>, [Priyanka Dutt](#)<sup>3,4</sup>, [Rajani Ved](#)<sup>9,10</sup>, [Diwakar Mohan](#)<sup>2</sup>, [Kilkari Impact Evaluation Team](#)

#### Abstract

**Background:** Direct-to-beneficiary communication mobile programmes are among the few examples of digital health programmes to have scaled widely in low-resource settings. Yet, evidence on their impact at scale is limited. This study aims to assess whether exposure to mobile health information calls during pregnancy and postpartum improved infant feeding and family planning practices.

**Methods:** We conducted an individually randomised controlled trial in four districts of Madhya Pradesh, India. Study participants included Hindi speaking women 4-7 months pregnant ( $n=5095$ ) with access to a mobile phone and their husbands ( $n=3842$ ). Women were randomised to either an intervention group where they received up to 72 Kilkari messages or a control group where they received none. Intention-to-treat (ITT) and instrumental variable (IV) analyses are presented.

**Results:** An average of 65% of the 2695 women randomised to receive Kilkari listened to  $\geq 50\%$  of the cumulative content of calls answered. Kilkari was not observed to have a significant impact on the primary outcome of exclusive breast feeding (ITT, relative risk (RR): 1.04, 95% CI 0.88 to 1.23,  $p=0.64$ ; IV, RR: 1.10, 95% CI 0.67 to 1.81,  $p=0.71$ ). Across study arms, Kilkari was associated with a 3.7% higher use of modern reversible contraceptives (RR: 1.12, 95% CI 1.03 to 1.21,  $p=0.007$ ), and a 2.0% lower proportion of men or women sterilised since the birth of the child (RR: 0.85, 95% CI 0.74 to 0.97,  $p=0.016$ ). Higher reversible method use was driven by increases in condom use and greatest among those women exposed to Kilkari with any male child (9.9% increase), in the poorest socioeconomic strata (15.8% increase), and in disadvantaged castes (12.0% increase). Immunisation at 10 weeks was higher among the children of Kilkari listeners (2.8% higher; RR: 1.03, 95% CI 1.00 to 1.06,  $p=0.048$ ). Significant differences were not observed for other maternal, newborn and child health outcomes assessed.



**Conclusion:** Study findings provide evidence to date on the effectiveness of the largest mobile health messaging programme in the world.

JAMIA Open. 2022 Oct 4;5(4):ooac081.

doi: 10.1093/jamiaopen/ooac081. eCollection 2022 Dec.

**[A mobile health app may improve maternal and child health knowledge and practices among rural women with limited education in Uganda: a pilot randomized controlled trial](#)**

[Angella Musiimenta](#)<sup>1,2</sup>, [Wilson Tumuhimbise](#)<sup>1</sup>, [Esther C Atukunda](#)<sup>1</sup>, [Aaron T Mugaba](#)<sup>1,2</sup>, [Justus Asasira](#)<sup>1</sup>, [Jane Katusiime](#)<sup>1</sup>, [Raphael Zender](#)<sup>3</sup>, [Niels Pinkwart](#)<sup>3</sup>, [Godfrey Rwambuka Mugenyi](#)<sup>1</sup>, [Jessica E Haberer](#)<sup>4,5</sup>

**Abstract**

**Objective:** This article describes the impact of a mobile health app (*MatHealth App*) on maternal and child health knowledge and practices among women with limited education.

**Materials and methods:** Pregnant women initiating antenatal care (ANC) were randomized (1:1) to the *MatHealth App* versus routine care. Participants were followed until 6 weeks after delivery. Questionnaires for assessing knowledge and practices were administered to participants from both arms at baseline and endline. Using logistic regression, we estimated the difference in odds of having maternal health knowledge. We reviewed clinic records to capture maternal health practices.

**Results:** Of the 80 enrolled participants, 69 (86%) completed the study with a median follow-up of 6 months. Women in the *MatHealth* arm had 8.2 ( $P = .19$ ), 3.6 ( $P = .14$ ), and 6.4 ( $P = .25$ ), respectively higher odds of knowing (1) the recommended gestation period for starting ANC, (2) the recommended number of ANC visits, and (3) the timing and frequency of recommended human immunodeficiency virus (HIV) testing, respectively, compared to those in the routine care arm. All women in the *MatHealth App* arm exclusively breastfed their babies, and brought them at 6 weeks for HIV testing, compared to the routine care arm. Just over half of the women attended at least 4 prenatal visits across the 2 arms. The main reason for noncompliance to ANC appointments was a lack of transport to the clinic.

**Discussion and conclusion:** The app increased knowledge and practices although not reaching statistical significance. Future efforts can focus on addressing social and economic issues and assessing clinical outcomes.

Contracept Reprod Med. 2022 Jul 3;7(1):12.

doi: 10.1186/s40834-022-00180-1.

**[A randomized controlled trial on mobile phone text messaging to improve sexual reproductive health among adolescent girls in Cameroon](#)**

[Frankline Sevidzem Wirsiy](#)<sup>1,2,3</sup>, [Catherine Atuhaire](#)<sup>4</sup>, [Joseph Ngonzi](#)<sup>5</sup>, [Samuel Nambile Cumber](#)<sup>6,7,8,9</sup>

**Abstract**

**Background:** We conducted a single-centered randomized controlled single-blinded trial (i.e. trained interviewers; blinded to group allocation). The target population included adolescent girls in the Kumbo West Health District (KWHD) of Cameroon. This trial tested the

efficacy of weekly educational one-way text messages to improve perception of adolescent girls on sexo-reproductive health.

**Methods:** Allocation concealment (1:1) was determined by sequentially numbered sealed opaque envelopes. A total of 398 participants either received the mobile phone sexo-reproductive health text messages (199) or not (199). A blinded program secretary send out text messages and recorded delivery. Data was collected and managed at baseline and at 6 month intervals using an interviewer-administered questionnaire before and after intervention, then analysed using the independent T-test (mean differences) and ANOVA on SPSS version 21.

**Results:** The mean knowledge, attitude and practice scores respectively increased significantly from 6.03, 4.01 and 3.45 at baseline to 7.99, 5.83 and 4.99 at the end of the study. After performing ANOVA for the overall correct knowledge, positive attitudes and good practices respectively for between and within the intervention groups, we obtained: ( $F = 15.12$ ,  $P = 0.023$ ), ( $F = 60.21$ ,  $P = 0.001$ ) and ( $F = 57.$ ,  $P = 0.013$ ) which showed statistical significance thus indicating the overall improvement in adolescents girls perception as a result of the intervention and not by chance. Majority (65.3%) of the participants were satisfied with the Short Message Service (SMS).

**Conclusion:** This trial has contributed to the body of knowledge and evidence on the use of mobile phone technology using educative SMS to improve adolescent girl's perception on sexo-reproductive health in Cameroon.

J Public Health Afr. 2022 Sep 12;13(3):2222.

doi: 10.4081/jphia.2022.2222. eCollection 2022 Sep 7.

**[Effects of a mHealth voice messaging intervention on antenatal care utilisation at primary care level in Lagos, Nigeria: a cluster randomised trial](#)**

[Gbemisola E Osanyin<sup>1</sup>](#), [Aduragbemi Bankethomas<sup>2,3</sup>](#), [Esther O Oluwole<sup>4</sup>](#), [Adesumbo K Odeseye<sup>5</sup>](#), [Bosede B Afolabi<sup>1,2</sup>](#)

**Abstract**

**Background:** Nigeria has one of the lowest antenatal care (ANC) utilization rates compared to other low- and middle-income nations. In order to ensure a *positive pregnant experience*, the World Health Organization recommends at least eight ANC visits during pregnancy. This study intends to examine the impact of a mobile phone-based voice message intervention on ANC use in Lagos, Nigeria.

**Methods:** In this cluster-randomized experiment, primary healthcare centres were divided into five intervention and five control groups using multistage simple random sampling. The intervention consisted of a weekly voice message transmitted through mobile phone from the time of recruitment in the first trimester until two weeks postpartum. Attending at least eight ANC visits before birth was the primary outcome. STATA v17.0 was used to conduct descriptive and bivariate analyses as well as multivariate linear models to calculate crude risk ratios.

**Results:** 458 women participated. All intervention group women (269 women, or 58.7% of the sample) received the text message. These ladies were mostly married, Christian, had several children, and had completed high school. Women who received the intervention were more likely to attend eight ANC visits.

**Conclusion:** A voice message-based intervention can boost ANC utilization, according to the conclusion. This contributes to the existing body of information about the influence of mHealth treatments on maternal health outcomes and serves as a useful tool for ensuring that no woman is left behind.

Eur Arch Paediatr Dent. 2022 Aug;23(4):629-639.

doi: 10.1007/s40368-022-00731-9. Epub 2022 Jul 16.

**[Impact of smartphone application usage by mothers in improving oral health and its determinants in early childhood: a randomised controlled trial in a paediatric dental setting](#)**

[M Shirmohammadi](#)<sup>1,2</sup>, [S Razeghi](#)<sup>1,2</sup>, [A R Shamshiri](#)<sup>1,2</sup>, [S Z Mohebbi](#)<sup>3,4</sup>

**Abstract**

**Purpose:** Integration of smartphones has overcome barriers in traditional education; this trial aimed at exploring this ubiquitous platform in oral health education. A smartphone application promoting preschooler's oral health was designed and its effectiveness was compared with that of common oral health education delivered in paediatric dental settings.

**Methods:** This controlled clinical trial was performed on preschooler-mother dyads referring to the clinic of Tehran School of Dentistry in 2019-2020. Initially, the dyads were randomly partitioned to application intervention or common training groups. The mothers answered an interviewer-administered questionnaire on paediatric dentistry knowledge, attitude and practice regarding children's oral health; modified plaque index (m-PI) and modified gingival index (m-GI) of children were measured. Subsequently, the smartphone application was installed for application intervention group and an educational pamphlet and verbal explanations were given to common training group. In 1-month and 3-month follow-ups, the questionnaires and clinical measurement were re-done. A generalized estimating equation (GEE) was used to investigate the effect of training methods.

**Results:** Among the participants 51 dyad attended baseline and follow-up assessments. The preschoolers mean age was  $4.6 \pm 1.2$  years and 54.4% were girls. Both trainings improved mothers' knowledge and practice regarding children's oral health and reduced children's m-PI and m-GI ( $p < 0.050$ ). The 3-month follow-up revealed a better m-GI in application intervention group ( $p < 0.001$ ).

**Conclusions:** Considering the greater improvement of paediatric gingival status in the application intervention group, it appears that smartphone applications may provide a promising tool for more prolonged impacts in children oral health care.

## **Mortality – post discharge**

Lancet Child Adolesc Health. 2022 Jul;6(7):474-483.

doi: 10.1016/S2352-4642(22)00074-8. Epub 2022 May 21.

**[Post-discharge morbidity and mortality in children admitted with severe anaemia and other health conditions in malaria-endemic settings in Africa: a systematic review and meta-analysis](#)**

[Titus K Kwambai<sup>1</sup>](#), [Amani T Mori<sup>2</sup>](#), [Sarah Nevitt<sup>3</sup>](#), [Anna Maria van Eijk<sup>4</sup>](#), [Aaron M Samuels<sup>5</sup>](#), [Bjarne Robberstad<sup>2</sup>](#), [Kamija S Phiri<sup>6</sup>](#), [Feiko O Ter Kuile<sup>7</sup>](#)

## Abstract

**Background:** Severe anaemia is associated with high in-hospital mortality among young children. In malaria-endemic areas, surviving children also remain at increased risk of mortality for several months after hospital discharge. We aimed to compare the risks of morbidity and mortality among children discharged from hospital after recovery from severe anaemia versus other health conditions in malaria-endemic settings in Africa.

**Methods:** Following PRISMA guidelines, we searched PubMed, Scopus, Web of Science, and Cochrane Central from inception to Nov 30, 2021, without language restrictions, for prospective or retrospective cohort studies and randomised controlled trials that followed up children younger than 15 years for defined periods after hospital discharge in malaria-endemic countries in Africa. We excluded the intervention groups in trials and studies or subgroups involving children with sickle cell anaemia, malignancies, or surgery or trauma, or those reporting follow-up data that were combined with the in-hospital period. Two independent reviewers extracted the data and assessed the quality and risk of bias using the Newcastle Ottawa Scale or the Cochrane Collaboration's tool. The coprimary outcomes were all-cause death and all-cause readmissions 6 months after discharge. This study is registered with PROSPERO, CRD42017079282.

**Findings:** Of 2930 articles identified in our search, 27 studies were included. For children who were recently discharged following hospital admission with severe anaemia, all-cause mortality by 6 months was higher than during the in-hospital period (n=5 studies; Mantel-Haenszel odds ratio 1.72, 95% CI 1.22-2.44; p=0.0020; I<sup>2</sup>=51.5%) and more than two times higher than children previously admitted without severe anaemia (n=4 studies; relative risk [RR] 2.69, 95% CI 1.59-4.53; p<0.0001; I<sup>2</sup>=69.2%). Readmissions within 6 months of discharge were also more common in children admitted with severe anaemia than in children admitted with other conditions (n=1 study; RR 3.05, 1.12-8.35; p<0.0001). Children admitted with severe acute malnutrition (regardless of severe anaemia) also had a higher 6-month mortality after discharge than those admitted for other reasons (n=2 studies; RR=3.12, 2.02-4.68; p<0.0001; I<sup>2</sup>=54.7%). Other predictors of mortality after discharge included discharge against medical advice, HIV, bacteraemia, and hypoxia.

**Interpretation:** In malaria-endemic settings in Africa, children admitted to hospital with severe anaemia and severe acute malnutrition are at increased risk of mortality in the first 6 months after discharge compared with children admitted with other health conditions. Improved strategies are needed for the management of these high-risk groups during the period after discharge.

## Neurocysticercosis

Indian Pediatr. 2022 Dec 15;59(12):916-919.

Epub 2022 Oct 29.

[Fourteen Days vs 28 Days of Albendazole Therapy for Neurocysticercosis in Children: An Open Label Randomized Controlled Trial](#)

[Ankit Singla<sup>1</sup>](#), [Seema Lekhwani<sup>2</sup>](#), [Narain Das Vaswani<sup>1</sup>](#), [Jaya Shankar Kaushik<sup>3</sup>](#), [Surekha Dabla<sup>4</sup>](#)

## Abstract

**Background:** There is a paucity of literature to support 14-days albendazole therapy for neurocysticercosis (NCC).

**Objective:** To compare the efficacy of 14-day and 28-day albendazole therapy in the management of children with newly diagnosed active NCC.

**Study design:** Open-labelled randomized controlled trial.

**Participants:** Children aged 1-14 years with newly diagnosed active neurocysticercosis.

**Intervention:** Albendazole (15 mg/kg/day) for either 14 days or 28 days.

**Outcome:** The primary outcome measure was proportion of children with radiological resolution of active lesion at 6-month follow up. Secondary outcome measures were proportion of children with seizure recurrence, duration to seizure recurrence and calcification on follow up imaging.

**Results:** 65 children with newly diagnosed NCC were randomized to receive albendazole therapy for 14 days (n=32) or 28 days (n=33). The proportion of children with complete resolution was comparable between the two groups [6 (18.8%) vs. 9 (27.3%); OR (95%CI):0.61 (0.19 to 1.98); P=0.56]. Similarly, proportion of children with seizure recurrence [5(15.6%) vs 2(6.1%); OR (95%CI): 2.87(0.51-16.0); P=0.26] and proportion of children with calcification on follow-up imaging [26(81.2%) vs 23(69.7%); OR (95%CI): 1.88 (0.59-5.99); P=0.39] were also comparable. There were no major side-effects noted during the study.

**Conclusion:** 14-day treatment with albendazole therapy is as effective as 28-day treatment in achieving radiological resolution at six-month follow up. However, high rate of calcification in both the groups indicates need for further evaluation with an adequately powered study and longer follow up.

## Neurodevelopmental conditions and cerebral palsy

### Cerebral palsy

Dev Neurorehabil. 2023 Apr;26(3):193-205.

doi: 10.1080/17518423.2023.2193265. Epub 2023 Apr 5.

### [Effect of Trunk Targeted Interventions on Functional Outcomes in Children with Cerebral Palsy- A Systematic Review](#)

[Aishwarya J Talgeri<sup>1</sup>](#), [Akshatha Nayak<sup>1</sup>](#), [Shreekanth D Karnad<sup>1</sup>](#), [Preyal Jain<sup>1</sup>](#), [Jaya Shanker Tedla<sup>2</sup>](#), [Ravi Shankar Reddy<sup>2</sup>](#), [Devika Rani Sangadala<sup>2</sup>](#)

## Abstract

Objective of this review was to collate information on the effectiveness of trunk targeted intervention on children with cerebral palsy (CP) on three functional outcomes that are gross motor function, trunk control and balance. A comprehensive search was conducted on online databases from inception to August 2021, using relevant keywords. A total of 15 randomized controlled trials which enrolled children with cerebral palsy under 18 years met the inclusion criteria. A significant improvement was seen in the trunk targeted training

groups on applying trunk targeted interventions. Trunk targeted interventions improve gross motor function, trunk control as well as balance, hence should be incorporated in the conventional physical therapy program delivered to children with CP and would help in greater functional recovery.

PM R. 2023 Jan 19.

doi: 10.1002/pmrj.12947. Online ahead of print.

**[Evaluation of a computer game-assisted rehabilitation program for manual dexterity of children with cerebral palsy: Feasibility randomized control trial](#)**

[Anuprita Kanitkar<sup>1</sup>](#), [Sanjay Tejraj Parmar<sup>2</sup>](#), [Tony Joseph Szturm<sup>3</sup>](#), [Gayle Restall<sup>3</sup>](#), [Gina Ruth Rempel<sup>4</sup>](#), [Nariman Sepehri<sup>5</sup>](#), [Nilahri Naik<sup>6</sup>](#)

**Abstract**

**Introduction:** There is a need for innovation to improve the engagement and compliance of rehabilitation programs for children with upper extremity (UE) motor impairments due to Cerebral Palsy (CP); a computer games-based rehabilitation platform (GRP) was developed to address this need. The GRP provides engaging task-specific exercises targeting manual dexterity (object handling and manipulation).

**Objective:** An exploratory randomized clinical trial was conducted to evaluate the therapeutic value and treatment effect size of an exercise program using the GRP in children with CP.

**Methods:** A total of sixty-three children with CP, aged 4 to 10 years, were recruited. The Peabody Developmental Motor Scale-2 (PDMS-2) Grasp and Visual-Motor Integration subscores and Computer game-based Upper Extremity (CUE) assessment of manual dexterity was used to assess participants before and after a 16-week intervention program, delivered three times per week. The experimental group (XG) received a computer games-based exercise program targeting object manipulation tasks. The active control arm (CG) consisted of task-specific training similar to the tasks used in constrained induced movement therapy.

**Results:** There were only a few dropouts during the 16-week program, and compliance was high. Both groups showed significant improvements with medium to large effect sizes. Improvements in the PDMS-2 Grasp and VMI subscores observed in the XG were significantly greater than that in the CG. There was a significant improvements ( $p < 0.01$ ) in PDMS-2 grasp and VMI subscores for XG with moderate to large effect sizes, (0.5-0.8). For CG, the Grasp and VMI subscores did improve but these changes were not statistically significant. There was a significant improvement observed in the majority of CUE object manipulation test scores for XG ( $p < 0.01$ ) with moderate to large effect sizes (0.50-1.2) Although CG did show improvements in all CUE object manipulation test scores the changes did not reach statistical significance ( $p < 0.01$ ).

**Conclusion:** This study demonstrates the utility of the GRP to practice a broad range of object manipulation tasks in children with CP. The present findings are positive and support further research and development. The long-term effects of the GRP program in children with CP will need to be confirmed in a future randomized controlled trial. In addition to measures of structure and function, future RCT should also include outcome measures such as health-related quality of life and level of participation to validate the findings.



Medicine (Baltimore). 2022 Nov 4;101(44):e31565.

doi: 10.1097/MD.00000000000031565.

**[Effect of task-oriented training on gross motor function, balance and activities of daily living in children with cerebral palsy: A systematic review and meta-analysis](#)**

[Weiyi Zai<sup>1</sup>](#), [Ning Xu<sup>1</sup>](#), [Wei Wu<sup>2</sup>](#), [Yueying Wang<sup>1</sup>](#), [Runfang Wang<sup>1</sup>](#)

**Abstract**

**Background:** To systematically evaluate task-oriented training (TOT) on the improvement of gross motor function, balance and activities of daily living in children with cerebral palsy (CP).

**Methods:** A number of randomized controlled trials (RCTs) of TOT in children with CP were searched from Pubmed, Cochrane Library, Web of Science, EmBase, China National Knowledge Infrastructure, Chinese Biology Medicine, Chinese Scientific Journals Database and Wanfang data from the establishment of database to March 2022. The methodological quality of the included studies was evaluated, and meta-analysis was performed by RevMan5.4 software.

**Results:** A total of 16 studies were included in the systematic review (n = 893). Meta-analysis showed that the gross motor function measure (GMFM) (MD = 11.05, 95%CI [8.26, 13.83], P < .00001), dimension D (MD = 3.05, 95%CI [1.58, 4.53], P < .0001) of the GMFM, dimension E (MD = 7.36, 95%CI [5.88, 8.84], P < .00001) of the GMFM, the Berg Balance Scale (BBS) (MD = 6.23, 95%CI [3.31, 9.15], P < .0001), the pediatric evaluation of disability inventory (PEDI) mobile function (MD = 6.44, 95%CI [3.85, 9.02], P < .00001) score improved significantly in the TOT group compared with the control group.

**Conclusions:** Current evidence shows that TOT could effectively improve gross motor function, balance and activities of daily living in children with CP. Due to the limitations of the number and quality of the included studies, the above conclusions need to be verified by more high-quality studies.

Dev Med Child Neurol. 2023 Jun;65(6):773-782.

doi: 10.1111/dmcn.15445. Epub 2022 Nov 6.

**[Supporting People in extreme POverty with Rehabilitation and Therapy \(SUPPORT CP\): A trial among families of children with cerebral palsy in Bangladesh](#)**

[Mahmudul Hassan Al Imam<sup>1,2,3,4</sup>](#), [Israt Jahan<sup>1,2,3</sup>](#), [Manik Chandra Das<sup>1,2</sup>](#), [Sk Md Kamrul Bashar<sup>1,2</sup>](#), [Arifuzzaman Khan<sup>1,2,4,5</sup>](#), [Mohammad Muhit<sup>1,2</sup>](#), [Rosalie Power<sup>2,6</sup>](#), [Delwar Akbar<sup>7</sup>](#), [Nadia Badawi<sup>8,9</sup>](#), [Gulam Khandaker<sup>3,4,8</sup>](#)

**Abstract**

**Aim:** To test the efficacy of an integrated microfinance/livelihood and community-based rehabilitation (IMCBR) programme in improving health-related quality of life (HRQoL) and motor function of children with cerebral palsy (CP) and gain in social capital to their ultra-poor families in rural Bangladesh.

**Method:** This was an open-label cluster randomized control trial. Children with CP aged 5 years or under were randomly allocated to three arms; Arm A: IMCBR; Arm B: community-based rehabilitation (CBR); and Arm C: care-as-usual. The CBR was modified with phone follow-up followed by home-based CBR at 2.5 months post-enrolment because of the COVID-19 pandemic. Intention-to-treat analysis was performed.

**Results:** Twenty-four clusters constituting 251 children-primary caregivers' dyads were assigned to three arms (Arm A = 80; Arm B = 82; Arm C = 89). Between baseline and endline,

the percentage mean change in the physical functioning domain of HRQoL was highest in Arm A (30.0%) with a significant mean difference between Arm A and Arm B ( $p = 0.015$ ). Improvement in the mean social capital score was significantly higher in Arm A compared to Arm C ( $p < 0.001$ ).

**Interpretation:** The findings suggest that IMCBR could improve the HRQoL of children with CP and the social capital of their ultra-poor families. Long-term follow-up of the trial participants and future exploration of such interventions are essential. The integrated livelihood and CBR programme holds potential to improve health and well-being of children with CP and their ultra-poor families.

**What this paper adds:** Half of the families who received livelihoods were impacted by a cold-wave, suggesting the need for a more disaster-resilient livelihood asset. The integration of livelihood with community-based rehabilitation programme helps to improve health-related quality of life of children with cerebral palsy and the social capital of their ultra-poor families.

Neurorehabil Neural Repair. 2023 May 11;15459683231174222.

doi: 10.1177/15459683231174222. Online ahead of print.

### [Brain Stimulation and Constraint Induced Movement Therapy in Children With Unilateral Cerebral Palsy: A Randomized Controlled Trial](#)

[Juhi Gupta<sup>1</sup>](#), [Sheffali Gulati<sup>1</sup>](#), [Upinder Pal Singh<sup>2</sup>](#), [Atin Kumar<sup>3</sup>](#), [Prashant Jauhari<sup>1</sup>](#), [Biswaroop Chakrabarty<sup>1</sup>](#), [Ravindra Mohan Pandey<sup>4</sup>](#), [Renu Bhatia<sup>5</sup>](#), [Suman Jain<sup>5</sup>](#), [Achal Srivastava<sup>6</sup>](#)

#### **Abstract**

**Background:** There is a crucial need to devise optimum rehabilitation programs for children with cerebral palsy (CP).

**Objective:** This study aimed to assess the feasibility, safety, and efficacy of combining 6-Hz primed, low-frequency, repetitive transcranial magnetic stimulation (rTMS) with modified constraint-induced movement therapy (mCIMT) in improving upper limb function in children with unilateral CP.

**Methods:** Children aged 5 to 18 years with unilateral CP were randomized (23 in each arm) to receive 10 sessions of mCIMT with real rTMS (intervention arm) or mCIMT with sham rTMS (control arm), on alternate weekdays over 4 weeks. The primary outcome was the difference in mean change in Quality of Upper Extremity Skills Test (QUEST) scores. Secondary outcomes were changes in QUEST domain scores, speed and strength measures, CP quality of life (CP-QOL) scale scores, and safety of rTMS.

**Results:** All 46 children completed the trial except one. At 4 weeks, the mean change in total QUEST scores was significantly higher in the intervention arm as compared to the control arm ( $11.66 \pm 6.97$  vs  $6.56 \pm 4.3$ ,  $d = 5.1$ , 95% CI 1.7-8.5,  $P = .004$ ). Change in "weight bearing" and "protective extension" domain score was significantly higher for children in the intervention arm. These improvements were sustained at 12 weeks ( $P = .028$ ). CP-QOL scores improved at 12 weeks. No serious adverse events were seen.

**Conclusion:** A 6-Hz primed rTMS combined with mCIMT is safe, feasible, and superior to mCIMT alone in improving the upper limb function of children with unilateral CP.

JAMA Netw Open. 2022 Nov 1;5(11):e2240383.

doi: 10.1001/jamanetworkopen.2022.40383.

### **Efficacy of a Hip Brace for Hip Displacement in Children With Cerebral Palsy: A Randomized Clinical Trial**

[Bo Ryun Kim<sup>1</sup>](#), [Jin A Yoon<sup>2</sup>](#), [Hyun Jung Han<sup>3</sup>](#), [Young Il Yoon<sup>4</sup>](#), [Jiwoon Lim<sup>5</sup>](#), [Seungeun Lee<sup>5</sup>](#), [Seon Cho<sup>5</sup>](#), [Yong Beom Shin<sup>2</sup>](#), [Hyun Jung Lee<sup>6</sup>](#), [Jee Hyun Suh<sup>7</sup>](#), [Joonyoung Jang<sup>5</sup>](#), [Jaewon Beom<sup>5</sup>](#), [Yulhyun Park<sup>5</sup>](#), [Jung-Hwa Choi<sup>8</sup>](#), [Ju Seok Ryu<sup>5</sup>](#)

#### **Abstract**

**Importance:** There is no consensus on interventions to slow the progress of hip displacement in patients with cerebral palsy.

**Objective:** To investigate the efficacy of a novel hip brace in preventing progressive hip displacement in patients with cerebral palsy.

**Design, setting, and participants:** This 2-group randomized clinical trial was conducted at 4 tertiary hospitals in South Korea from July 2019 to November 2021. Participants included children aged 1 to 10 years with nonambulatory cerebral palsy (Gross Motor Function Classification System level IV or V). Block randomization was used to assign an equal number of patients to the study and control groups via computerized random allocation sequences. Data were analyzed from November to December 2021.

**Interventions:** The intervention group wore the hip brace for at least 12 hours a day for the study duration (ie, 12 months). Follow-up evaluations were performed after 6 and 12 months of wearing the brace. Both groups proceeded with conventional rehabilitation therapy during the trial.

**Main outcomes and measures:** The primary outcome was the Reimers migration index (MI) on radiography, as assessed by 3 blinded investigators. Primary outcome variables were analyzed using linear mixed models. Secondary outcomes include change in the Caregiver Priorities & Child Health Index of Life with Disabilities, on which lower scores indicate better quality of life.

**Results:** A total of 66 patients were included, with 33 patients (mean [SD] age, 68.7 [31.6] months; 25 [75.8%] boys) randomized to the intervention group and 33 patients (mean [SD] age, 60.7 [24.9] months; 20 [60.6%] boys) randomized to the control group. The baseline mean (SD) MI was 37.4% (19.3%) in the intervention group and 30.6% (16.3%) in the control group. The mean difference of the MI between the intervention group and control group was -8.7 (95% CI, -10.2 to -7.1) percentage points at 6 months and -12.7 (95% CI, -14.7 to -10.7) percentage points at 12 months. The changes in the Caregiver Priorities & Child Health Index of Life with Disabilities were favorable in the study group and reached statistical significance at the 6-month follow-up compared with the control group (difference, -14.2; 95% CI, -25.2 to -3.3).

**Conclusions and relevance:** In this randomized clinical trial, the novel hip brace was significantly effective in preventing the progression of hip displacement, compared with the control group. It effectively improved quality of life in patients with nonambulatory cerebral palsy. Therefore, hip brace use could be a promising treatment method to delay hip surgery and improve the quality of life of patients with nonambulatory cerebral palsy.

Indian J Pediatr. 2022 Jul 22.

doi: 10.1007/s12098-022-04265-2. Online ahead of print.

## [Gabapentin as Add-on Therapy to Trihexyphenidyl in Children with Dyskinetic Cerebral Palsy: A Randomized, Controlled Trial](#)

[Sonu Kumar<sup>1</sup>](#), [Jaya Shankar Kaushik<sup>2</sup>](#), [Savita Verma<sup>3</sup>](#), [Surekha Dabla<sup>4</sup>](#)

### **Abstract**

**Objective:** To compare the efficacy of gabapentin as add-on therapy to trihexyphenidyl in the treatment of children with dyskinetic cerebral palsy (CP).

**Methods:** An open-labelled, randomized, controlled trial was conducted among children aged 3-9 y with dyskinetic CP [Gross Motor Functional Classification System (GMFCS) 4-5]. Participants were assigned into two groups: gabapentin with trihexyphenidyl (n = 30) and trihexyphenidyl alone (n = 30). Dyskinesia Impairment Scale (DIS), Dystonia Severity Assessment Plan (DSAP), and International Classification of Functioning, Disability, and Health-Children and Youth Version (ICF-CY) were measured at baseline, 4 and 12 wk.

**Results:** There was significant reduction in baseline dystonia in both the groups (DIS:  $p < 0.001$ ; DSAP:  $p = 0.007$ ; ICF-CY:  $p < 0.001$ ) but when data were compared between the groups, there was no significant difference in the severity of dystonia at 4 wk and at 12 wk (DIS:  $p = 0.09$ ; DSAP:  $p = 0.49$ ; ICF-CY:  $p = 0.25$ ). Constipation was the commonest side effect observed in both the groups [3 (11.5%) vs. 4 (14.3%)].

**Conclusion:** Trihexyphenidyl alone is as effective as combination of gabapentin with trihexyphenidyl in decreasing the severity of dystonia at 12 wk. Hence, there is no added benefit of gabapentin as add-on therapy for dystonia among children with dyskinetic CP.

Note: Trihexyphenidyl is an anticholinergic (antimuscarinic class), antispasmodic drug that reduces extrapyramidal side effects, is often used to treat Parkinson's disease, and is active in dystonia. Symptoms of overdose include mydriasis, dryness of mucous membranes, facial flushing, atonic bowels and bladder, and fever. Trihexyphenidyl may also cause agitation, confusion, hallucinations, and respiratory depression due to its effects on the central nervous system. Also called Artane.

## Autism

J Environ Public Health. 2022 Aug 31;2022:9350841.

doi: 10.1155/2022/9350841. eCollection 2022.

## [Comprehensive Intervention and Effect of Martial Arts Routines on Children with Autism](#)

[Li Li<sup>1,2</sup>](#), [Hui Li<sup>3</sup>](#), [Zhe Zhao<sup>4</sup>](#), [Shijie Xu<sup>2</sup>](#)

### **Abstract**

Autism in children is a representative disease of pervasive developmental disorder, and there is currently no matching treatment. In the course of treatment, people generally use special education training, but this training mode cannot meet the comprehensive development of children. The traditional treatment mode cannot meet the changing new situation due to its poor adaptability. Martial arts routine movements are the soul of martial arts training, which can lay the foundation for movement training. Based on this, this article takes children with autism as research objects and aims to analyze the comprehensive intervention effect of martial arts routines on autism so as to provide some references for the treatment of children with autism. The article first analyzes the intervention forms of martial arts routine

movements and realizes the combination of martial arts routine movements and children's autism intervention treatment from a theoretical point of view. Then, the article randomly divides the experimental subjects into the experimental group and the control group and conducts an evaluation and analysis of various indicators before and after the training of children with autism. Finally, the article falls back from the experimental results to related theories, aiming to provide a scientific basis for the comprehensive intervention treatment of children with autism. The experimental results showed that the scale evaluation results of the experimental group are different from those of the control group, and various indicators have been improved and improved, including language, perception, and social skills. Among them, the language and behavior of children with autism increased by 19.1%. The perception ability increased by 20.7%, and the social ability increased by 5.9%. The above experiments and analysis fully demonstrated that martial arts routines have a good effect in the intervention and treatment of children with autism, which can well improve the comprehensive quality of patients.

Explore (NY). 2022 Dec 25;S1550-8307(22)00216-6.

doi: 10.1016/j.explore.2022.12.004. Online ahead of print.

[\*\*Effect of yoga on the social responsiveness and problem behaviors of children with ASD in special schools: A randomized controlled trial\*\*](#)

[Sindhu Shanker<sup>1</sup>, Balaram Pradhan<sup>2</sup>](#)

**Abstract**

**Context:** Autism spectrum disorder (ASD) is the most common neurodevelopmental disorder and is increasingly reported among school-age children in India. Many children with ASD attend special schools which extend support for learning basic functional and academic skills. Problem behaviors and lack of social responsiveness are frequently associated with children with ASD in a school environment. Many evidence-based studies have explored various interventions in mitigating the lack of social responsiveness and problem behaviors in children. Few studies have examined the impact of yoga on social responsiveness and problem behaviors in special schools.

**Objective:** The objective of the study was to highlight the effect of school-based yoga on the social responsiveness and problem behaviors of children with ASD in special schools. Forty-three children with ASD from four special schools participated in the study.

**Design:** A randomized controlled trial (RCT) design was employed for the study. Children with ASD (n = 43) from four special schools were assessed by their teachers for social responsiveness and problem behaviors with the Social Responsiveness Scale-2 (SRS-2) and Aberrant Behavior Checklist-2 (ABC-2) at the baseline and after the yoga intervention.

**Intervention:** Structured yoga of 45 min for 12 weeks was conducted across four special schools with simple yoga practices conducive to children with ASD.

**Results:** Significant changes were observed post-intervention in the mean scores of the social communication aspect in social responsiveness (p = .021), irritability (p = .041), and social withdrawal (p = .047) aspects of problem behaviors.

J Glob Health. 2022 Dec 29;12:04102.

doi: 10.7189/jogh.12.04102.

**[Effectiveness of multi-modal cognitive behavioural therapy in improving mental well-being among caregivers of children with disabilities in urban Uganda: A cluster-randomized controlled trial](#)**

[Mariam Namasaba](#)<sup>1</sup>, [Sumaya Nabunje](#)<sup>2</sup>, [Ali Ayub Baguwemu](#)<sup>1</sup>

**Abstract**

**Background:** In Sub-Saharan Africa, 41 to 58% of the caregivers of children with disabilities experience psychological distress and have poor mental well-being. Cognitive behavioural therapy (CBT) has a moderate effect on improving mental well-being. However, no study has examined its effects among caregivers of children with disabilities at home and in schools. This study evaluated the effectiveness of CBT in improving mental well-being among caregivers of children with disabilities in urban Uganda.

**Methods:** We conducted a two-arm cluster-randomized controlled trial in 11 schools across the Kampala district of Uganda. The intervention was a multi-modal CBT training program conducted for six months among 392 home and school caregivers of children with disabilities. In the first three months, caregivers received group-based CBT, and in the next three months, they received phone-based CBT. We used generalized linear mixed-effects regression to examine the differences in the mental well-being of caregivers in the control group vs those in the intervention group.

**Results:** Home caregivers' mental well-being was significantly higher after phone-based CBT (unstandardized coefficient of the estimate (B) = 4.31, 95% CI = 1.18-6.82; P < 0.001, Cohen's D (d) = 0.27). School caregivers' mental well-being was significantly higher after group-based CBT (B = 3.98, 95% CI = 0.22-7.47; P = 0.038, d = 0.25).

**Conclusions:** Group-based CBT improved mental well-being among school caregivers, and phone-based CBT improved mental well-being among home caregivers. Interventions targeting school caregivers of children with disabilities should employ group settings and those targeting home caregivers should utilize peer-to-peer networks to enhance the caregivers' mental well-being.

PLoS One. 2022 Sep 16;17(9):e0274664.

doi: 10.1371/journal.pone.0274664. eCollection 2022.

**[Performance of the UNICEF/UN Washington Group tool for identifying functional difficulty in rural Zimbabwean children](#)**

[Thomas Frederick Dunne](#)<sup>1</sup>, [Jaya Chandna](#)<sup>1,2</sup>, [Florence Majo](#)<sup>2</sup>, [Naume Tavengwa](#)<sup>2</sup>, [Batsirai Mutasa](#)<sup>2</sup>, [Bernard Chasekwa](#)<sup>2</sup>, [Robert Ntozini](#)<sup>2</sup>, [Andrew J Prendergast](#)<sup>2,3,4</sup>, [Jean H Humphrey](#)<sup>2,4</sup>, [Melissa J Gladstone](#)<sup>1</sup>

**Abstract**

**Introduction:** Over one billion people live with disability worldwide, of whom 80% are in developing countries. Robust childhood disability data are limited, particularly as tools for identifying disability function poorly at young ages.

**Methods:** A subgroup of children enrolled in the Sanitation Hygiene Infant Nutrition Efficacy (SHINE) trial (a cluster-randomised, community-based, 2x2 factorial trial in two rural districts in Zimbabwe) had neurodevelopmental assessments at 2 years of age. We evaluated functional difficulty prevalence in HIV-exposed and HIV-unexposed children using the Washington Group Child Functioning Module (WGCFM), comparing absolute difference using chi-squared or Fisher's exact tests. Concurrent validity with the Malawi Developmental



Assessment Tool (MDAT) was assessed using logistic regression with cohort MDAT score quartiles, linear regression for unit-increase in raw scores and a Generalised Estimating Equation approach (to adjust for clusters) to compare MDAT scores of those with and without functional difficulty. A 3-step, cluster-adjusted multivariable regression model was then carried out to examine risk factors for functional difficulty.

**Findings:** Functional Difficulty prevalence was 4.2% (95%CI: 3.2%, 5.2%) in HIV-unexposed children (n = 1606) versus 6.1% (95%CI: 3.5%, 8.9%) in HIV-exposed children (n = 314) (absolute difference 1.9%, 95%CI: -0.93%, 4.69%; p = 0.14). Functional difficulty score correlated negatively with MDAT: for each unit increase in WGCFM score, children completed 2.6 (95%CI: 2.2, 3.1) fewer MDAT items (p = 0.001). Children from families with food insecurity and poorer housing were more at risk of functional difficulty.

**Interpretation:** Functional difficulty was identified in approximately 1-in-20 children in rural Zimbabwe, which is comparable to prevalence in previous studies. WGCFM showed concurrent validity with the MDAT, supporting its use in early childhood.

Sci Rep. 2022 Jul 29;12(1):13051.  
doi: 10.1038/s41598-022-16332-x.

### [Therapeutic exercise to improve motor function among children with Down Syndrome aged 0 to 3 years: a systematic literature review and meta-analysis](#)

[Eliana-Isabel Rodríguez-Grande<sup>1,2</sup>](#), [Adriana Buitrago-López<sup>3,4,5</sup>](#), [Martha-Rocio Torres-Narváez<sup>6</sup>](#), [Yannely Serrano-Villar<sup>7</sup>](#), [Francisca Verdugo-Paiva<sup>8,9</sup>](#), [Camila Ávila<sup>2</sup>](#)

#### **Abstract**

The effects and the prescription parameters of therapeutic exercise are not clear. For this reason, is needed to determine the effect of therapeutic exercises on the motor function of children with Down Syndrome (DS) aged 0 to 3 years. The present study is systematic review and meta-analysis of effectiveness outcomes in this population: gait, balance, motor development, fine motor skills, and executive functions. The databases of PubMed, PEDro, EMBASE, SCIELO, Lilacs, Cochrane library were searched from January to December 2019. We recruited Randomized Controlled Trials (RCTs) which met the inclusion criteria in our study. Six studies and 151 participants were included. Two types of therapeutic exercises, aerobic and neuromuscular, were identified. Both types of exercise were effective in improving outcomes. There were no differences between the modes of application of the exercise. No differences were identified between the treadmill and the physiotherapy plan for the reduction of the time to reach independent walking, Mean Difference (MD) 46.79, 95% Confidence Interval (IC) (- 32.60, 126.19), nor for the increase in walking speed MD 0.10 IC (- 0.02, 0.21) m/s. This study suggests that aerobic exercise therapy has a potentially effective role to promote the gait and motor development of children with DS aged 0 to 3 years when it is applied using a treadmill with a frequency of 5 days, a duration of 6-8 min, and an intensity of between 0.2 and 0.5 m/s. Studies with less heterogeneity and larger sample sizes are required.

## Newborn care

### Essential newborn care

#### Avoiding hypothermia

Resuscitation. 2022 Sep 27;180:81-98.

doi: 10.1016/j.resuscitation.2022.09.014. Online ahead of print.

#### [Maintaining normal temperature immediately after birth in late preterm and term infants: A systematic review and meta-analysis](#)

[V V Ramaswamy](#)<sup>1</sup>, [M F de Almeida](#)<sup>2</sup>, [J A Dawson](#)<sup>3</sup>, [D Trevisanuto](#)<sup>4</sup>, [F L Nakwa](#)<sup>5</sup>, [C O Kamlin](#)<sup>3</sup>, [S Hosono](#)<sup>6</sup>, [M H Wyckoff](#)<sup>7</sup>, [H G Liley](#)<sup>8</sup>, [International Liaison Committee on Resuscitation Neonatal Life Support Task Force](#)

#### Abstract

**Aim:** Prevention of hypothermia after birth is a global problem in late preterm and term neonates. The aim of this systematic review and meta-analysis was to evaluate delivery room strategies to maintain normothermia and improve survival in late preterm and term neonates ( $\geq 34$  weeks' gestation).

**Methods:** Medline, Embase, CINAHL, CENTRAL and international clinical trial registries were searched. Randomized controlled trials (RCTs), quasi-RCTs and observational studies were eligible for inclusion. Risk of bias for each study and GRADE certainty of evidence for each outcome were assessed.

**Results:** 25 RCTs and 10 non-RCTs were included. Room temperature of 23 °C compared to 20 °C improved normothermia [Risk Ratio (RR), 95% Confidence Interval (CI): 1.26, 1.11-1.42] and body temperature [Mean Difference (MD), 95% CI: 0.30 °C, 0.23-0.37 °C], and decreased moderate hypothermia (RR, 95% CI: 0.26, 0.16-0.42). Skin to skin care (SSC) compared to no SSC increased body temperature (MD, 95% CI: 0.32, 0.10-0.52), reduced hypoglycemia (RR, 95% CI: 0.16, 0.05-0.53) and hospital admission (RR, 95% CI: 0.34, 0.14-0.83). Though plastic bag or wrap (PBW) alone or when combined with SSC compared to SSC alone improved temperatures, the risk-benefit balance is uncertain. Clinical benefit or harm could not be excluded for the primary outcome of survival for any of the interventions. Certainty of evidence was low to very low for all outcomes.

**Conclusions:** Room temperature of 23 °C and SSC soon after birth may prevent hypothermia in late preterm and term neonates. Though PBW may be an effective adjunct intervention, the risk-benefit balance needs further investigation.

#### Cord management

Neonatology. 2022 Dec 14;1-16.

doi: 10.1159/000527454. Online ahead of print.

#### [Placental Transfusion Strategies in Preterm Infants in Low- and Middle-Income Countries: A Systematic Review and Network Meta-Analysis](#)

[Viraghavan Vadakkencherry Ramaswamy](#)<sup>1</sup>, [Tapas Bandyopadhyay](#)<sup>2</sup>, [Thangaraj Abiramalatha](#)<sup>3</sup>, [Nasreen Banu Shaik](#)<sup>4</sup>, [Abdul Kareem Pullattayil S](#)<sup>5</sup>, [Bonny Jasani](#)<sup>6</sup>, [Vandana Hegde](#)<sup>7</sup>, [Daniele Trevisanuto](#)<sup>8</sup>, [Gary M Weiner](#)<sup>9</sup>

## Abstract

**Introduction:** Placental transfusion strategies in preterm newborns have not been evaluated in low- and middle-income countries (LMICs). The objective of this systematic review was to compare placental transfusion strategies in preterm newborns in LMICs, including delayed cord clamping (DCC) for various time intervals, DCC until cord pulsations stop, umbilical cord milking, and immediate cord clamping (ICC).

**Methods:** Medline, Embase, CINAHL, and CENTRAL were searched from inception. Observational studies and randomized controlled trials (RCTs) were included. Two authors independently extracted data for Bayesian random-effects network meta-analysis (NMA) if more than 3 interventions reported an outcome or a pairwise meta-analysis was utilized.

**Results:** Among newborns <34 weeks of gestation, NMA of 9 RCTs could not rule out benefit or harm for survival from DCC 30-60 s compared to ICC: relative risk (RR) (95% credible interval) 0.96 (0.78-1.12), moderate certainty, or any included strategy compared to each other (low to very low certainty). Among late preterm newborns, DCC 120 s might be associated with improved survival: RR (95% confidence interval) 1.11 (1.01-1.22), very low certainty. We could not detect differences in the risk of intraventricular hemorrhage grade > II and bronchopulmonary dysplasia for any included intervention (low to very low certainty). DCC 60 s and 120 s might improve the hematocrit level among all preterm newborns (very low certainty), and DCC 45 s may decrease the risk of receipt of inotropes among newborns <34 weeks of gestation (low certainty).

**Conclusions:** In LMICs, DCC for 60 s and 120 s might improve hematocrit level in preterm newborns, and DCC for 45 s may decrease the risk of receipt of inotropes in newborns <34 weeks, with no conclusive effect on survival.

Eur J Pediatr. 2023 Jun 19.

doi: 10.1007/s00431-023-05063-4. Online ahead of print.

### [Cut umbilical cord milking \(C-UCM\) as a mode of placental transfusion in non-vigorous preterm neonates: a randomized controlled trial](#)

[Rajib Losan Bora](#)<sup>1</sup>, [Sambhunath Bandyopadhyay](#)<sup>2</sup>, [Bijan Saha](#)<sup>3</sup>, [Suchandra Mukherjee](#)<sup>1</sup>, [Abhijit Hazra](#)<sup>4</sup>

## Abstract

Routine practice of delayed cord clamping (DCC) is the standard of care in vigorous neonates. However there is no consensus on the recommended approach to placental transfusion in non-vigorous neonates. In this trial, we tried to examine the effect of cut umbilical cord milking (C-UCM) as compared to early cord clamping (ECC) on hematological and clinical hemodynamic parameters in non-vigorous preterm neonates of 30-35 weeks gestation. The primary outcome assessed was venous hematocrit (Hct) at 48 ( $\pm$  4) hours of postnatal age. The important secondary outcomes assessed were serum ferritin at 6 weeks of age, mean blood pressure in the initial transitional phase along with important neonatal morbidities and potential complications. In this single centre randomized controlled trial, 134 non vigorous neonates of 30-35 weeks gestation were allocated in a 1:1 ratio to either C-UCM (n = 67) or ECC (n = 67). For statistical analysis, unpaired Student t and Chi square or Fisher's exact test were used. The mean Hct at 48 h was higher in the C-UCM group as compared to the control group, 50.24(4.200) vs 46.16(2.957),  $p < .0001$ . Also significantly higher was the mean Hct at 12 h, 6 weeks and mean serum ferritin at 6 weeks of age in the milked group ( $p < .0001$ ). Mean blood pressure at 1 h and 6 h was also significantly higher in

the milked arm. Need for transfusion and inotropes was less in the milked group but not statistically significant. No significant difference in potential complications was observed between the groups. Conclusion: C-UCM stabilizes initial blood pressure and results in higher hematocrit and improved iron stores. It can be an alternative to DCC in non-vigorous preterm neonates of 30-35 weeks' gestation. Further large multicentric studies are needed to fully establish its efficacy and safety.

Am J Obstet Gynecol. 2023 Feb;228(2):217.e1-217.e14.

doi: 10.1016/j.ajog.2022.08.015. Epub 2022 Aug 13.

**[Umbilical cord milking in nonvigorous infants: a cluster-randomized crossover trial](#)**

[Anup C Katheria<sup>1</sup>](#), [Erin Clark<sup>2</sup>](#), [Bradley Yoder<sup>3</sup>](#), [Georg M Schmölder<sup>4</sup>](#), [Brenda Hiu Yan Law<sup>4</sup>](#), [Walid El-Naggar<sup>5</sup>](#), [David Rittenberg<sup>6</sup>](#), [Sheetal Sheth<sup>7</sup>](#), [Mohamed A Mohamed<sup>8</sup>](#), [Courtney Martin<sup>9</sup>](#), [Farha Vora<sup>9</sup>](#), [Satyan Lakshminrusimha<sup>10</sup>](#), [Mark Underwood<sup>10</sup>](#), [Jan Mazela<sup>11</sup>](#), [Joseph Kaempf<sup>12</sup>](#), [Mark Tomlinson<sup>12</sup>](#), [Yvonne Gollin<sup>13</sup>](#), [Kevin Fulford<sup>14</sup>](#), [Yvonne Goff<sup>14</sup>](#), [Paul Wozniak<sup>15</sup>](#), [Katherine Baker<sup>13</sup>](#), [Wade Rich<sup>13</sup>](#), [Ana Morales<sup>13</sup>](#), [Michael Varner<sup>2</sup>](#), [Debra Poeltler<sup>13</sup>](#), [Yvonne Vaucher<sup>16</sup>](#), [Judith Mercer<sup>13</sup>](#), [Neil Finer<sup>13</sup>](#), [Laure El Ghormli<sup>17</sup>](#), [Madeline Murguia Rice<sup>17</sup>](#); [of the Milking In Nonvigorous Infants group](#)

**Abstract**

**Background:** Delayed cord clamping and umbilical cord milking provide placental transfusion to vigorous newborns. Delayed cord clamping in nonvigorous newborns may not be provided owing to a perceived need for immediate resuscitation. Umbilical cord milking is an alternative, as it can be performed more quickly than delayed cord clamping and may confer similar benefits.

**Objective:** We hypothesized that umbilical cord milking would reduce admission to the neonatal intensive care unit compared with early cord clamping in nonvigorous newborns born between 35 and 42 weeks' gestation.

**Study design:** This was a pragmatic cluster-randomized crossover trial of infants born at 35 to 42 weeks' gestation in 10 medical centers in 3 countries between January 2019 and May 2021. The centers were randomized to umbilical cord milking or early cord clamping for approximately 1 year and then crossed over for an additional year or until the required number of consented subjects was reached. Waiver of consent as obtained in all centers to implement the intervention. Infants were eligible if nonvigorous at birth (poor tone, pale color, or lack of breathing in the first 15 seconds after birth) and were assigned to umbilical cord milking or early cord clamping according to their birth hospital randomization assignment. The baseline characteristics and outcomes were collected following deferred informed consent. The primary outcome was admission to the neonatal intensive care unit for predefined criteria. The main safety outcome was hypoxic-ischemic encephalopathy. Data were analyzed by the intention-to-treat concept.

**Results:** Among 16,234 screened newborns, 1780 were eligible (905 umbilical cord milking, 875 early cord clamping), and 1730 had primary outcome data for analysis (97% of eligible; 872 umbilical cord milking, 858 early cord clamping) either via informed consent (606 umbilical cord milking, 601 early cord clamping) or waiver of informed consent (266 umbilical cord milking, 257 early cord clamping). The difference in the frequency of neonatal intensive care unit admission using predefined criteria between the umbilical cord milking (23%) and early cord clamping (28%) groups did not reach statistical significance (modeled

odds ratio, 0.69; 95% confidence interval, 0.41-1.14). Umbilical cord milking was associated with predefined secondary outcomes, including higher hemoglobin (modeled mean difference between umbilical cord milking and early cord clamping groups 0.68 g/dL, 95% confidence interval, 0.31-1.05), lower odds of abnormal 1-minute Apgar scores (Apgar  $\leq 3$ , 30% vs 34%, crude odds ratio, 0.72; 95% confidence interval, 0.56-0.92); cardiorespiratory support at delivery (61% vs 71%, modeled odds ratio, 0.57; 95% confidence interval, 0.33-0.99), and therapeutic hypothermia (3% vs 4%, crude odds ratio, 0.57; 95% confidence interval, 0.33-0.99). Moderate-to-severe hypoxic-ischemic encephalopathy was significantly less common with umbilical cord milking (1% vs 3%, crude odds ratio, 0.48; 95% confidence interval, 0.24-0.96). No significant differences were observed for normal saline bolus, phototherapy, abnormal 5-minute Apgar scores (Apgar  $\leq 6$ , 15.7% vs 18.8%, crude odds ratio, 0.81; 95% confidence interval, 0.62-1.06), or a serious adverse event composite of death before discharge.

**Conclusion:** Among nonvigorous infants born at 35 to 42 weeks' gestation, umbilical cord milking did not reduce neonatal intensive care unit admission for predefined criteria. However, infants in the umbilical cord milking arm had higher hemoglobin, received less delivery room cardiorespiratory support, had a lower incidence of moderate-to-severe hypoxic-ischemic encephalopathy, and received less therapeutic hypothermia. These data may provide the first randomized controlled trial evidence that umbilical cord milking in nonvigorous infants is feasible, safe and, superior to early cord clamping.

Eur J Pediatr. 2023 Jun 6;1-11.

doi: 10.1007/s00431-023-05053-6. Online ahead of print.

**[Effects of delayed cord clamping at different time intervals in late preterm and term neonates: a randomized controlled trial](#)**

[Pankaj Chaudhary](#)<sup>1</sup>, [Mayank Priyadarshi](#)<sup>1</sup>, [Poonam Singh](#)<sup>1</sup>, [Suman Chaurasia](#)<sup>1</sup>, [Jaya Chaturvedi](#)<sup>2</sup>, [Sriparna Basu](#)<sup>3</sup>

**Abstract**

Delayed cord clamping (DCC) at delivery has well-recognized benefits; however, current scientific guidelines lack uniformity in its definition. This parallel-group, three-arm assessor-blinded randomized controlled trial compared the effects of three different timings of DCC at 30, 60, and 120 s on venous hematocrit and serum ferritin levels in late preterm and term neonates not requiring resuscitation. Eligible newborns (n = 204) were randomized to DCC 30 (n = 65), DCC 60 (n = 70), and DCC 120 (n = 69) groups immediately after delivery. The primary outcome variable was venous hematocrit at 24  $\pm$  2 h. Secondary outcome variables were respiratory support, axillary temperature, vital parameters, incidences of polycythemia, neonatal hyperbilirubinemia (NNH), need and duration of phototherapy, and postpartum hemorrhage (PPH). Additionally, serum ferritin levels, the incidence of iron deficiency, exclusive breastfeeding (EBF) rate, and anthropometric parameters were assessed during post-discharge follow-up at 12  $\pm$  2 weeks. Over one-third of the included mothers were anemic. DCC 120 was associated with a significant increase in the mean hematocrit by 2%, incidence of polycythemia, and duration of phototherapy, compared to DCC30 and DCC60; though the incidence of NNH and need for phototherapy was similar. No other serious neonatal or maternal adverse events including PPH were observed. No significant difference was documented in serum ferritin, incidences of iron deficiency, and growth parameters at 3

months even in the presence of a high EBF rate. Conclusion: The standard recommendation of DCC at 30-60 s may be considered a safe and effective intervention in the busy settings of low-middle-income countries with a high prevalence of maternal anemia.

J Matern Fetal Neonatal Med. 2022 Dec;35(25):5478-5488.

doi: 10.1080/14767058.2021.1884676. Epub 2021 Feb 10.

**[Umbilical cord milking versus delayed cord clamping in term and late-preterm infants: a systematic review and meta-analysis](#)**

[Amrit Jeevan](#)<sup>1</sup>, [Anitha Ananthan](#)<sup>2</sup>, [Manjari Bhuwan](#)<sup>1</sup>, [Haribalakrishna Balasubramanian](#)<sup>3</sup>, [Shripada Rao](#)<sup>4</sup>, [Nandkishor S Kabra](#)<sup>3</sup>

**Abstract**

**Objective:** To conduct a systematic review and meta-analysis to compare the efficacy and safety of umbilical cord milking (UCM) versus delayed cord clamping (DCC) in term and late-preterm infants.

**Methods:** MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, Clinical trial registries, and Gray literature were searched for randomized controlled trials (RCTs) comparing UCM with DCC in term and late-preterm infants for both short-term and long-term outcomes. Intact and cut UCM were compared separately with DCC using subgroup analysis. We used fixed effect model to pool the data. Random effects model was used when there was significant heterogeneity.

**Results:** Nine studies (1632 infants) were included in the systematic review. Milking was performed on intact cord (i-UCM) in five studies ( $n = 829$ ) and on cut cord (c-UCM) in four studies ( $n = 803$ ). Cord milking significantly improved hemoglobin level at 48-72 h of life when compared to DCC (six studies,  $n = 924$ , mean difference 0.36 g/dL; 95% CI: 0.19-0.53). In addition, hemoglobin level at six to eight weeks of age was also significantly higher in the studies comparing i-UCM with DCC (two studies,  $n = 550$ : mean difference 0.16 g/dL; 95% CI: 0.06-0.27). There was no difference between the UCM group and DCC group for any other outcome. Only one study provided information on growth and hematological parameters at one year of age. Neurodevelopmental outcomes were not reported. None of the studies included non-vigorous infants. The grade of evidence was low to very low for all the outcomes studied.

**Conclusion:** UCM is comparable to DCC in improving short-term hematological outcomes in term and late-preterm vigorous infants. Trials assessing the effect of UCM on important clinical and long-term outcomes among non-vigorous mature preterm infants are urgently required.

**Kangaroo mother care / skin to skin contact**

Matern Child Nutr. 2022 Oct;18(4):e13419.

doi: 10.1111/mcn.13419. Epub 2022 Aug 10.

**[Effect of community-initiated kangaroo mother care on breastfeeding performance in low birthweight infants: A randomized clinical trial](#)**



[Bireswar Sinha](#)<sup>1,2,3</sup>, [Halvor Sommerfelt](#)<sup>4,5</sup>, [Per Ashorn](#)<sup>2</sup>, [Sarmila Mazumder](#)<sup>1</sup>, [Sunita Taneja](#)<sup>1</sup>, [Rajiv Bahl](#)<sup>6</sup>, [Nita Bhandari](#)<sup>1</sup>

### Abstract

This individually randomized trial was conducted to estimate the effect of promoting community-initiated kangaroo mother care (ciKMC) in low birthweight (LBW) infants on infant breastfeeding performance. It was designed as a substudy within a larger primary trial on ciKMC and infant survival. Five hundred fifty stable LBW mother-infant dyads (1500-2250 g) who provided consent, were consecutively enrolled for breastfeeding performance assessment. The ciKMC intervention included promotion and support of continuous skin-to-skin contact and exclusive breastfeeding (EBF) through home visits during the neonatal period. The primary outcome was effective breastfeeding performance indicated by an infant breastfeeding assessment tool score of  $\geq 10$  after the end of the neonatal period. As secondary outcomes, we reported maternal satisfaction related to infant breastfeeding, and EBF after the end of the neonatal period. We completed outcome assessments in 96% of participants. In the ciKMC arm, 92% of the infants showed effective breastfeeding performance against 81% in the control arm [adjusted prevalence ratio (aPR): 1.24, 95% confidence interval (CI): 1.16-1.32]. In the ciKMC arm, 65% of the mothers reported to be very satisfied with their infants' breastfeeding against 51% in the control arm (aPR: 1.22, 95% CI: 1.05-1.41). The proportion of infants practicing EBF was 89% in the ciKMC arm against 45% in the control arm (aPR: 1.62, 95% CI: 1.45-1.81). Our study findings suggest that promotion of ciKMC can improve effective breastfeeding, EBF and maternal satisfaction related to breastfeeding in LBW infants.

Bull World Health Organ. 2023 Jun 1;101(6):391-402G.

doi: 10.2471/BLT.22.288977. Epub 2023 Mar 31.

### [Effects of kangaroo mother care on maternal and paternal health: systematic review and meta-analysis](#)

[Barsha Gadapani Pathak](#)<sup>1</sup>, [Bireswar Sinha](#)<sup>1</sup>, [Neeraj Sharma](#)<sup>1</sup>, [Sarmila Mazumder](#)<sup>1</sup>, [Nita Bhandari](#)<sup>1</sup>

### Abstract

**Objective:** To investigate the effect of kangaroo mother care for low-birth-weight and preterm infants on parents' mental and physical health.

**Methods:** The Cochrane Central Register of Controlled Trials, Cochrane Register of Studies Online, PubMed®, Web of Science, Scopus and EMBASE® databases were searched on 16 January 2023 for randomized and quasi-randomized trials on kangaroo mother care. Records identified were screened independently by two reviewers. Pooled relative risks (RRs) are reported for categorical variables, and standardized mean differences (SMDs) or mean differences are reported for continuous variables. Evidence quality was assessed using the GRADE approach.

**Findings:** The search identified 30 studies involving 7719 preterm or low-birth-weight infants. There was high-certainty evidence that kangaroo mother care substantially reduced the risk of moderate-to-severe postpartum maternal depressive symptoms compared with no kangaroo mother care (RR: 0.76; 95% confidence interval, CI: 0.59 to 0.96). In addition, there was low-certainty evidence that kangaroo mother care reduced scores for maternal stress (SMD: -0.82; 95% CI: -1.32 to -0.32) and anxiety (SMD: -0.62; 95% CI: -1.01 to -0.23) and

increased mother-infant attachment and bonding scores (SMD: 1.19; 95% CI: 0.27 to 2.10). Limited evidence indicated father-infant interactions may be improved, though no marked effect on paternal depression or stress was observed. No trial reported parental physical health outcomes.

**Conclusion:** Kangaroo mother care for preterm and low-birth-weight infants was associated with less postpartum maternal depression, stress and anxiety and better mother-infant attachment and bonding. More research is required to evaluate effects on paternal health.

Sci Rep. 2023 Mar 16;13(1):4368.

doi: 10.1038/s41598-023-29388-0.

**[Impact of hypothermia alert device \(BEMPU\) on improvement of duration of Kangaroo Mother Care \(KMC\) provided at home: parallel-group randomized control trial](#)**

[Somashekhar Marutirao Nimbalkar<sup>1,2</sup>](#), [Viral Thakorbbhai Patel<sup>3</sup>](#), [Dipen Vasudev Patel<sup>3</sup>](#), [Ajay Gajanan Phatak<sup>4</sup>](#)

**Abstract**

The objective of the study was to determine if using the hypothermia-detecting bracelet (named BEMPU) improves the duration of Kangaroo Mother Care (KMC) at home by one hour. This parallel-group randomized controlled trial was conducted at a step-down nursery of a teaching hospital. Neonates between 1000 and 2000 g were randomized to BEMPU and control groups at the time of discharge. BEMPU was applied at the wrist of each newborn in the BEMPU (intervention) group. Parents were advised to keep the BEMPU in place till 4 weeks post-discharge. The BEMPU generates a beep sound as an alarm when a newborn's temperature drops below 36.5 °C. Parents in both groups were trained to provide KMC at home. Parents in the BEMPU group received the "KMC chart" and "BEMPU beep chart," while the control group received the "KMC chart" only. In the "KMC chart," parents entered information about KMC hours on a real-time basis, and in the "BEMPU beep chart," they entered information about alarm beeps from BEMPU on a real-time basis till 4 weeks post-discharge. Independent samples t-test was used to compare mean KMC hours between the two groups. A total of 128 neonates participated in the study (64 in BEMPU and 64 in Control groups). The mean(SD) gestational age for the BEMPU group was 34.04(2.84) weeks vs 34.75(2.70) weeks for the control group. In BEMPU group, mean(SD) daily time spent doing KMC was significantly higher in 1st week [4.78(2.93) vs. 3.22(2.44) h,  $p = 0.003$ ], in 2nd week [4.52(3.43) vs. 2.84(2.95) h,  $p = 0.008$ ], in 3rd week [4.23(3.71) vs. 2.30(2.70) h,  $p = 0.003$ ], in 4th week [3.72(3.30) vs. 1.95(2.65) h,  $p = 0.003$ ] as compared to control group. BEMPU improved the daily duration of KMC hours at home compared to the control group over four weeks.

BMJ Glob Health. 2022 Nov;7(11):e010000.

doi: 10.1136/bmjgh-2022-010000.

**[Effect of kangaroo mother care initiated in community settings on financial risk protection of low-income households: a randomised controlled trial in Haryana, India](#)**

[Tarun Shankar Choudhary<sup>1,2</sup>](#), [Sarmila Mazumder<sup>2</sup>](#), [Oystein A Haaland<sup>3</sup>](#), [Sunita Taneja<sup>2</sup>](#), [Rajiv Bahl<sup>4</sup>](#), [Jose Martinez<sup>5</sup>](#), [Maharaj Kishan Bhan<sup>6</sup>](#), [Ole Frithjof Norheim<sup>5,3</sup>](#), [Halvor Sommerfelt<sup>5,7</sup>](#), [Nita Bhandari<sup>2</sup>](#), [Kjell Arne Johansson<sup>5,3</sup>](#)

## Abstract

**Introduction:** Many families in low-income and middle-income countries have high out-of-pocket expenditures (OOPE) for healthcare, and some face impoverishment. We aimed to assess the effect of Kangaroo Mother Care initiated in community setting (ciKMC) on financial risk protection estimated by healthcare OOPE, catastrophic healthcare expenditure (CHE) and impoverishment due to healthcare seeking for low birthweight infants, using a randomised controlled trial design.

**Methods:** We included 4475 low birthweight infants randomised to a ciKMC (2491 infants) and a control (1984 infants) arm, in a large trial conducted between 2017 and 2018 in Haryana, India. We used generalised linear models of the Gaussian family with an identity link to estimate the mean difference in healthcare OOPE, and Cox regression to estimate the HRs for CHE and impoverishment, between the trial arms.

**Results:** Overall, in the 8-week observation period, the mean healthcare OOPE per infant was lower (US\$20.0) in the ciKMC arm compared with the control arm (US\$25.6) that is, difference of -US\$5.5, 95% CI -US\$11.4 to US\$0.3,  $p=0.06$ ). Among infants who sought care it was US\$8.5 (95% CI -US\$17.0 to -US\$0.03,  $p=0.03$ ) lower in the ciKMC arm compared with the control arm. The HR for impoverishment due to healthcare seeking was 0.56 (95% CI 0.36 to 0.89,  $p=0.01$ ) and it was 0.91 (95% CI 0.74 to 1.12,  $p=0.37$ ) for CHE.

**Conclusion:** ciKMC can substantially reduce the cost of care seeking and the risk of impoverishment for households. Our findings show that supporting mothers to provide KMC to low birthweight infants at home, in addition to reducing early infant mortality, may provide financial risk protection.

J Paediatr Child Health. 2022 Dec;58(12):2248-2253.

doi: 10.1111/jpc.16212. Epub 2022 Sep 21.

### [Effect of kangaroo mother care on pain during orogastric tube insertion in low-birthweight newborns: An open label, randomised trial](#)

[Geetika Srivastava](#)<sup>1</sup>, [Anantika Garg](#)<sup>2</sup>, [Nanda Chhavi](#)<sup>1</sup>, [Mma Faridi](#)<sup>1</sup>

## Abstract

**Aim:** Non-pharmacological methods are commonly used to reduce the procedural pain in newborns. In this open label, randomised control trial, we studied the pain-reducing effect of kangaroo mother care (KMC) during orogastric tube insertion.

**Methods:** Newborns, with birthweight 1500-2499 g and admitted to nursery, were randomised into control (no-KMC) or intervention (KMC) arms. In intervention arm, KMC was given for 60 min before and after the procedure. Premature Infant Pain Profile-Revised (PIPP-R) score was used to assess the pain response and the pain severity was graded as minimal or no pain ( $\leq 6$ ), mild-to-moderate (7-12) and severe ( $>12$ ). The PIPP-R scoring was done before, during and at 3- and 15-min after procedure. Change in PIPP-R scores from baseline was calculated.

**Results:** Newborns included in no-KMC ( $n = 40$ ) or KMC ( $n = 40$ ) arms were comparable for major confounders ( $P > 0.05$ ). Pre-procedural pain scores were comparable ( $P = 0.72$ ). Pain scores measured during and after procedure were significantly higher in no-KMC group than KMC arm. The KMC reduced the pain score by 39%, 32% and 30% during and at 3- and 15-min after procedure respectively as compared to control ( $P < 0.01$ ). The increase in PIPP-R score from pre-procedural level was 40%, 35% and 31% lower in KMC than no-KMC arm ( $P < 0.01$ ).

A greater proportion of newborns had significantly less severe grades of pain in the intervention arm compared to the no-KMC arm ( $P < 0.01$ ).

**Conclusion:** Orogastric tube placement is a painful procedure. KMC significantly reduces periprocedural pain and its effect continues for at least 15 min after the procedure.

Matern Child Health J. 2022 Sep;26(9):1891-1906.

doi: 10.1007/s10995-022-03409-2. Epub 2022 Apr 6.

### [Can Flip-Chart Assisted Maternal Education Improve Essential New Born Care Knowledge and Skills? A Randomized Controlled Trial](#)

[Swathi Eluri<sup>1</sup>](#), [B Shantharam Baliga<sup>1</sup>](#), [Suchetha S Rao<sup>1</sup>](#), [V Vinayagamoorthy<sup>2</sup>](#), [Nutan Kamath<sup>3</sup>](#)

#### **Abstract**

**Background:** Despite the implementation of essential newborn care (ENC) by the World Health Organization, knowledge gaps among postpartum women persist. Inappropriate breastfeeding practices and lack of knowledge regarding ENC among mothers has resulted in higher neonatal mortality.

**Purpose:** Our study focused on evaluating the effectiveness of flip-chart assisted postpartum maternal education in improving ENC knowledge and skills.

**Material and methods:** A single blind parallel randomized controlled trial was carried out with 120 primigravidae. Participants were allocated to the intervention group (IG) or the control group (CG) by block randomization. A pretested validated questionnaire was administered to participants in both groups within 24 h post-delivery. Women in the IG were provided flip-chart assisted education regarding ENC approximately 24 h post-delivery. Women in both groups received verbal advice on ENC from the postnatal ward nurses, as per the existing hospital policy. ENC skills were observed in all participants in postnatal wards by independent observers. 6 months later, knowledge retention was assessed and analyzed in both groups.

**Results:** Antenatal education remained at 32% among all postnatal women. Postnatal flip-chart-assisted maternal education had a significant impact on ENC skills in the IG ( $p < 0.01$ ) and precipitated higher knowledge scores at the end of 6 months ( $p < 0.01$ ) in the IG.

**Conclusion for practice:** Flip-chart assisted education soon after delivery had a sustained effect on ENC knowledge and practices that persisted for 6 months post-delivery.

## Neonatal sepsis

J Neonatal Perinatal Med. 2022 Sep 26.

doi: 10.3233/NPM-221025. Online ahead of print.

### [Adjuvant therapy in neonatal sepsis to prevent mortality - A systematic review and network meta-analysis](#)

[T Abiramalatha<sup>1</sup>](#), [V V Ramaswamy<sup>2</sup>](#), [T Bandyopadhyay<sup>3</sup>](#), [S H Somanath<sup>4</sup>](#), [N B Shaik<sup>2</sup>](#), [V R Kallem<sup>5</sup>](#), [A K Pullattayil<sup>6</sup>](#), [M Kaushal<sup>7</sup>](#)

## Abstract

**Background:** Despite appropriate antibiotic therapy, the risk of mortality in neonatal sepsis still remains high. We conducted a systematic review to comprehensively evaluate different adjuvant therapies in neonatal sepsis in a network meta-analysis.

**Methods:** We included randomized controlled trials (RCTs) and quasi-RCTs that evaluated adjuvant therapies in neonatal sepsis. Neonates of all gestational and postnatal ages, who were diagnosed with sepsis based on blood culture or sepsis screen were included. We searched MEDLINE, CENTRAL, EMBASE and CINAHL until 12th April 2021 and reference lists. Data extraction and risk of bias assessment were performed in duplicate. A network meta-analysis with bayesian random-effects model was used for data synthesis. Certainty of evidence (CoE) was assessed using GRADE.

**Results:** We included 45 studies involving 6,566 neonates. Moderate CoE showed IVIG [Relative Risk (RR); 95% Credible Interval (CrI): 1.00; (0.67-1.53)] as an adjunctive therapy probably does not reduce all-cause mortality before discharge, compared to standard care. Melatonin [0.12 (0-0.08)] and granulocyte transfusion [0.39 (0.19-0.76)] may reduce mortality before discharge, but CoE is very low. The evidence is also very uncertain regarding other adjunctive therapies to reduce mortality before discharge. Pentoxifylline may decrease the duration of hospital stay [Mean difference; 95% CrI: -7.48 days (-14.50-0.37)], but CoE is very low.

**Conclusion:** Given the biological plausibility for possible efficacy of these adjuvant therapies and that the CoE from the available trials is very low to low except for IVIG, we need large adequately powered RCTs to evaluate these therapies in sepsis in neonates.

Trop Doct. 2023 Jan 18;494755221138689.

doi: 10.1177/00494755221138689. Online ahead of print.

### [Intravenous immunoglobulin in the management of neonatal sepsis: A randomised controlled trial](#)

[Mohammad Qaim Rizvi](#)<sup>1</sup>, [Mukesh Vir Singh](#)<sup>1</sup>, [Nandita Mishra](#)<sup>1</sup>, [Anubha Shrivastava](#)<sup>1</sup>, [Manisha Maurya](#)<sup>1</sup>, [Shahid Akhtar Siddiqui](#)<sup>1</sup>

## Abstract

Sepsis is a leading cause of neonatal mortality and morbidity in low and middle-income countries. We designed a double-blinded randomised controlled trial in a neonatal intensive care unit (NICU) of a tertiary care teaching hospital to determine the role of intravenous immunoglobulin (IVIG) in decreasing hospital stay. Eighty neonates with clinical features of sepsis were enrolled in the study and placebo groups to receive 500 mg/kg of IVIG for three consecutive days or a placebo. The primary outcome measure was duration of hospital stay in days. The babies in both groups were comparable in terms of birth weight, gestation and sex distribution. There was no significant difference in duration of hospital stay (days) in the study and placebo groups. We found that treatment with IVIG did not shorten the duration of hospital stay in our setting.

## Low birth weight and prematurity - prevention

\*\*\* PNAS Nexus. 2023 Jan 27;2(1):pgac309.

doi: 10.1093/pnasnexus/pgac309. eCollection 2023 Jan.

### [Maternal nutritional status modifies heat-associated growth restriction in women with chronic malnutrition](#)

[Kartik Shankar](#)<sup>1</sup>, [Sumera A Ali](#)<sup>2</sup>, [Meghan L Ruebel](#)<sup>1,3</sup>, [Saleem Jessani](#)<sup>2</sup>, [Sarah J Borengasser](#)<sup>1</sup>, [Stephanie P Gilley](#)<sup>1</sup>, [Puujee Jambal](#)<sup>1</sup>, [Deaunabah N Yazza](#)<sup>1</sup>, [Nicholas Weaver](#)<sup>4</sup>, [Jennifer F Kemp](#)<sup>1</sup>, [Jamie L Westcott](#)<sup>1</sup>, [Audrey E Hendricks](#)<sup>4</sup>, [Sarah Saleem](#)<sup>2</sup>, [Robert L Goldenberg](#)<sup>5</sup>, [K Michael Hambidge](#)<sup>1</sup>, [Nancy F Krebs](#)<sup>1</sup>

#### Abstract

Rapid changes in the global climate are deepening existing health disparities from resource scarcity and malnutrition. Rising ambient temperatures represent an imminent risk to pregnant women and infants. Both maternal malnutrition and heat stress during pregnancy contribute to poor fetal growth, the leading cause of diminished child development in low-resource settings. However, studies explicitly examining interactions between these two important environmental factors are lacking. We leveraged maternal and neonatal anthropometry data from a randomized controlled trial focused on improving preconception maternal nutrition (Women First Preconception Nutrition trial) conducted in Thatta, Pakistan, where both nutritional deficits and heat stress are prevalent. Multiple linear regression of ambient temperature and neonatal anthropometry at birth ( $n = 459$ ) showed a negative association between daily maximal temperatures in the first trimester and Z-scores of birth length and head circumference. Placental mRNA-sequencing and protein analysis showed transcriptomic changes in protein translation, ribosomal proteins, and mTORC1 signaling components in term placenta exposed to excessive heat in the first trimester. Targeted metabolomic analysis indicated ambient temperature associated alterations in maternal circulation with decreases in choline concentrations. Notably, negative impacts of heat on birth length were in part mitigated in women randomized to comprehensive maternal nutritional supplementation before pregnancy suggesting potential interactions between heat stress and nutritional status of the mother. Collectively, the findings bridge critical gaps in our current understanding of how maternal nutrition may provide resilience against adverse effects of heat stress in pregnancy.

BMJ Glob Health. 2022 Aug;7(8):e007537.

doi: 10.1136/bmjgh-2021-007537.

### [Preconception and periconception interventions to prevent low birth weight, small for gestational age and preterm birth: a systematic review and meta-analysis](#)

[Uttara Partap](#)<sup>1</sup>, [Ranadip Chowdhury](#)<sup>2</sup>, [Sunita Taneja](#)<sup>2</sup>, [Nita Bhandari](#)<sup>2</sup>, [Ayesha De Costa](#)<sup>3</sup>, [Rajiv Bahl](#)<sup>3</sup>, [Wafaie Fawzi](#)<sup>4</sup>

#### Abstract

**Background:** Low birth weight (LBW), including preterm birth (PTB) and small for gestational age (SGA), contributes a significant global health burden. We aimed to summarise current evidence on the effect of preconception and periconception interventions on LBW, SGA and PTB.



**Methods:** In this systematic review and meta-analysis, we searched PubMed, Embase, Cochrane Library and WHO Global Index Medicus for randomised controlled trials and quasi-experimental studies published by 28 November 2020, which assessed interventions delivered in preconception and periconception or preconception and pregnancy. Primary outcomes were LBW, SGA and PTB. Studies were categorised by intervention type and delivery during preconception and periconception or during preconception and pregnancy. Estimates were pooled using fixed-effects or random-effects restricted maximum likelihood method meta-analyses. Quality of evidence for primary outcomes was assessed using the Grades of Recommendations, Assessment, Development and Evaluation approach.

**Results:** We included 58 studies. Twenty-eight studies examined nutrition interventions (primarily micronutrient or food supplementation). Thirty studies (including one reporting a nutrition intervention) provided health interventions (general preconception health, early adverse pregnancy outcome prevention, non-communicable disease and infectious disease prevention and management). One study assessed a social intervention (reproductive planning). Studies varied in terms of specific interventions, including delivery across preconception or pregnancy, resulting in few studies for any single comparison. Overall, the evidence was generally very uncertain regarding the impact of any intervention on LBW, SGA and PTB. Additionally, preconception and periconception nutritional supplementation containing folic acid was associated with reduced risk of birth defects (10 studies, N=3 13 312, risk ratio: 0.37 (95% CI: 0.24 to 0.55), I<sup>2</sup>: 74.33%).

**Conclusion:** We found a paucity of evidence regarding the impact of preconception and periconception interventions on LBW, SGA and PTB. Further research on a wider range of interventions is required to clearly ascertain their potential effectiveness.

Int J Epidemiol. 2022 Dec 13;51(6):1785-1799.

doi: 10.1093/ije/dyab248.

[Prevalence, risk factors and short-term consequences of adverse birth outcomes in Zimbabwean pregnant women: a secondary analysis of a cluster-randomized trial](#)

[Bernard Chasekwa<sup>1</sup>, Robert Ntozini<sup>1</sup>, James A Church<sup>2</sup>, Florence D Majo<sup>1</sup>, Naume Tavengwa<sup>1</sup>, Batsirai Mutasa<sup>1</sup>, Christie Noble<sup>2</sup>, Nadia Koyratty<sup>3</sup>, John A Maluccio<sup>4</sup>, Andrew J Prendergast<sup>1,2,5</sup>, Jean H Humphrey<sup>1,5</sup>, Laura E Smith<sup>1,3</sup>; Sanitation Hygiene Infant Nutrition Efficacy \(SHINE\) Trial Team](#)

**Abstract**

**Background:** Globally, 15 million children are born preterm each year and 10.7 million are born at term but with low birthweight (<2500 g).

**Methods:** The Sanitation Hygiene Infant Nutrition Efficacy (SHINE) cluster-randomized trial enrolled 5280 pregnant women between 22 November 2012 and 27 March 2015 to test the impact of improved water supply, sanitation and hygiene, and improved infant feeding, on child growth and anaemia. We conducted a secondary analysis to estimate the prevalence and risk factors of miscarriage, stillbirth, preterm birth, size small for gestational age (SGA), low birthweight (LBW), perinatal mortality, and neonatal mortality, and to estimate the effects of adverse birth outcomes on infant survival and growth.

**Results:** The prevalence of adverse birth outcomes was: miscarriage: 5.0% [95% confidence interval (CI), 4.4, 5.7]; stillbirth: 2.3% (95% CI 1.9, 2.7); preterm birth: 18.2% (95% CI 16.9, 19.5); SGA: 16.1% (95% CI 15.0, 17.3); LBW: 9.8% (95% CI 9.0, 10.7); and neonatal mortality:

31.4/1000 live births (95% CI 26.7, 36.5). Modifiable risk factors included maternal HIV infection, anaemia, lack of antenatal care and non-institutional delivery. Preterm infants had higher neonatal mortality [risk ratio (RR): 6.1 (95% CI 4.0, 9.2)], post-neonatal infant mortality [hazard ratio (HR): 2.1 (95% CI 1.1, 4.1)] and stunting at 18 months of age [RR: 1.5 (95% CI 1.4, 1.7)] than term infants; 56% of stillbirths and 57% of neonatal deaths were among preterm births.

**Conclusions:** Neonatal mortality and stillbirth are high in Zimbabwe and appear to be driven by high preterm birth. Interventions for primary prevention of preterm birth and strengthened management of preterm labour and ill and small neonates are required to reduce neonatal mortality in Zimbabwe and other African countries with similar profiles.

Malar J. 2023 Mar 17;22(1):101.

doi: 10.1186/s12936-023-04530-5.

**Effects of maternal antenatal treatment with two doses of azithromycin added to monthly sulfadoxine-pyrimethamine for the prevention of low birth weight in Burkina Faso: an open-label randomized controlled trial**

[Moussa Lingani](#)<sup>1,2</sup>, [Serge H Zango](#)<sup>3</sup>, [Innocent Valéa](#)<sup>3</sup>, [Sékou Samadoulougou](#)<sup>4</sup>, [Georges Somé](#)<sup>3</sup>, [Maïmouna Sanou](#)<sup>3</sup>, [Berenger Kaboré](#)<sup>3</sup>, [Toussaint Rouamba](#)<sup>3</sup>, [Herman Sorgho](#)<sup>3</sup>, [Marc C Tahita](#)<sup>3</sup>, [Karim Derra](#)<sup>3</sup>, [Michèle Dramaix](#)<sup>5</sup>, [Halidou Tinto](#)<sup>3</sup>, [Philippe Donnen](#)<sup>5</sup>, [Annie Robert](#)<sup>6</sup>

**Abstract**

**Background:** Exposure during pregnancy to malaria and sexually-transmitted infections is associated with adverse birth outcomes including low birth weight (LBW). This study aimed at assessing if the adjunction of two doses of azithromycin to sulfadoxine-pyrimethamine for the intermittent preventive treatment of malaria in pregnancy can reduce LBW.

**Methods:** A two parallel-groups, open-label randomized controlled trial involving pregnant women (16 to 35 years of age and 12 to 24 weeks of gestation as confirmed by last menstrual period or fundal height) was conducted in rural Burkina Faso. Women were assigned in a 1:1 ratio either to use azithromycin (1 g daily for 2 days) during the second and third trimesters of pregnancy plus monthly sulfadoxine-pyrimethamine (1500/75 mg) (SPAZ) (intervention) or to continue using a monthly sulfadoxine-pyrimethamine (1500/75 mg) (SP) (control). Primary outcome was a LBW (birth weight measured within 24 h after birth < 2500 g). Secondary outcomes including stillbirth, preterm birth or miscarriage are reported together with safety data.

**Results:** A total of 992 pregnant women underwent randomization (496 per group) and 898 (90.5%) valid birth weights were available (450 in SPAZ and 448 in SP). LBW incidence was 8.7% (39/450) in SPAZ and 9.4% (42/448) in controls (p-value = 0.79). Compared with controls, pregnant women with SPAZ showed a risk ratio (RR) of 1.16 (95% confidence interval (CI) 0.64-2.08] for preterm births, 0.75 (95% CI 0.17-3.35) for miscarriage and 0.64 (95% CI 0.25-1.64) for stillbirths. No treatment-related serious adverse events (SAEs) have been observed, and there was no significant difference in the number of SAEs (13.5% [67/496] in SPAZ, 16.7% [83/496] in SP, p-value = 0.18) or AEs (17.1% [85/496] in SPAZ, 18.8% [93/496] in SP, p-value = 0.56).

**Conclusion:** Adequate prevention regimen with monthly sulfadoxine-pyrimethamine given to all pregnant women has been proved to reduce the risk of LBW in malaria endemic areas.

Adding azithromycin to the regimen does not offer further benefits, as far as women receive a malaria prevention regimen early enough during pregnancy.

Int J Epidemiol. 2022 Dec 13;51(6):1803-1812.

doi: 10.1093/ije/dyac093.

**[A secondary data analysis of a cluster randomized controlled trial: improved cookstoves associated with reduction in incidence of low birthweight in rural Malawi](#)**

[Rebecca Best](#)<sup>1</sup>, [Jullita Malava](#)<sup>2</sup>, [Albert Dube](#)<sup>2</sup>, [Cynthia Katundu](#)<sup>2</sup>, [Fredrick Kalobekamo](#)<sup>2</sup>, [Kevin Mortimer](#)<sup>3</sup>, [Stephen B Gordon](#)<sup>4</sup>, [Moffat Nyirenda](#)<sup>1</sup>, [Amelia Crampin](#)<sup>1,2</sup>, [Estelle McLean](#)<sup>1,2</sup>

**Abstract**

**Background:** In northern rural Malawi, the majority of households cook using open fires and there is also a high burden of adverse birth outcomes. The use of open fires or highly polluting cookstoves is associated with low birthweight in babies. There is mixed evidence on whether implementation of cleaner burning cookstoves reduces the number of babies born with low birthweight.

**Methods:** This is a secondary analysis of a cluster randomized control trial in Malawi, conducted over 2014-17. Households were randomized to receive improved cookstoves or to continue current practices. For this analysis, the primary outcome was low birthweight in households under routine demographic surveillance, among births occurring within the trial time frame (N = 4010). A subset of data with stricter exposure definitions respecting the original randomized allocation was also analysed (N = 1050). A causal, forwards modelling approach was used.

**Results:** The main dataset showed evidence of effect of the intervention on low birthweight [adjusted odds ratio (aOR) 0.69; 95% CI 0.48-0.99, n = 2788]. The subset analysis lacked power to provide evidence of association between improved cookstoves and low birthweight in the stricter exposure definition (aOR 0.62; 95% CI 0.35-1.09, n = 932).

**Conclusions:** This study provides some evidence that an improved cookstove intervention in rural Malawi reduced the number of babies born with low birthweight by 30%. This direction of the effect was also seen in the subset analysis. The analysis suggests that the intervention reduced the number of infants born prematurely or with intra-uterine growth restriction, indicating that improved cookstoves could be a useful maternal health intervention.

Lancet Glob Health. 2022 Oct;10(10):e1523-e1533.

doi: 10.1016/S2214-109X(22)00340-0.

**[Antenatal dexamethasone for improving preterm newborn outcomes in low-resource countries: a cost-effectiveness analysis of the WHO ACTION-I trial](#)**

[WHO ACTION Trial Collaborators](#)

**Abstract**

**Background:** After considerable debate, there is now unequivocal evidence that use of antenatal corticosteroids improves outcomes in preterm neonates when used in women at risk of early preterm birth in reasonably equipped hospitals in low-resource countries. We aimed to evaluate the cost-effectiveness of dexamethasone administration in the

management of preterm birth in a cohort of pregnant women from five low-resource countries.

**Methods:** We performed a cost-effectiveness analysis using data from 2828 women (and 3051 babies) who participated in the WHO ACTION-I trial, a multicentre, randomised, placebo-controlled trial that assessed the safety and efficacy of dexamethasone in pregnant women at risk of early preterm birth in 29 hospitals across Bangladesh, India, Kenya, Nigeria, and Pakistan. We used a decision tree model to assess the cost-effectiveness of dexamethasone treatment compared with no intervention from a health-care sector perspective. Outcome data were taken from the primary results of the trial and primary data on cost were collected in 28 hospitals. The primary cost-effectiveness outcome was cost per neonatal death or the cost per disability-adjusted life-years (DALYs) averted, or costs saved per 1000 woman-baby units if the intervention was found to be cost-saving.

**Findings:** Administration of dexamethasone averted 38 neonatal deaths per 1000 woman-baby units and 1132 DALYs per 1000 woman-baby units. Compared with no intervention, use of antenatal corticosteroids was cost-saving in all five countries, ranging from a saving of US\$1778 per 1000 woman-baby units (95% uncertainty interval [UI] -13 878 to 9483) in Nigeria, to \$20 531 per 1000 woman-baby units (-46 387 to 4897) in Pakistan, to \$36 870 per 1000 woman-baby units (-61 569 to -15 672) in Bangladesh, to \$38 303 per 1000 woman-baby units (-64 183 to -10 753) in India, and to \$53 681 per 1000 woman-baby units (-113 822 to 2394) in Kenya. Findings remained consistent following sensitivity analyses. In all five countries, dexamethasone was more effective and cost less compared with no treatment.

**Interpretation:** Antenatal dexamethasone for early preterm birth was cost-saving when used in hospitals in low-resource countries. Decision makers in low-resource settings can be confident that use of antenatal dexamethasone for early preterm birth is cost-effective, and often cost-saving when used in reasonably equipped hospitals in low-resource countries.

Int J Environ Res Public Health. 2022 Sep 23;19(19):12072.

doi: 10.3390/ijerph191912072.

### [\*\*Incidence and Risk Factors for Low Birthweight and Preterm Birth in Post-Conflict Northern Uganda: A Community-Based Cohort Study\*\*](#)

[Beatrice Odongkara<sup>1,2,3</sup>](#), [Victoria Nankabirwa<sup>4</sup>](#), [Grace Ndeezi<sup>3</sup>](#), [Vincentina Achora<sup>5</sup>](#), [Anna Agnes Arach<sup>6</sup>](#), [Agnes Napyo<sup>7</sup>](#), [Milton Musaba<sup>7</sup>](#), [David Mukunya<sup>7</sup>](#), [James K Tumwine<sup>3</sup>](#), [Tylleskar Thorkild<sup>2</sup>](#)

#### **Abstract**

**Background:** Annually, an estimated 20 million (13%) low-birthweight (LBW) and 15 million (11.1%) preterm infants are born worldwide. A paucity of data and reliance on hospital-based studies from low-income countries make it difficult to quantify the true burden of LBW and PB, the leading cause of neonatal and under-five mortality. We aimed to determine the incidence and risk factors for LBW and preterm birth in Lira district of Northern Uganda.

**Methods:** This was a community-based cohort study, nested within a cluster-randomized trial, designed to study the effect of a combined intervention on facility-based births. In total, 1877 pregnant women were recruited into the trial and followed from 28 weeks of gestation until birth. Infants of 1556 of these women had their birthweight recorded and 1279 infants were assessed for preterm birth using a maturity rating, the New Ballard Scoring system. Low

birthweight was defined as birthweight  $\leq$  2.5kg and preterm birth was defined as birth before 37 completed weeks of gestation. The risk factors for low birthweight and preterm birth were analysed using a multivariable generalized estimation equation for the Poisson family.

**Results:** The incidence of LBW was 121/1556 or 7.3% (95% Confidence interval (CI): 5.4-9.6%). The incidence of preterm births was 53/1279 or 5.0% (95% CI: 3.2-7.7%). Risk factors for LBW were maternal age  $\geq$ 35 years (adjusted Risk Ratio or aRR: 1.9, 95% CI: 1.1-3.4), history of a small newborn (aRR: 2.1, 95% CI: 1.2-3.7), and maternal malaria in pregnancy (aRR: 1.7, 95% CI: 1.01-2.9). Intermittent preventive treatment (IPT) for malaria, on the other hand, was associated with a reduced risk of LBW (aRR: 0.6, 95% CI: 0.4-0.8). Risk factors for preterm birth were maternal HIV infection (aRR: 2.8, 95% CI: 1.1-7.3), while maternal education for  $\geq$ 7 years was associated with a reduced risk of preterm birth (aRR: 0.2, 95% CI: 0.1-0.98) in post-conflict northern Uganda.

**Conclusions:** About 7.3% LBW and 5.0% PB infants were born in the community of post-conflict northern Uganda. Maternal malaria in pregnancy, history of small newborn and age  $\geq$ 35 years increased the likelihood of LBW while IPT reduced it. Maternal HIV infection was associated with an increased risk of PB compared to HIV negative status. Maternal formal education of  $\geq$ 7 years was associated with a reduced risk of PB compared to those with 0-6 years. Interventions to prevent LBW and PBs should include girl child education, and promote antenatal screening, prevention and treatment of malaria and HIV infections.

## Management of the preterm infant

J Matern Fetal Neonatal Med. 2022 Oct;35(19):3633-3639.

doi: 10.1080/14767058.2020.1836148. Epub 2020 Oct 22.

### [Delayed cord clamping for prevention of intraventricular hemorrhage in preterm neonates: a randomized control trial](#)

[Fariba Hemmati](#)<sup>1</sup>, [Deepak Sharma](#)<sup>2</sup>, [Bahia Namavar Jahromi](#)<sup>3</sup>, [Leila Salarian](#)<sup>4</sup>, [Nazanin Farahbakhsh](#)<sup>5</sup>

#### **Abstract**

**Background:** Intraventricular hemorrhage (IVH) is a common condition in preterm neonates and is responsible for substantial adverse neurodevelopmental outcome in preterm neonates. Prevention of IVH is an important intervention for better neurological outcome in these preterm neonates.

**Aims and objective:** This study aimed to determine whether delayed cord clamping (DCC) was superior to immediate cord clamping (ICC) for the prevention of IVH in preterm neonates.

**Patients and methods:** In this two centered prospective double-blind randomized controlled trial, eligible neonates with gestational age from 26 to 34 weeks were randomized to receive either ICC (cord clamped in 10-15 s) or DCC (cord clamped in 30-45 s) groups. The grading and severity of IVH were evaluated by cranial ultrasound scan done on the 3-4th and 7-10th days after birth.

**Results:** Among the 148 enrolled neonates, 79 were in the ICC group and 69 were in the DCC group. There was no difference in maternal and neonatal baseline characteristics except the neonates in the DCC group weighed more (ICC 1528.77 ± 365.5 g vs. DCC 1658.11 ± 419.52 g;  $p = .047$ ) at birth. There was no significant difference in the incidence of any grade of IVH in both groups (ICC 12.8% vs. DCC 14.5%;  $p = .745$ ). There was a significantly higher incidence of grade I IVH (ICC 2.5% vs. DCC 13%;  $p = .024$ ) in the DCC group. The incidence of grade II IVH (ICC 5.1% vs. DCC 0%;  $p = .123$ ); grade III IVH (ICC 3.8% vs. DCC 1.4%;  $p = .623$ ); and grade IV IVH (ICC 1.3% vs. DCC 0%;  $p > .999$ ) were comparable between the two groups. The incidence of a significant IVH (grades II, III, and IV) was significantly less in the DCC group (ICC 10.1% vs. DCC 1.4%,  $p = .036$ ). The mean initial hemoglobin levels were significantly higher in neonates enrolled in DCC (15.41 ± 2.1 vs. 16.46 ± 2.45 g/dL;  $p = .007$ ). There was a significant reduction in the number of days of hospital stay (ICC 18.78 ± 15.42 vs. DCC 13.21 ± 16.16;  $p = .002$ ). There was no difference in initial hematocrit, platelet count, maximum bilirubin level, and Apgar score ( $p > .05$ ).

**Conclusions:** Although there was no reduction in any grade of IVH, the incidence of significant IVH (grades II, III, and IV) was significantly decreased with the use of DCC in preterm neonates. Delayed cord clamping also resulted in a significant increase in birth weight, higher hemoglobin levels, and shorter hospital stays without any increase in the risks of hyper-bilirubinemia, low Apgar score, and neonatal mortality.

Indian Pediatr. 2022 Nov 15;59(11):847-851.

Epub 2022 Aug 26.

**[Simulation Based vs Conventional Training for Initial Steps in Delivery Room Care of Preterm Neonates: An Open Label Randomized Trial](#)**

[Dilip Neupane](#)<sup>1</sup>, [Akash Sharma](#)<sup>1</sup>, [Anu Thukral](#)<sup>2</sup>, [M Jeeva Sankar](#)<sup>1</sup>, [Ramesh Agarwal](#)<sup>1</sup>, [Ashok K Deorari](#)<sup>1</sup>

**Abstract**

**Objective:** To assess whether simulation based education (SBE) improves the practices and knowledge of junior residents for stabilization of a preterm neonate in delivery room as compared to conventional education (CE).

**Methods:** This trial randomized 24 pediatric residents to either SBE (n=12) or CE (n=12) groups. One-time SBE was imparted to the SBE group. Both the groups had similar facilitator participant ratio and equally timed sessions. The individual skills scores and performance by preterm stabilization performance evaluation (PSPE) score in real time were recorded using a validated tool within 8 weeks of the training. Knowledge gain was evaluated using pre and post-test scores.

**Results:** The mean (SD) skill and PSPE scores were comparable between the two groups (skill score 51.1 (8.1), 46.5 (7.8), respectively mean difference 4.6; 95% CI -2.1 to 11.3; PSPE-score 80.2 (14.2) vs. 82.9 (10.3); mean difference -2.68; 95% CI -8.35 to 13.71). The mean (SD) knowledge gain was similar in the groups [4.4 (1.9), 5.3 (4.1); mean difference 0.91; 95% CI, -1.81 to 3.64.

**Conclusion:** In junior residents, a one-time SBE session, when compared to conventional task training, did not lead to improvement in the performance of the initial steps of neonatal resuscitation.



J Matern Fetal Neonatal Med. 2022 Aug;35(15):2992-2994.

doi: 10.1080/14767058.2020.1814244. Epub 2020 Sep 22.

[\*\*The role of a neonatal hypothermia alert device in promoting weight gain in LBW infants\*\*](#)

[Mohammad Azad<sup>1</sup>](#), [Surender Singh Bisht<sup>1</sup>](#), [Amity Tyagi<sup>1</sup>](#), [M L Jaipal<sup>1</sup>](#)

**Abstract**

**Background:** Neonatal hypothermia is a significant risk factor for preterm and low birth weight (LBW) newborns, especially in India. Kangaroo Mother Care (KMC) is one recommended method of thermal control. A wearable device, TempWatch, has been developed to monitor for and detect hypothermia and to promote KMC for preterm and LBW infants.

**Purpose:** This randomized controlled trial was designed to evaluate TempWatch's impact on weight gain, amount of KMC received, and length of hospital stay for LBW infants as compared to standard care.

**Methods:** Otherwise healthy LBW infants (with birthweights 1500-2300 g) admitted to a KMC ward of a government hospital in New Delhi, India were randomly allocated to a TempWatch group or a control group and wore the device until their time of discharge. 50 infants were enrolled in each group. All participants received standard-of-care temperature monitoring, and those in the control group were monitored using the hand-touch method. Each group also received sixth-hourly temperature monitoring. Infants' daily weight and the number of hypothermia episodes they experienced per day were recorded, and mothers of infants in both groups completed daily KMC diaries.

**Results:** The TempWatch group experienced statistically significant weight gain as compared to the control group (0.06 vs. 0.02 kg,  $p = .024$ ). There were no statistically significant differences between the groups in the number of hypothermia events detected, the amount of KMC received.

**Conclusion:** TempWatch promotes statistically significant weight gain for LBW infants as compared to standard care.

Breastfeed Med. 2022 Aug;17(8):647-652.

doi: 10.1089/bfm.2021.0371. Epub 2022 May 25.

[\*\*Effect of Maternal Diet on Any Necrotizing Enterocolitis in Neonates: A Randomized Double-Blind Study\*\*](#)

[Nasrin Khalesi<sup>1</sup>](#), [Narges Mazloomi Nobandegani<sup>1</sup>](#), [Nastaran Khosravi<sup>1</sup>](#), [Maryam Saboute<sup>2</sup>](#), [Seyyede Faride Farahi<sup>1</sup>](#), [Zinat Shakeri<sup>1</sup>](#), [Leila Allahqoli<sup>3</sup>](#), [Ibrahim Alkatout<sup>4</sup>](#)

**Abstract**

**Background:** The etiology of necrotizing enterocolitis (NEC) is controversially discussed. One of the most recently proposed causes of NEC is an allergy to cow's milk protein. This study was designed to evaluate the effect of a maternal diet without bovine protein on the incidence of any NEC in very low birth weight (VLBW) infants. **Materials and Methods:** A pilot randomized controlled clinical trial was performed at Akbarabadi Hospital, Tehran, Iran, from December 2019 to July 2020, in women with VLBW infants. One hundred twenty mothers with VLBW neonates were randomly assigned to the intervention or the control group (60 in each). In the intervention group, mothers were given a dairy-free diet during the first 14 days after the newborn's onset of feeding. No special diet was given to the control group. The primary outcome of the study was the rate of any NEC in neonates, which was

compared between groups. Any NEC was defined as Bell stage I or greater. **Results:** The minimum and maximum gestational ages were 26 and 33 weeks, respectively. The minimum birth weight of neonates was 700 g. The two groups did not differ significantly in terms of demographic and preinterventional clinical characteristics. Any NEC was reported in 0% and 10% (5/52) of neonates in the intervention and control groups, respectively; the difference was statistically significant ( $p = 0.028$ ). The NEC symptoms began ~34 days after birth. Four cases of NEC were classified as Bell stage I, and one was classified as Bell stage II. No statistical association was registered between sex, gestational age, birth weight, and the onset of feeding with the incidence of any NEC. **Conclusion:** The use of a cow's milk protein-free diet in mothers and exclusive breastfeeding in preterm VLBW infants may reduce the incidence of NEC. We recommend further studies with larger sample sizes in a multicenter setting.

\*\*\* Nutr Rev. 2023 Jan 30;nuad002.

doi: 10.1093/nutrit/nuad002. Online ahead of print.

**[Oropharyngeal application of colostrum or mother's own milk in preterm infants: a systematic review and meta-analysis](#)**

[Jogender Kumar<sup>1</sup>](#), [Jitendra Meena<sup>1</sup>](#), [Ankit Ranjan<sup>1</sup>](#), [Praveen Kumar<sup>1</sup>](#)

**Abstract**

**Context:** Many preterm neonates often cannot be fed enterally and hence do not receive the benefits of colostrum. Oropharyngeal application of colostrum is a novel way of harnessing the immunological benefits of colostrum. Randomized controlled trials (RCTs) investigating the efficacy of this approach have shown variable results.

**Objective:** The aim of this systematic review was to synthesize available data on the effect of oropharyngeal application of colostrum or mother's own milk (CMOM) in preterm infants.

**Data sources:** Six electronic databases (MEDLINE, Embase, CINAHL, Scopus, Web of Science, and Cochrane Library) were searched until January 13, 2022. Only RCTs comparing oral application of CMOM with placebo/routine care in preterm infants were eligible. Studies enrolling term neonates or administering enteral feeds were excluded.

**Data extraction:** Two investigators independently extracted data using a structured proforma.

**Data analysis:** The Cochrane Risk of Bias 2 tool was used to assess bias. Random-effects meta-analysis was undertaken using RevMan 5.4 software. From 2787 records identified, 17 RCTs enrolling 4106 preterm infants were included. There was no significant difference between groups in incidence of necrotizing enterocolitis (NEC) stage 2 or higher (RR = 0.65; 95%CI, 0.36-1.20; 1089 participants in 12 trials). Application of CMOM significantly reduced the incidence of sepsis (RR = 0.72; 95%CI, 0.56-0.92; 1511 participants in 15 studies) and any stage of NEC (RR = 0.58; 95%CI, 0.37-0.92; 1616 participants in 16 trials). The CMOM group achieved full enteral feeds 1.75 days sooner (95%CI, 0.3-3.2 days; 1580 participants in 14 studies) and had higher weight at discharge (MD = 43.9 g; 95%CI, 3-85 g; 569 participants in 3 studies). There were no statistically significant differences in other outcomes.

**Conclusions:** Evidence with low to very low certainty suggests CMOM has a beneficial effect on NEC (any stage), sepsis, and time to full enteral feeds. Given its low cost and minimal risk of harm, routine CMOM use may be considered in preterm neonates.

Eur J Pediatr. 2022 Nov 30;1-10.

doi: 10.1007/s00431-022-04711-5. Online ahead of print.

[\*\*Supplementation of mother's own milk with term versus preterm donor human milk: a randomized controlled trial\*\*](#)

[Vimlesh Soni<sup>1</sup>](#), [Suksham Jain<sup>2</sup>](#), [Deepak Chawla<sup>1</sup>](#), [Supreet Khurana<sup>1</sup>](#), [Shikha Rani<sup>3</sup>](#)

**Abstract**

The purpose of this is to evaluate the effect of supplementation of enteral feed volume with preterm versus term donor human milk (DHM) on short-term physical growth in very low birth weight (VLBW) neonates. In this open-label, variable block-sized, superiority, randomized controlled trial with allocation concealment, VLBW neonates with insufficient volume of mother's own milk (MOM) were assigned to receive either preterm (n = 48) or term (n = 54) DHM till discharge. Preterm DHM was defined as the breast milk expressed within 28 days of delivery at  $\leq 34$  weeks of gestation. The primary outcome was days to regain birth weight. Maternal and neonatal demographic variables were comparable in the two study groups. Days to regain birth weight were significantly more in the preterm DHM group, 17.4 (7.7) vs 13.6 (7.2) days, mean difference (95% CI) being 3.74 (0.48-7.0) days,  $P = 0.02$ ). The proportion of MOM use was 82% in preterm vs 91.1%,  $P = 0.03$  in the term milk group. Duration of skin-to-skin contact was also significantly lower in the preterm vs term milk group, the median (IQR) was 4 (0, 6) vs 4 (2, 6) hours/day,  $P < 0.01$ . However, bronchopulmonary dysplasia was higher in the preterm milk group (13% vs. 4%,  $P = 0.17$ ). The velocity of gain in weight was similar in the two groups from week 1-3 but higher in the term DHM supplementation group during the 4th week. Conclusion: Supplementing MOM with preterm DHM did not result in a faster regaining of birth weight.

Breastfeed Med. 2023 Feb 8.

doi: 10.1089/bfm.2022.0197. Online ahead of print.

[\*\*Nifty Cup Versus Katori-Spoon Feeding in Preterm Infants: A Randomized Controlled Trial\*\*](#)

[Neetu Gujjar<sup>1</sup>](#), [Geetanjali Kalyan<sup>1</sup>](#), [Jogender Kumar<sup>2</sup>](#), [Praveen Kumar<sup>2</sup>](#), [Shivalli Sirswal<sup>1</sup>](#)

**Abstract**

**Background:** Many preterm infants cannot breastfeed directly and depend on other feeding methods. Multiple studies have compared feeding methods for such infants; however, the best method remains unknown. We compared Nifty cup with Katori-spoon feeding in preterm neonates deemed fit for oral feeding. **Methods:** This open-label randomized controlled trial was performed in a level III neonatal unit. Preterm (<34 weeks) neonates deemed fit to initiate oral feeding were randomly allocated to the Nifty cup and Katori-spoon groups. Patients were followed up until 40 ( $\pm 2$ ) weeks of postmenstrual age or until death, whichever occurred earlier. The primary outcome was time to achieve full oral feeding. The secondary outcomes included the time spent per feeding session, time to full direct breastfeeding, anthropometry at discharge, duration of hospitalization, and mortality. The opinions of mothers and nurses were recorded using a structured questionnaire. **Results:** A total of 106 participants (53 in each group) were randomized and analyzed for the primary outcome. The median (1st, 3rd quartile) time to achieve complete oral feeds was 5 (2, 11) versus 6 (4, 11) days in the Nifty cup versus Katori-spoon groups, respectively ( $p = 0.2$ ).

Infants in the Nifty cup group reached full breastfeeds earlier (mean difference = 12.6 days; 95% confidence interval: 4.3 to 20.8,  $p = 0.003$ ) and had less vomiting (9.4% versus 26.4%,  $p = 0.023$ ). Mothers and nurses felt that breast milk expression and feeding with a Nifty cup was easier. **Conclusions:** Compared to the Katori-spoon, feeding with a Nifty cup did not shorten the time to full oral feeds. However, it helps in attaining full breastfeeds earlier than the Katori-spoon.

Am J Perinatol. 2023 May 19.

doi: 10.1055/a-2074-1960. Online ahead of print.

**[Comparison of Three Modalities of Feeding in Preterm Infants  \$\leq 32\$  Weeks and  \$\leq 1,250\$  G: A Randomized Controlled Trial](#)**

[Vijay Kumar](#)<sup>1</sup>, [Anup Thakur](#)<sup>2</sup>, [Pankaj Garg](#)<sup>2</sup>, [Neelam Kler](#)<sup>2</sup>

**Abstract**

**Objective:** Early establishment of enteral feeds is desirable in very preterm infants, but it may be associated with feeding intolerance. Several feeding methods have been studied with no strong evidence to suggest the preferred feeding method to establish early full enteral feeds. We studied three modalities of feeding in preterm infants  $\leq 32$  weeks and  $\leq 1,250$  g: continuous infusion (CI), intermittent bolus by infusion (IBI), and intermittent bolus by gravity (IBG) for their effect on time to reach full enteral feeds of 180 mL/kg/d.

**Study design:** We randomized 146 infants, 49 infants in each CI and IBI group and 48 infants in the IBG group. In the CI group, feeds were delivered by an infusion pump continuously over 24 hours. In the IBI group, feeds were given every 2 hours and infused over 15 minutes by an infusion pump. In the IBG group, feeds were delivered by gravity over 10 to 30 minutes. The intervention was continued till infants reached direct breast/cup feeds.

**Results:** The mean (standard deviation) gestation in CI, IBI, and IBG groups were 28.4 (2.2), 28.5(1.9), and 28.6 (1.8) weeks, respectively. The time to reach full feeds in CI, IBI, and IBG were not significantly different (median [interquartile range]: 13 [10-16], 11.5 [9-17], and 13 [9.5-14.2] d, respectively,  $p = 0.71$ ). The proportions of infants who developed feeding intolerance in CI, IBI, and IBG were similar ( $n$  [%]: 21 [51.2%], 20 [52.6%], and 22 [64.7%], respectively,  $p = 0.45$ ). There was no difference in necrotizing enterocolitis  $\geq 2$  ( $p = 0.80$ ), bronchopulmonary dysplasia ( $p = 0.86$ ), intraventricular hemorrhage  $\geq 2$  ( $p = 0.35$ ), patent ductus arteriosus requiring treatment ( $p = 0.44$ ), retinopathy of prematurity requiring treatment ( $p = 0.51$ ), and growth parameters at discharge.

**Conclusion:** In preterm infants,  $\leq 32$  weeks of gestation and birth weight  $\leq 1,250$  g, there was no difference in time to reach full enteral feeds in the three modalities of feeding

Pediatrics. 2022 Aug 1;150(Suppl 1):e2022057092K.

doi: 10.1542/peds.2022-057092K.

**[Enteral Vitamin D Supplementation in Preterm or Low Birth Weight Infants: A Systematic Review and Meta-analysis](#)**

[Mohan Kumar](#)<sup>1</sup>, [Saijuddin Shaikh](#)<sup>1</sup>, [Bireswar Sinha](#)<sup>1,2</sup>, [Ravi Prakash Upadhyay](#)<sup>1,2</sup>, [Tarun Shankar Choudhary](#)<sup>1,3</sup>, [Temsunaro Rongsen Chandola](#)<sup>1</sup>, [Sarmila Mazumder](#)<sup>1</sup>, [Sunita Taneja](#)<sup>1</sup>, [Nita Bhandari](#)<sup>1</sup>, [Ranadip Chowdhury](#)<sup>1,2</sup>

**Abstract**

**Background and objectives:** Many preterm and low birth weight (LBW) infants have low vitamin D stores. The objective of this study was to assess effects of enteral vitamin D supplementation compared with no vitamin D supplementation in human milk fed preterm or LBW infants.

**Methods:** Data sources include Cochrane Central Register of Controlled Trials, Medline, and Embase from inception to March 16, 2021. The study selection included randomized trials. Data were extracted and pooled with fixed and random-effects models.

**Results:** We found 3 trials (2479 participants) that compared vitamin D to no vitamin D. At 6 months, there was increase in weight-for-age z-scores (mean difference 0.12, 95% confidence interval [CI] 0.01 to 0.22, 1 trial, 1273 participants), height-for-age z-scores (mean difference 0.12, 95% CI 0.02 to 0.21, 1 trial, 1258 participants); at 3 months there was decrease in vitamin D deficiency (risk ratio 0.58, 95% CI 0.49 to 0.68, I<sup>2</sup>=58%, 2 trials, 504 participants) in vitamin D supplementation groups. However, there was little or no effect on mortality, any serious morbidity, hospitalization, head circumference, growth to 6 years and neurodevelopment. The certainty of evidence ranged from very low to moderate. Fourteen trials (1969 participants) assessed dose and reported no effect on mortality, morbidity, growth, or neurodevelopment, except on parathyroid hormone and vitamin D status. No studies assessed timing. Limitations include heterogeneity and small sample size in included studies.

**Conclusions:** Enteral vitamin D supplementation improves growth and vitamin D status in preterm and LBW infants.

Eur J Nutr. 2022 Oct;61(7):3637-3648.

doi: 10.1007/s00394-022-02905-z. Epub 2022 May 31.

**[Maternal and infant probiotic administration for morbidity of very low birth weight infants: a three-arm randomized placebo-controlled trial](#)**

[Mahtab Matin](#)<sup>1</sup>, [Aziz Homayouni-Rad](#)<sup>2</sup>, [Manizheh Mostafa-Gharehbaghi](#)<sup>3</sup>, [Mojgan Mirghafourvand](#)<sup>4</sup>, [Sakineh Mohammad-Alizadeh-Charandabi](#)<sup>5</sup>

**Abstract**

**Purpose:** To determine whether oral probiotic administration ( $1.5 \times 10^9$  CFU/g Lacticaseibacillus paracasei subsp. paracasei) to breastfeeding mothers or to their very low birth weight (VLBW) infants reduces total serum bilirubin (TSB) level and increases weight gain of the infants.

**Methods:** In this double-blind trial, breastfeeding mothers and their VLBW infants at 48-72 h of age were allocated into three groups using stratified block randomization; administering probiotic to the mothers and placebo to their infants, probiotic to the infants and placebo to their mothers, or placebo to the both. The intervention continued for 28 days.

**Results:** All 25 mothers and their 26 infants allocated into each group were fully followed up. There were three positive blood culture only in the placebo group. On the 3rd day of intervention, TSB level was not significantly different among the groups but on the 7th day, it was significantly lower in the both probiotic groups compared with the placebo group (mean difference -2.4 mg/dL [95% confidence interval -3.6 to -1.2] in the both comparisons). Mean rank of infant weight gain during the first 7 days of intervention was significantly higher in the both maternal and infant probiotic groups compared with the placebo group ( $p = 0.007$  and  $p = 0.003$ , respectively), but there was no statistically significant difference among the groups during the 8th-28th days.

**Conclusion:** Administration of Lacticaseibacillus paracasei to breastfeeding mothers of VLBW infants or to their infants reduces infant TSB level but has no significant effect on weight gain after the first week of the intervention.

Pediatrics. 2022 Aug 1;150(Suppl 1):e2022057092N.

doi: 10.1542/peds.2022-057092N.

**Enteral Multiple Micronutrient Supplementation in Preterm and Low Birth Weight Infants: A Systematic Review and Meta-analysis**

[Mohan Kumar<sup>1</sup>](#), [Ranadip Chowdhury<sup>1,2</sup>](#), [Bireswar Sinha<sup>1,2</sup>](#), [Ravi Prakash Upadhyay<sup>1,2</sup>](#), [Temsunaro Rongsen Chandola<sup>1</sup>](#), [Sarmila Mazumder<sup>1</sup>](#), [Sunita Taneja<sup>1</sup>](#), [Karen Edmond<sup>3</sup>](#), [Rajiv Bahl<sup>3</sup>](#), [Nita Bhandari<sup>1</sup>](#), [Usha Ramakrishnan<sup>4,5</sup>](#), [Juan A Rivera<sup>6</sup>](#), [Sonia Tandon<sup>5</sup>](#), [Christopher P Duggan<sup>7,8</sup>](#), [Enju Liu<sup>7,9</sup>](#), [Wafae Fawzi<sup>8,10</sup>](#), [Karim Manji<sup>11</sup>](#), [Tarun Shankar Choudhary<sup>1,12</sup>](#)

**Abstract**

**Objectives:** To assess effects of supplementation with 3 or more micronutrients (multiple micronutrients; MMN) compared to no MMN in human milk-fed preterm and low birth weight (LBW) infants.

**Results:** Data on a subgroup of 414 preterm or LBW infants from 2 randomized controlled trials (4 reports) were included. The certainty of evidence ranged from low to very low. For growth outcomes in the MMN compared to the non-MMN group, there was a small increase in weight-for-age (2 trials, 383 participants) and height-for-age z-scores (2 trials, 372 participants); a small decrease in wasting (2 trials, 398 participants); small increases in stunting (2 trials, 399 participants); and an increase in underweight (2 trials, 396 participants). For neurodevelopment outcomes at 78 weeks, we found small increases in Bayley Scales of Infant Development, Version III (BISD-III), scores (cognition, receptive language, expressive language, fine motor, gross motor) in the MMN compared to the non-MMN group (1 trial, 27 participants). There were no studies examining dose or timing of supplementation.

**Conclusions:** Evidence is insufficient to determine whether enteral MMN supplementation to preterm or LBW infants who are fed mother's own milk is associated with benefit or harm. More trials are needed to generate evidence on mortality, morbidity, growth, and neurodevelopment.

Pediatrics. 2022 Aug 1;150(Suppl 1):e2022057092M.

doi: 10.1542/peds.2022-057092M.

**Enteral Calcium or Phosphorus Supplementation in Preterm or Low Birth Weight Infants: a Systematic Review and Meta-analysis**

[Mohan Kumar<sup>1</sup>](#), [Ranadip Chowdhury<sup>1,2</sup>](#), [Bireswar Sinha<sup>1,2</sup>](#), [Ravi Prakash Upadhyay<sup>1,2</sup>](#), [Temsunaro Rongsen Chandola<sup>1</sup>](#), [Sarmila Mazumder<sup>1</sup>](#), [Sunita Taneja<sup>1</sup>](#), [Nita Bhandari<sup>1</sup>](#), [Tarun Shankar Choudhary<sup>1,3</sup>](#)

**Abstract**

**Objectives:** To assess effects of calcium or phosphorous supplementation compared with no supplementation in human milk-fed preterm or low birth weight infants.



**Methods:** Data sources include Cochrane Central Register of Controlled Trials, Medline and Embase. We included Randomized controlled trials (RCTs) and non-randomized trials (quasi-randomized).

**Results:** Three studies (4 reports; 162 infants) were included. At latest follow-up (38 weeks), there was reduction in osteopenia (3 studies, 159 participants, relative risk 0.68, 95% confidence interval [CI] 0.46-0.99). At latest follow-up (6 weeks), there was no effect on weight (1 study, 40 participants, mean difference [MD] 138.50 g, 95% CI -82.16 to 359.16); length (1 study, 40 participants, MD 0.77 cm, 95% CI -0.93 to 2.47); and head circumference (1 study, 40 participants, MD 0.33 cm, 95% CI -0.30 to 0.96). At latest follow-up, there was no effect on alkaline phosphatase (55 weeks) (2 studies, 122 participants, MD -126.11 IU/L, 95% CI -298.5 to 46.27, I<sup>2</sup> = 73.4%); serum calcium (6 weeks) (1 study, 40 participants, MD 0.54 mg/dL, 95% CI -0.19 to 1.27); and serum phosphorus (6 weeks) (1 study, 40 participants, MD 0.07 mg/dL, 95% CI -0.22 to 0.36). The certainty of evidence ranged from very low to low. No studies reported on mortality and neurodevelopment outcomes.

**Conclusions:** The evidence is insufficient to determine whether enteral supplementation with calcium or phosphorus for preterm or low birth weight infants who are fed mother's own milk or donor human milk is associated with benefit or harm.

Pediatrics. 2022 Aug 1;150(Suppl 1):e2022057092L.

doi: 10.1542/peds.2022-057092L.

**[Enteral Low-Dose Vitamin A Supplementation in Preterm or Low Birth Weight Infants to Prevent Morbidity and Mortality: a Systematic Review and Meta-analysis](#)**

[Rukman M Manapurath](#)<sup>#1</sup>, [Mohan Kumar](#)<sup>#1</sup>, [Barsha Gadapani Pathak](#)<sup>1</sup>, [Ranadip Chowdhury](#)<sup>1,2</sup>, [Bireshwar Sinha](#)<sup>1,2</sup>, [Tarun Choudhary](#)<sup>1</sup>, [Naro Chandola](#)<sup>1</sup>, [Sarmila Mazumdar](#)<sup>1</sup>, [Sunita Taneja](#)<sup>1</sup>, [Nita Bhandari](#)<sup>1</sup>, [Ravi Prakash Upadhyay](#)<sup>1,2</sup>

**Abstract**

**Objectives:** To assess effects of enteral "low" dose (daily doses of ≤10 000 international unit) vitamin A supplementation compared with no vitamin A supplementation in human milk-fed preterm and low birth weight (LBW) infants.

**Data sources:** Cochrane Central Register of Controlled Trials; Medline, Embase, Scopus, Web of Science, CINAHL from inception to 16 March 2021.

**Study selection:** Randomized trials were screened. Primary outcomes were mortality, morbidity, growth, neurodevelopment. Secondary outcomes were feed intolerance and duration of hospitalization. We also assessed the dose and timing of vitamin A supplementation. Data were extracted and pooled with fixed and random-effects models.

**Results:** Four trials including 800 very LBW <1.5 kg or <32 weeks' gestation infants were found. At latest follow-up, we found little or no effect on: mortality, sepsis, bronchopulmonary dysplasia, retinopathy of prematurity, duration of hospitalisation. However, we found an increased level of serum retinol mean difference of 4.7 µg/ml (95% CI 1.2 to 8.2, I<sup>2</sup> = 0.00%, one trial, 36 participants.). Evidence ranged from very low to moderate certainty. There were no outcomes reported for length, head circumference or neurodevelopment.

**Limitations:** Heterogeneity and small sample size in the included studies.

**Conclusions:** Low-dose vitamin A increased serum retinol concentration among very LBW and very preterm infants but had no effect on other outcomes. More trials are needed to

assess effects on clinical outcomes and to assess effects in infants 1.5 to 2.4 kg or 32 to 26 weeks' gestation.

Front Nutr. 2022 Jul 12;9:884207.

doi: 10.3389/fnut.2022.884207. eCollection 2022.

### [Anthropometric Indicators as Predictors of Mortality in Early Life Among Low Birthweight Indian Infants](#)

[Tarun Shankar Choudhary<sup>1,2</sup>](#), [Mohan Kumar<sup>1</sup>](#), [Bireshwar Sinha<sup>3,4</sup>](#), [Saijuddin Shaikh<sup>3</sup>](#), [Sarmila Mazumder<sup>3</sup>](#), [Sunita Taneja<sup>3</sup>](#), [Nita Bhandari<sup>1</sup>](#)

#### **Abstract**

**Background:** Low birthweight (LBW) babies (<2.5 kg) are at higher risk of mortality and weight for height z score is currently recommended for identifying infants at risk of mortality.

**Objective:** To compare different anthropometric measures at 28-day of age in a cohort of LBW Indian infants for predicting mortality between 28-day and 180-day of age.

**Methods:** We used data from an individually randomized controlled trial of LBW infants weighing between 1,500 and 2,250 g. Sensitivity, specificity, positive, and negative likelihood ratios, positive and negative predictive values, and area under receiver operating characteristics curves (AUC) were used to estimate the discrimination of mortality risk. The Cox regression was used to estimate hazard ratios and population attributable fraction for each anthropometric indicator. These estimates were calculated for individual as well as combinations of anthropometric indicators at the cut-off of -2 and -3 SD of the WHO 2006 growth standards.

**Results:** Severe underweight (weight-for-age z-scores [WAZ] < -3) had a sensitivity of 75.0%, specificity of 68.0% with an AUC of 0.72. The risk of death was higher (HR 6.18; 95% CI 4.29-8.90) with a population attributable fraction of 0.63 (95% CI 0.52-0.72) for infants severely underweight at 28-day of age. Combination of different anthropometric measures did not perform better than individual measures.

**Conclusion:** Severe underweight (WAZ < -3) better discriminated deaths among LBW infants < 6 months of age. It can be considered for diagnosis of nutritionally at-risk infants in this age group.

Adv Neonatal Care. 2022 Dec 1;22(6):E196-E206.

doi: 10.1097/ANC.0000000000001036. Epub 2022 Oct 17.

### [Effect of the Premature Infant Oral Motor Intervention on Sucking Capacity in Preterm Infants in Turkey: A Randomized Controlled Trial](#)

[Selver Guler<sup>1</sup>](#), [Zerrin Cigdem](#), [Brenda S Lessen Knoll](#), [Tulay Ortabag](#), [Yavuz Yakut](#)

#### **Abstract**

**Background:** Preterm infants have oral feeding difficulty that often delays discharge, indicating a need for evidence-based interventions for oral-motor development.

**Purpose:** To test the Premature Infant Oral Motor Intervention (PIOMI) on the development of oral-motor function, feeding, and anthropometric outcomes using sucking manometry.

**Methods:** A single-blind randomized experimental design was conducted with a sample of 60 preterm infants from 2 neonatal intensive care units between May 2019 and March 2020. The experimental group received PIOMI for 5 min/d for 14 consecutive days. Sucking capacity,

anthropometrics (weight and head circumference), bottle feeding, breast/chest feeding initiation, and length of hospital stay were measured. The Yakut Sucking Manometer (PCT/TR2019/050678) was developed specifically for this study and tested for the first time.

**Results:** The experimental group had a statistically significant percent increase over controls in sucking power (69%), continuous sucking before releasing the bottle (16%), sucking time (13%), and sucking amount (12%) with partial  $\eta^2$  values of interaction between the groups of 0.692, 0.164, 0.136, and 0.121, respectively. The experimental group had a higher increase in weight (89%) and head circumference (81%) over controls ( $F = 485.130$ ,  $P < .001$ ;  $F = 254.754$ ,  $P < .001$ , respectively). The experimental group transitioned to oral feeding 9.9 days earlier than controls ( $t = -2.822$ ;  $P = .007$ ), started breast/chest feeding 10.8 days earlier ( $t = 3.016$ ;  $P = .004$ ), and were discharged 3.0 days earlier.

**Implications for research/practice:** The PIOMI had a significant positive effect on anthropometrics, sucking capacity, readiness to initiate bottle and breast/chest feeding, and a 3-day reduction in length of hospital stay.

J Pediatr Rehabil Med. 2022 Nov 21.

doi: 10.3233/PRM-210132. Online ahead of print.

**[Pre-feeding premature infant oral motor intervention \(PIOMI\) for transition from gavage to oral feeding: A randomised controlled trial](#)**

[Tapas Bandyopadhyay](#)<sup>1</sup>, [Arti Maria](#)<sup>1</sup>, [Nagaratna Vallamkonda](#)<sup>1</sup>

**Abstract**

**Purpose:** To assess the performance of premature infant oral motor intervention for transition from gavage to full spoon feeding in preterm infants.

**Methods:** Preterm neonates born between 28 + 0-32 + 6 weeks gestation ( $n = 32$ ) were randomised into an intervention group (premature infant oral motor intervention) for five minutes twice a day along with routine care ( $n = 16$ ) and a control group (routine care,  $n = 16$ ) once they reached a feed volume of at least 150 ml/kg/day administered by gavage method. The primary outcome measure was time (in days) to transition from gavage to full spoon feeds.

**Results:** The mean (SD) time to transition from gavage to full spoon feeds was attained significantly earlier in the intervention group than the control group (9.93 [5.83] vs 16.43 [10.46] days; mean difference, -6.5 days; 95% CI, -12.58 to -0.41). There was no significant difference between the two groups in terms of the duration of hospital stay, rates of physiological stability, and culture positive sepsis.

**Conclusion:** Premature infant oral motor intervention, as used in this specific population, significantly reduces the time to transition to full spoon feeds without increasing culture positive sepsis and physiological instability.

Am J Perinatol. 2023 Apr 14.

doi: 10.1055/a-2074-1960. Online ahead of print.

**[Comparison of Three Modalities of Feeding in Preterm Infants  \$\leq 32\$  weeks and  \$\leq 1250\$ g: A Randomized Controlled Trial](#)**

[Vijay Kumar Krishnegowda](#)<sup>1</sup>, [Anup Thakur](#)<sup>2</sup>, [Pankaj Garg](#)<sup>2</sup>, [Neelam Kler](#)<sup>2</sup>

## Abstract

**Introduction:** Early establishment of enteral feeds is desirable in very preterm infants, but it may be associated with feeding intolerance. Several feeding methods have been studied with no strong evidence to suggest the preferred feeding method to establish early full enteral feeds.

**Objective:** We studied three modalities of feeding in preterm infants  $\leq 32$ wk and  $\leq 1250$ g- continuous infusion (CI), intermittent bolus by infusion (IBI) and intermittent bolus by gravity (IBG) for their effect on time to reach full enteral feeds of 180ml/kg/day.

**Methods:** We randomized 146 infants, 49 infants in each CI and IBI group and 48 infants in the IBG group. In the CI group, feeds were delivered by an infusion pump continuously over 24 hours. In the IBI group, feeds were given every 2 hours and infused over 15 minutes by an infusion pump. In the IBG group, feeds were delivered by gravity over 10-30 minutes. The intervention was continued till infants reached direct breast/cup feeds.

**Results:** The mean (SD) gestation in CI, IBI and IBG groups were 28.4 (2.2) wk, 28.5(1.9) wk and 28.6 (1.8) wk, respectively. The time to reach full feeds in CI, IBI and IBG were not significantly different [median (IQR) 13(10-16), 11.5(9-17) and 13(9.5-14.2) days, respectively, ( $p=0.71$ )]. The proportion of infants who developed feeding intolerance in CI, IBI and IBG were similar [ $n$  (%) 21 (51.2%), 20(52.6%) and 22(64.7%), respectively, ( $p=0.45$ )]. There was no difference in necrotising enterocolitis (NEC)  $>2$  ( $p=0.80$ ), bronchopulmonary dysplasia (BPD) ( $p=0.86$ ), intraventricular Hemorrhage (IVH)  $>2$  ( $p=0.35$ ), patent ductus arteriosus (PDA) requiring treatment ( $p=0.44$ ), retinopathy of prematurity (ROP) requiring treatment ( $p=0.51$ ) and growth parameters at discharge.

**Conclusion:** In preterm infants,  $\leq 32$ wk of gestation and birth weight  $\leq 1250$ g, there was no difference in time to reach full enteral feeds in the three modalities of feeding.

J Perinatol. 2023 Jan 5.

doi: 10.1038/s41372-022-01597-x. Online ahead of print.

[The dilemma of feeding during the treatment of patent ductus arteriosus with oral ibuprofen in preterm infants  \$\leq 30\$  weeks of gestation-a randomized controlled trial](#)  
[Samandeep Kaur<sup>1</sup>](#), [Swati Manerkar<sup>2</sup>](#), [Jayashree Mondkar<sup>1</sup>](#), [Pavan Kalamdani<sup>1</sup>](#), [Saikat Patra<sup>1</sup>](#), [Thaslima Kalathingal<sup>1</sup>](#)

## Abstract

**Objectives:** To evaluate the effect of minimal enteral feeding (MEN) versus withholding feeding on time to reach full feeds during treatment of hs-PDA with oral ibuprofen in infants  $\leq 30$  weeks.

**Study design:** We performed a single-center, randomized control trial of 126 premature infants born  $\leq 30$  weeks gestation,  $<7$  days of age with hs-PDA comparing continuation of MEN ( $n=64$ ) vs no feeding ( $n=62$ ) during treatment. The primary outcome was time to reach a feed volume of 150 ml/kg/day. Secondary outcomes included were episodes of feed intolerance, GI bleed, NEC and other comorbidities.

**Results:** There was no difference in the time to reach full feeds - median age of 16 days in both groups ( $p=0.573$ ). Incidence of feed intolerance, NEC and other secondary outcomes were also similar in both groups.

**Conclusions:** Continuing MEN during treatment of hs-PDA with oral ibuprofen does not decrease time to reach full enteral feeds in very preterm infants.

Arch Dis Child Fetal Neonatal Ed. 2023 Mar;108(2):130-135.

doi: 10.1136/archdischild-2022-323781. Epub 2022 Aug 8.

**[Low dose paracetamol for management of patent ductus arteriosus in very preterm infants: a randomised non-inferiority trial](#)**

[Haribalakrishna Balasubramanian<sup>1</sup>](#), [Vaibhav Jain<sup>2</sup>](#), [Parag Bhalgat<sup>2</sup>](#), [Shalin Parikh<sup>2</sup>](#), [Nandkishore Kabra<sup>2</sup>](#), [Diwakar Mohan<sup>3</sup>](#), [Kshitij Sheth<sup>2</sup>](#)

**Abstract**

**Objective:** To compare the efficacy of low dose-short course intravenous paracetamol with a conventional dose regimen for early targeted closure of patent ductus arteriosus (PDA).

**Design:** Single-centre, double-blinded, active controlled, randomised non-inferiority trial.

**Setting:** Level III neonatal intensive care unit in Western India.

**Patients:** Preterm infants <30 weeks of gestation requiring mechanical ventilation, or continuous positive airway pressure with  $\text{FiO}_2 \geq 0.35$  and diagnosed with a haemodynamically significant PDA (hsPDA) at 18-24 hours of postnatal age.

**Interventions:** Low dose (10 mg/kg/dose 6 hourly for 72 hours) versus conventional dose (15 mg/kg/dose 6 hourly for 120 hours) intravenous paracetamol treatment.

**Main outcome measures:** Comparison of the rates of ductal closure at completion of sixth postnatal day, using a prespecified non-inferiority margin of 20%.

**Results:** A total of 102 infants were enrolled. The median gestational age and birth weight of the included infants were 26.4 weeks and 830 g. At completion of the sixth postnatal day, closure of PDA was achieved in 92% of infants in the low dose group as compared with 94% of those in the standard dose group (risk difference: -1.6%, 95% CI: -11.6% to 8.5%,  $p=0.38$ ). The rates of rescue therapies, adverse effects and other neonatal morbidities were comparable in both groups.

**Conclusion:** In very preterm infants on significant respiratory support, low dose-short course intravenous paracetamol treatment was non-inferior to a conventional dosing regime of paracetamol for closure of hsPDA in the first week of postnatal age. Larger studies with narrow margins of non-inferiority are required to confirm our findings.

Glob Health. 2022 Dec 29;12:04073.

doi: 10.7189/jogh.12.04073.

**[Effect of a quality improvement intervention for management of preterm births on outcomes of all births in Kenya and Uganda: A secondary analysis from a facility-based cluster randomized trial](#)**

[Rakesh Ghosh<sup>#1</sup>](#), [Phelgona Otieno<sup>#2</sup>](#), [Elizabeth Butrick<sup>1</sup>](#), [Nicole Santos<sup>1</sup>](#), [Peter Waiswa<sup>3,4</sup>](#), [Dilys Walker<sup>1,5</sup>](#); [Preterm Birth Initiative Kenya and Uganda Implementation Research Collaborative](#)

**Abstract**

**Background:** A large proportion of early neonatal deaths occur at the time or on the first day of birth. The Preterm Birth Initiative East Africa (PTBi EA) set out to decrease mortality among preterm births through improving quality of facility-based intrapartum care. The PTBi EA cluster randomized trial's primary analysis showed the package reduced intrapartum stillbirth and neonatal death among preterm infants. This secondary analysis examines the

impact of the PTBi intervention package on stillbirth and pre-discharge newborn deaths combined, among all births in 20 participating facilities in Kenya and Uganda.

**Methods:** Eligible facilities were pair-matched and randomly assigned (1:1) into either the intervention or the control group. All facilities received support for data strengthening and a modified World Health Organization (WHO) Safe Childbirth Checklist; facilities in the intervention group additionally received provider mentoring using PRONTO simulation and team training as well as quality improvement collaboratives. We abstracted data from maternity registers.

**Results:** Of the total 29 442 births that were included, Kenya had 8468 and 6465 births and Uganda had 8719 and 5790 births, in the control and intervention arms, respectively. There were 935 stillbirths and pre-discharge newborn deaths in the control arm and 439 in the intervention arm. The adjusted odds ratio (aOR) for the effect of the intervention on the combined outcome, among all births, was 0.96 (95% confidence interval (CI) = 0.69-1.32), which was different by country: Kenya - 1.12 (95% CI = 0.72-1.73); Uganda - 0.65 (95% CI = 0.44-0.98);  $P_{\text{interaction}} = 0.025$ . These trends were similar after excluding the PTBi primary cohort.

**Conclusions:** The intervention package improved survival among all births in Uganda but not in Kenya. These results suggest the importance of context and facility differences that were observed between the two countries.

## Neonatal intensive care

Am J Perinatol. 2022 Nov;39(15):1693-1701.

doi: 10.1055/s-0041-1726122. Epub 2021 Mar 23.

### [Efficacy and Safety of Two Different Flow Rates of Nasal High-Flow Therapy in Preterm Neonates \$\geq\$ 28 Weeks of Gestation: A Randomized Controlled Trial](#)

[Haribalakrishna Balasubramanian<sup>1</sup>](#), [Sachin Sakharkar<sup>1</sup>](#), [Swati Majarikar<sup>1</sup>](#), [Lakshmi Srinivasan<sup>2</sup>](#), [Nandkishor S Kabra<sup>1</sup>](#), [Bhawandeep Garg<sup>1</sup>](#), [Javed Ahmed<sup>1</sup>](#)

#### Abstract

**Objective:** The study aimed to compare the efficacy and safety of two different nasal high-flow rates for primary respiratory support in preterm neonates. **STUDY DESIGN:** In this single-center, double-blinded randomized controlled trial, preterm neonates  $\geq$ 28 weeks of gestation with respiratory distress from birth were randomized to treatment with either increased nasal flow therapy (8-10 L/min) or standard nasal flow therapy (5-7 L/min). The primary outcome of nasal high-flow therapy failure was a composite outcome defined as the need for higher respiratory support (continuous positive airway pressure [CPAP] or mechanical ventilation) or surfactant therapy.

**Results:** A total of 212 neonates were enrolled. Nasal high-flow failure rate in the increased flow group was similar to the standard flow group (22 vs. 29%, relative risk = 0.81 [95% confidence interval: 0.57-1.15]). However, nasal flow rate escalation was significantly more common in the standard flow group (64 vs. 43%,  $p = 0.004$ ). None of the infants in the increased flow group developed air leak syndromes.



**Conclusion:** Higher nasal flow rate (8-10 L/min) when compared with lower nasal flow rate of 5 to 7 L/min did not reduce the need for higher respiratory support (CPAP/mechanical ventilation) or surfactant therapy in moderately and late preterm neonates. However, initial flow rates of 5 L/min were not optimal for most preterm infants receiving primary nasal flow therapy.

**Key points:** · Use of high nasal flows (8-10 L/min) did not reduce the need for higher respiratory support in moderately and late preterm infants.. · Nasal flow rate of 5 L/min was not optimal for most preterms with respiratory distress from birth.. · Careful patient selection and optimized flow settings could enhance nasal flow success in neonates..

J Trop Pediatr. 2022 Oct 6;68(6):fmac095.

doi: 10.1093/tropej/fmac095.

[\*\*Feasibility of bubble non-invasive positive pressure ventilation, a first-in-human study\*\*](#)

[Stephen C John<sup>1,2</sup>](#), [Bikash Raj Adhikari<sup>3</sup>](#), [Anna V John<sup>2</sup>](#), [Eric O Cheng<sup>4</sup>](#), [Gary M Weiner<sup>5</sup>](#), [Sunil P John<sup>3</sup>](#)

**Abstract**

**Purpose:** Infant respiratory distress is a significant cause of mortality globally. Bubble continuous positive airway pressure (CPAP) is a simple and effective therapy, but sicker infants may require additional support such as non-invasive positive-pressure ventilation (NIPPV). We investigated the feasibility of a simple, low-cost, non-electric bubble NIPPV device.

**Methods:** In this cross-over feasibility study, seven newborns with moderate respiratory distress (Downes score  $\geq 3$ ), weight  $\geq 1500$  g and gestational age  $\geq 32$  weeks were randomized to 4 h of treatment with bubble CPAP (5-8 cm H<sub>2</sub>O) vs. bubble NIPPV (P<sub>high</sub> 8-10 cm H<sub>2</sub>O/P<sub>low</sub> 5-8 cm H<sub>2</sub>O) followed by 4 h of the alternate treatment. Treatment order (CPAP vs. NIPPV) was randomized. Outcome measures included hourly vital signs, Downes score and O<sub>2</sub> saturation. Adverse events including pneumothorax, nasal septal necrosis, necrotizing enterocolitis and death before discharge were also recorded.

**Results:** It took nurses 39 (7.3) s to assemble the bubble NIPPV device. Patients had similar vital signs and Downes scores on both treatments; median (IQR) values on bubble CPAP vs. bubble NIPPV were: heart rate 140 (134.5, 144), 140 (134.5, 144); respiratory rate 70 (56, 80), 65 (58, 82), Downes score 4 (3, 5.75), 4 (3, 5), O<sub>2</sub> 96 (94, 98), 97 (96, 98). All newborns survived to discharge and there were no adverse events. .

**Conclusions:** A simple, low-cost, non-electric method of providing NIPPV for newborns with respiratory distress is feasible in limited resource settings. Randomized-controlled trials comparing bubble CPAP and bubble NIPPV are justified.

Eur J Pediatr. 2022 Dec;181(12):4111-4119.

doi: 10.1007/s00431-022-04620-7. Epub 2022 Sep 17.

[\*\*RAM cannula versus short binasal prongs for nasal continuous positive airway pressure delivery in preterm infants: a randomized, noninferiority trial from low-middle-income country\*\*](#)

[S K Samim<sup>1</sup>](#), [Pradeep Kumar Debata<sup>2</sup>](#), [Anita Yadav<sup>1</sup>](#), [Jogender Kumar<sup>3</sup>](#), [Pratima Anand<sup>1</sup>](#), [Mehak Garg<sup>1</sup>](#)

### Abstract

To determine if RAM cannula is non-inferior to short binasal prongs (SBP) in providing nasal continuous positive airway pressure (CPAP) in preterm infants with respiratory distress syndrome (RDS). In this randomized, open-label, noninferiority trial from a low-middle-income country, we enrolled 254 preterm infants (28-34 weeks gestational age) with RDS who needed CPAP as primary respiratory support. The eligible infants were randomized to either RAM cannula or SBP interface groups. The primary outcome was CPAP failure (defined as the need for intubation or non-invasive positive pressure ventilation) within 72 h of randomization. The noninferiority margin was defined as a 10% or less absolute difference in CPAP failure rates. The secondary outcomes included nasal trauma and adverse events. We analyzed by per-protocol (primary) and intention to treat. CPAP failure has been seen in 25 infants (19.7%) in the RAM cannula group versus 22 (17.3%) in the SBP group (RD -2.36%; 95% CI -11.9 to 7.2 [beyond inferiority margin];  $p = 0.6$ ). Moderate and severe nasal trauma was less in RAM cannula (2.4 vs. 8.7%; RR 0.27; 95% CI 0.08-0.95;  $p 0.028$ ). Duration of CPAP was also significantly shorter in the RAM cannula group (MD -12.4 h; 95% CI -20.34 to -4.46,  $p 0.017$ ). There were no differences in other adverse events.

**Conclusions:** RAM cannula was not non-inferior to SBP in providing CPAP to preterm infants with respiratory distress syndrome.

Pediatr Pulmonol. 2022 Nov 23.

doi: 10.1002/ppul.26246. Online ahead of print.

### [Surfactant administration in preterm babies \(28-36 weeks\) with respiratory distress syndrome: LISA versus InSurE, an open-label randomized controlled trial](#)

[Aradhana Mishra<sup>1</sup>](#), [Amol Joshi<sup>1</sup>](#), [Atul Londhe<sup>1</sup>](#), [Laxmikant Deshmukh<sup>1</sup>](#)

### Abstract

**Introduction:** INTubate-SURfactant-Extubate (InSurE) approach is traditional method of surfactant delivery in preterm neonates with respiratory distress syndrome (RDS). Newer, less invasive surfactant administration (LISA) techniques lessen the need for mechanical ventilation and its adverse consequences. Evidence on the favorable effects of LISA can't be extrapolated from developed to developing countries. Aim of study is to compare the effectiveness of InSurE and LISA.

**Objectives:** Primary outcome was to find need of intubation and mechanical ventilation within 72 h of birth. Neonates were followed until discharge/death for adverse events and complications. **MATERIALS AND METHODS:** Open-label randomized controlled trial (RCT) was conducted at tertiary neonatal intensive care unit. Preterm neonates with diagnosis of RDS were randomized in two groups (InSurE or LISA) to receive surfactant soon after birth. Nasal intermittent positive pressure ventilation (NIPPV) was used as primary mode of respiratory support.

**Results:** A total of 150 neonates were analyzed (75 in each group). Insignificant statistical difference was seen in the need for intubation and mechanical ventilation within 72 h of birth between the two groups (InSurE, 30 [40%] and LISA, 30 [40%], relative risk 1.0, 95% confidence interval 0.68-1.48). Twelve percent ( $n = 9$ , LISA group) and 14.6% ( $n = 11$  InSurE group) had adverse events during the procedure. Also, we observed insignificant statistical

difference in the rates of major complications or duration of respiratory support, hospital stay, and mortality.

**Conclusion:** LISA and InSurE are equally effective for surfactant administration in the treatment of RDS, when NIPPV is the primary mode of respiratory support. More RCTs are required to compare the efficacy & long-term outcomes of LISA with InSurE.

Eur J Pediatr. 2023 Mar 27;1-10.

doi: 10.1007/s00431-023-04933-1. Online ahead of print.

**Systematic rotation versus continuous application of 'nasal prongs' or 'nasal mask' in preterm infants on nCPAP: a randomized controlled trial**

[Gaurav Gautam](#)<sup>#1</sup>, [Neeraj Gupta](#)<sup>#2</sup>, [Rohit Sasidharan](#)<sup>3</sup>, [Sivam Thanigainathan](#)<sup>3</sup>, [Bharti Yadav](#)<sup>3</sup>, [Kuldeep Singh](#)<sup>1</sup>, [Arun Singh](#)<sup>3</sup>

**Abstract**

To compare whether alternate rotation of nasal mask with nasal prongs every 8 h as compared to continuous use of either interface alone decreases the incidence of nasal injury in preterm infants receiving nasal Continuous Positive Airway Pressure (nCPAP). This was an open-label, three-arm, stratified randomized controlled trial where infants < 35 weeks receiving nCPAP were randomized into three groups using two different nasal interfaces (continuous prongs group, continuous mask group, and rotation group). All infants were assessed for nasal injury six hours post-removal of nCPAP using grading suggested by Fischer et al. The nursing care was uniform across all three groups. Intention-to-treat analysis was done. Fifty-seven infants were enrolled, with nineteen in each group. The incidence of nasal injury was 42.1% vs. 47.4% vs. 68.4% in the rotation group, continuous mask, and continuous prongs groups, respectively (P = 0.228). On adjusted analysis (gestational age, birth weight, and duration of nCPAP therapy), the incidence of nasal injury was significantly less in the rotation group as compared to continuous prongs group (Adjusted Odds Ratio [AOR], 95% confidence interval [CI]; 0.10 [0.01-0.69], P = 0.02) and a trend towards lesser nasal injury as compared to continuous mask group (AOR, 95% CI; 0.15 [0.02-1.08], P = 0.06). However, there was no significant difference in incidence of nasal injuries between continuous prongs versus continuous mask group (P = 0.60). The need for surfactant, nCPAP failure rate, duration of nCPAP, and common neonatal co-morbidities were similar across all three groups.

Conclusion: Systematic rotation of nasal mask with nasal prongs significantly reduced nasal injury among preterm infants on nCPAP as compared to continuous use of nasal prongs alone without affecting nCPAP failure rate.

Eur J Pediatr. 2023 Feb;182(2):785-793.

doi: 10.1007/s00431-022-04726-y. Epub 2022 Dec 8.

**Closed versus open endotracheal tube suction in mechanically ventilated neonates: a randomized controlled trial**

[Ajaya Kumar Gahan](#)<sup>1</sup>, [Suksham Jain](#)<sup>2</sup>, [Supreet Khurana](#)<sup>1</sup>, [Deepak Chawla](#)<sup>1</sup>

**Abstract**

This study aimed to evaluate the effect of closed versus open endotracheal tube suction in reducing ventilator-associated pneumonia in mechanically ventilated neonates. In this open-label, parallel-group, randomized controlled trial with allocation concealment, ventilated neonates ( $\geq 28$  weeks and  $\geq 800$  g) were either allocated to the closed-suction group ( $n = 41$ ) or open-suction group ( $n = 39$ ). The ventilator circuit of the babies enrolled in the closed-suction group was attached to the closed-suction catheter on the requirement of their first suction, and it was changed after every 48 h or earlier if visibly soiled whereas babies enrolled in the open-suction group were suctioned with a new suction catheter each time they require suction. The primary outcome was the incidence of VAP per 1000 days. Baseline maternal and neonatal characteristics were comparable between the two groups. The proportion of neonates with VAP in the closed-suction group was 3 (7.3%) and 1 (2.6%) in the open-suction group with an RR of 2.8 (95% CI: 0.30-26.28) and a p-value of 0.35. The incidence of VAP in the closed-suction group was 3.9 per 1000 ventilator days and 1.3 per 1000 ventilator days in the open-suction group. The incidence of clinical VAP/1000 ventilator days was  $33.63 \pm 22.96$  in the closed-suction group and  $28.67 \pm 12.32$  in the open-suction group with a mean difference of 5 (95% CI: - 3.26 to 13.26) and p-value of 0.24.

**Conclusion:** In a unit with a low incidence of VAP, the effect of the endotracheal suction method alone did not impact the occurrence of VAP in the study population.

Cochrane Database Syst Rev. 2023 May 4;5(5):CD013841.

doi: 10.1002/14651858.CD013841.pub2.

[Antiseptic solutions for skin preparation during central catheter insertion in neonates](#)

[Muhd Alwi Muhd Helmi](#)<sup>1</sup>, [Nai Ming Lai](#)<sup>2</sup>, [Hans Van Rostenberghe](#)<sup>3</sup>, [Izzudeen Ayub](#)<sup>4</sup>, [Emie Mading](#)<sup>5</sup>

**Abstract**

**Background:** Central venous catheters (CVC) are associated with potentially dangerous complications such as thromboses, pericardial effusions, extravasation, and infections in neonates. Indwelling catheters are amongst the main risk factors for nosocomial infections. The use of skin antiseptics during the preparation for central catheter insertion may prevent catheter-related bloodstream infections (CRBSI) and central line-associated bloodstream infections (CLABSI). However, it is still not clear which antiseptic solution is the best to prevent infection with minimal side effects.

**Objectives:** To systematically evaluate the safety and efficacy of different antiseptic solutions in preventing CRBSI and other related outcomes in neonates with CVC.

**Search methods:** We searched CENTRAL, MEDLINE, Embase, and trial registries up to 22 April 2022. We checked reference lists of included trials and systematic reviews that related to the intervention or population examined in this Cochrane Review. SELECTION CRITERIA: Randomised controlled trials (RCTs) or cluster-RCTs were eligible for inclusion in this review if they were performed in the neonatal intensive care unit (NICU), and were comparing any antiseptic solution (single or in combination) against any other type of antiseptic solution or no antiseptic solution or placebo in preparation for central catheter insertion. We excluded cross-over trials and quasi-RCTs.

**Data collection and analysis:** We used the standard methods from Cochrane Neonatal. We used the GRADE approach to assess the certainty of the evidence.

**Main results:** We included three trials that had two different comparisons: 2% chlorhexidine in 70% isopropyl alcohol (CHG-IPA) versus 10% povidone-iodine (PI) (two trials); and CHG-IPA

versus 2% chlorhexidine in aqueous solution (CHG-A) (one trial). A total of 466 neonates from level III NICUs were evaluated. All included trials were at high risk of bias. The certainty of the evidence for the primary and some important secondary outcomes ranged from very low to moderate. There were no included trials that compared antiseptic skin solutions with no antiseptic solution or placebo. CHG-IPA versus 10% PI Compared to PI, CHG-IPA may result in little to no difference in CRBSI (risk ratio (RR) 1.32, 95% confidence interval (CI) 0.53 to 3.25; risk difference (RD) 0.01, 95% CI -0.03 to 0.06; 352 infants, 2 trials, low-certainty evidence) and all-cause mortality (RR 0.88, 95% CI 0.46 to 1.68; RD -0.01, 95% CI -0.08 to 0.06; 304 infants, 1 trial, low-certainty evidence). The evidence is very uncertain about the effect of CHG-IPA on CLABSI (RR 1.00, 95% CI 0.07 to 15.08; RD 0.00, 95% CI -0.11 to 0.11; 48 infants, 1 trial; very low-certainty evidence) and chemical burns (RR 1.04, 95% CI 0.24 to 4.48; RD 0.00, 95% CI -0.03 to 0.03; 352 infants, 2 trials, very low-certainty evidence), compared to PI. Based on a single trial, infants receiving CHG-IPA appeared less likely to develop thyroid dysfunction compared to PI (RR 0.05, 95% CI 0.00 to 0.85; RD -0.06, 95% CI -0.10 to -0.02; number needed to treat for an additional harmful outcome (NNT<sub>H</sub>) 17, 95% CI 10 to 50; 304 infants). Neither of the two included trials assessed the outcome of premature central line removal or the proportion of infants or catheters with exit-site infection. CHG-IPA versus CHG-A The evidence suggests CHG-IPA may result in little to no difference in the rate of proven CRBSI when applied on the skin of neonates prior to central line insertion (RR 0.80, 95% CI 0.34 to 1.87; RD -0.05, 95% CI -0.22 to 0.13; 106 infants, 1 trial, low-certainty evidence) and CLABSI (RR 1.14, 95% CI 0.34 to 3.84; RD 0.02, 95% CI -0.12 to 0.15; 106 infants, 1 trial, low-certainty evidence), compared to CHG-A. Compared to CHG-A, CHG-IPA probably results in little to no difference in premature catheter removal (RR 0.91, 95% CI 0.26 to 3.19; RD -0.01, 95% CI -0.15 to 0.13; 106 infants, 1 trial, moderate-certainty evidence) and chemical burns (RR 0.98, 95% CI 0.47 to 2.03; RD -0.01, 95% CI -0.20 to 0.18; 114 infants, 1 trial, moderate-certainty evidence). No trial assessed the outcome of all-cause mortality and the proportion of infants or catheters with exit-site infection.

**Authors' conclusions:** Based on current evidence, compared to PI, CHG-IPA may result in little to no difference in CRBSI and mortality. The evidence is very uncertain about the effect of CHG-IPA on CLABSI and chemical burns. One trial showed a statistically significant increase in thyroid dysfunction with the use of PI compared to CHG-IPA. The evidence suggests CHG-IPA may result in little to no difference in the rate of proven CRBSI and CLABSI when applied on the skin of neonates prior to central line insertion. Compared to CHG-A, CHG-IPA probably results in little to no difference in chemical burns and premature catheter removal. Further trials that compare different antiseptic solutions are required, especially in low- and middle-income countries, before stronger conclusions can be made.

J Cardiovasc Pharmacol. 2022 Nov 1;80(5):746-752.

doi: 10.1097/FJC.0000000000001332.

**[Milrinone Versus Sildenafil in Treatment of Neonatal Persistent Pulmonary Hypertension: A Randomized Control Trial](#)**

[Safaa S Imam](#)<sup>1</sup>, [Rania A El-Farrash](#)<sup>1</sup>, [Amr S Taha](#)<sup>2</sup>, [Ghada A Saleh](#)<sup>1</sup>

**Abstract**

Persistent pulmonary hypertension of the newborn (PPHN) is a condition caused by failure of pulmonary vascular adaptation at birth, resulting in severe hypoxia. Several therapeutic

modalities are being tried in developing countries where established therapies (inhaled nitric oxide and extracorporeal membrane oxygenation) are widely unavailable. This study aimed to assess the efficacy of milrinone versus sildenafil as available alternative therapeutics in treating PPHN. Forty neonates (>34 weeks) admitted to neonatal intensive care units with evidence of PPHN were randomly allocated to receive either oral sildenafil (0.5-2 mg/kg/6 hours) or intravenous milrinone (0.25-0.75 mic/kg/min). Primary outcomes included improvements in systolic pulmonary artery pressure and oxygen saturation index (OSI) at 24 and 48 hours after treatment. Secondary outcomes included the duration of hospitalization and mechanical ventilation. The ClinicalTrials identifier is [NCT04391478](https://clinicaltrials.gov/ct2/show/study/NCT04391478). Both groups showed significant improvement in the post-treatment hemodynamic variables compared with pretreatment levels (  $P < 0.05$  for all parameters). Systolic pulmonary artery pressure and OSI values significantly improved in both study groups compared with baseline (  $P < 0.001$ ). The 24-hour and 48-hour post-treatment OSI values were much lower in the milrinone group than those in the sildenafil group (  $P < 0.05$ ). The length of hospital stay was significantly shorter in the milrinone group than that in the sildenafil group (  $P < 0.05$ ). There were no significant differences in the duration of mechanical ventilation, incidence of intracranial hemorrhage and pulmonary hemorrhage, or mortality between the 2 groups (  $P > 0.05$ ). In conclusion, milrinone and sildenafil are effective and well-tolerated in neonates with PPHN, particularly when inhaled nitric oxide and extracorporeal membrane oxygenation are not available. Milrinone is superior to sildenafil in improving oxygenation without lowering blood pressure parameters.

Indian J Pediatr. 2022 Nov;89(11):1093-1098.

doi: 10.1007/s12098-022-04295-w. Epub 2022 Jul 26.

### [\*\*Ultrasound-Guided Umbilical Venous Catheter Insertion to Reduce Rate of Catheter Tip Malposition in Neonates: A Randomized, Controlled Trial\*\*](#)

[Amandeep Kaur<sup>1</sup>](#), [Swati Manerkar<sup>2</sup>](#), [Saikat Patra<sup>1</sup>](#), [Pavan Kalamdani<sup>1</sup>](#), [Thaslima Kalathingal<sup>1</sup>](#), [Jayashree Mondkar<sup>1</sup>](#)

#### **Abstract**

**Objective:** To investigate whether ultrasound-guided umbilical venous catheter (UVC) insertion (US group) reduced the rate of malpositioning of the catheter tip compared to the standard method of insertion (SD group).

**Methods:** In this open-label, randomized, controlled trial, neonates admitted to NICU within the first week of life were randomly assigned to the US group (n = 26) or SD group (n = 27). Neonates with major congenital anomalies of the thorax and abdomen were excluded. The primary outcome was the rate of malpositioning of the catheter tip.

**Results:** The rate of malpositioning of the catheter tip was observed in a significantly lower number of neonates in the US group as compared to the SD group (11/26, 42.3% vs. 20/27, 74%; RR = 0.57, 95% CI: 0.34 to 0.94,  $p = 0.019$ ). As more of the UVCs were positioned optimally in the first attempt in the US group than SD group, the need for repeated attempts at catheter repositioning was reduced, resulting in reduced procedure time (minutes) [mean (SD), 23.96 (6.42) vs. 30 (1.83); mean difference 6.04 (95% CI: 3.46 to 8.62),  $p = 0.005$ ]. This also led to a reduction in the additional X-ray exposure in the US group (n = 11) compared to the SD group (n = 20) [95% CI: 3.12 to 44.26;  $p = 0.020$ ].

**Conclusion:** Ultrasound-guided UVC insertion significantly reduced the rate of catheter tip malposition. It also reduced the number of attempts at catheter manipulation, procedure



time, and X-ray exposures. With adequate training, it could be incorporated into routine bedside practice during UVC insertion for optimum placement.

Arch Dis Child Fetal Neonatal Ed. 2022 Jul;107(4):393-397.

doi: 10.1136/archdischild-2021-322890. Epub 2021 Oct 22.

**[Surfactant therapy in late preterm and term neonates with respiratory distress syndrome: a systematic review and meta-analysis](#)**

[Viraraghavan Vadakkencherry Ramaswamy](#)<sup>1</sup>, [Thangaraj Abiramalatha](#)<sup>2</sup>, [Tapas Bandyopadhyay](#)<sup>3</sup>, [Elaine Boyle](#)<sup>4</sup>, [Charles Christoph Roehr](#)<sup>5,6,7</sup>

**Abstract**

**Background:** There are no evidence-based recommendations for surfactant use in late preterm (LPT) and term infants with respiratory distress syndrome (RDS).

**Objective:** To investigate the safety and efficacy of surfactant in LPT and term infants with RDS.

**Methods:** Systematic review, meta-analysis and evidence grading.

**Interventions:** Surfactant therapy versus standard of care.

**Main outcome measures:** Mortality and requirement for invasive mechanical ventilation (IMV).

**Results:** Of the 7970 titles and abstracts screened, 17 studies (16 observational studies and 1 randomised controlled trial (RCT)) were included. Of the LPT and term neonates with RDS, 46% (95% CI 40% to 51%) were treated with surfactant. We found moderate certainty of evidence (CoE) from observational studies evaluating infants supported with non-invasive respiratory support (NRS) or IMV that surfactant use may be associated with a decreased risk of mortality (OR 0.45, 95% CI 0.32 to 0.64). Very low CoE from observational trials in which surfactant was administered at FiO<sub>2</sub> >0.30-0.40 to infants on Continuous Positive Airway Pressure (CPAP) indicated that surfactant did not decrease the risk of IMV (OR 1.20, 95% CI 0.40 to 3.56). Very low to low CoE from the RCT and observational trials showed that surfactant use was associated with a significant decrease in risk of air leak, persistent pulmonary hypertension of the newborn (PPHN), duration of IMV, NRS and hospital stay.

**Conclusions:** Current evidence base on surfactant therapy in LPT and term infants with RDS indicates a potentially decreased risk of mortality, air leak, PPHN and duration of respiratory support. In view of the low to very low CoE and widely varying thresholds for deciding on surfactant replacement in the included studies, further trials are needed.

Sci Rep. 2022 Oct 20;12(1):17569.

doi: 10.1038/s41598-022-22533-1.

**[Effect of a light-darkness cycle on the body weight gain of preterm infants admitted to the neonatal intensive care unit](#)**

[Manuel Sánchez-Sánchez](#)<sup>1,2</sup>, [Teodoro L García](#)<sup>1,3</sup>, [Donají Heredia](#)<sup>4</sup>, [Isaac Reséndiz](#)<sup>5</sup>, [Lorena Cruz](#)<sup>1</sup>, [Jacqueline Santiago](#)<sup>1</sup>, [Adelina Rojas-Granados](#)<sup>6</sup>, [Laura Ubaldo-Reyes](#)<sup>6</sup>, [Laura Pérez-Campos-Mayoral](#)<sup>3</sup>, [Eduardo Pérez-Campos](#)<sup>3,7</sup>, [Gervacio S Vásquez](#)<sup>6,8</sup>, [Juan M Moguel](#)<sup>1,5</sup>, [Romeo Zarate](#)<sup>1</sup>, [Oscar García](#)<sup>1</sup>, [Luisa Sánchez](#)<sup>4</sup>, [Fernando Torres](#)<sup>5</sup>, [Alberto Paz](#)<sup>1</sup>, [Jesús Elizarraras-Rivas](#)<sup>3,5</sup>, [María T Hernández-Huerta](#)<sup>3</sup>, [Manuel Angeles-Castellanos](#)<sup>2</sup>

**Abstract**

The Continuous bright light conditions to which premature infants are subjected while hospitalized in Neonatal Intensive Care Units (NICU) can have deleterious effects in terms of growth and development. This study evaluates the benefits of a light/darkness cycle (LDC) in weight and early hospital discharge from the NICU. Subjects were recruited from three participating institutions in Mexico. Eligible patients (n = 294) were premature infants who were hospitalized in the low-risk and high-risk neonatal units classified as stable. The subjects randomized to the experimental group (n = 150) were allocated to LDC conditions are as follows: light from 07:00 to 19:00 and darkness (25 lx) from 19:00 to 07:00. The control group (n = 144) was kept under normal room light conditions (CBL) 24 h a day. Main outcome was weight gain and the effect of reducing the intensity of nocturnal light in development of premature infants. Infants to the LDC gained weight earlier, compared with those randomized to CBL, and had a significant reduction in length of hospital stay. These results highlight those premature infants subjected to a LDC exhibit improvements in physiological development, favoring earlier weight gain and consequently a decrease in hospital stays

Altern Ther Health Med. 2023 Mar;29(2):148-154.

[\*\*The Effect of White Noise and Brahms' Lullaby on Pain in Infants during Intravenous Blood Draw: A Randomized Controlled Study\*\*](#)

[Tülay Sağkal Midilli](#), [Eda Ergin](#)

**Abstract**

**Objective:** This study investigates the effects of white noise and Brahms' lullaby in managing pain in infants who were administered with intravenous blood draws in a pediatric blood-sampling unit.

**Design:** This study was an experimental, randomized controlled trial.

**Setting:** This study was conducted on 0-12-month-old infants admitted to a pediatric blood-sampling unit of a university hospital in Turkey between July and October 2019.

**Participants:** The sample comprised 59 infants 0-12 months of age. The infants were randomly assigned to three groups: (a) white noise, (b) Brahms' lullaby, and (c) control.

**Outcome measures:** We evaluated the pain of the infants according to the Neonatal Infant Pain Scale (NIPS). We measured their pain and crying time before, during, and after the procedure.

**Results:** The means of the NIPS scores of the infants in the white noise and Brahms' lullaby groups were lower than that of the control group before, during, and after the procedure. The means of the NIPS scores of the infants in the white noise and Brahms' lullaby groups were significantly lower than that of the control group during and after the procedure ( $P < .05$ ). The crying time of the infants in the white noise and Brahms' lullaby groups were significantly lower than that of the control group after the procedure ( $P < .05$ ).

**Conclusion:** The white noise and Brahms' lullaby used during the intravenous blood draw procedure reduced the pain of infants.

## Neonatal resuscitation - perinatal asphyxia

J Paediatr Child Health. 2023 Jun;59(6):794-801.

doi: 10.1111/jpc.16391. Epub 2023 Apr 3.

**[Room air versus 100% oxygen for delivery room resuscitation of preterm neonates in low resource settings: A randomised, blinded, controlled trial](#)**

[Nishath A Liyakat](#)<sup>1,2</sup>, [Praveen Kumar](#)<sup>1</sup>, [Venkateshan Sundaram](#)<sup>1</sup>

**Abstract**

**Aim:** International Liaison Committee on Resuscitation (ILCOR-2020) report recommend starting delivery room resuscitation of all preterm neonates of <35 weeks' gestation with 21-30% oxygen. However, the correct initial oxygen concentration for resuscitation of preterm neonates in delivery room is inconclusive. In this blinded, randomised, controlled trial, we compared room air with 100% oxygen for oxidative stress and clinical outcomes in delivery room resuscitation of preterm neonates.

**Methods:** Preterm neonates 28-33 weeks' gestation requiring positive pressure ventilation at birth were randomly allocated to room air or 100% oxygen. Investigators, outcome assessors and data analysts were blinded. Rescue 100% oxygen was used whenever trial gas failed (need for positive pressure ventilation >60 s or chest compression).

**Primary outcome:** Plasma 8-isoprostane levels at 4 h of age.

**Secondary outcomes:** mortality by discharge, bronchopulmonary dysplasia, retinopathy of prematurity and neurological status at 40 weeks post-menstrual age. All subjects were followed till discharge. Intention to treat analysis was carried out.

**Results:** A total of 124 neonates were randomised to room air (n = 59) or 100% oxygen (n = 65). Isoprostane level at 4 h was similar in both the groups (median (interquartile range): 280 (180-430) vs. 250 (173-360) pg/mL, P = 0.47). No difference was observed in mortality and other clinical outcomes. Room air group had higher treatment failures (27 (46%) vs. 16 (25%); relative risk (RR) 1.9 (1.1-3.1)) and took longer time to establish regular respiration (230 ± 231 vs. 182 ± 261, mean difference = 48 (40, 136) seconds).

**Conclusions:** In preterm neonates 28-33 weeks' gestation requiring resuscitation in the delivery room, room air (21%) is not the correct concentration to initiate resuscitation. Larger controlled trials involving multiple centres in low- and middle-income countries are immediately required for a conclusive answer.

J Pediatr. 2022 Oct 17;S0022-3476(22)00898-8.

doi: 10.1016/j.jpeds.2022.08.061. Online ahead of print.

**[Resuscitation with intact versus clamped cord in late preterm and term neonates: A randomized controlled trial](#)**

[Jaspreet Singh Raina](#)<sup>1</sup>, [Deepak Chawla](#)<sup>2</sup>, [Suksham Jain](#)<sup>1</sup>, [Supreet Khurana](#)<sup>1</sup>, [Alka Sehgal](#)<sup>3</sup>, [Shikha Rani](#)<sup>3</sup>

**Abstract**

**Objective:** To compare the effect of intact cord versus clamped cord resuscitation on the physiological transition of neonates receiving positive pressure ventilation (PPV) at birth.

**Study design:** This open-label, parallel-group, randomized controlled superiority trial was conducted in a tertiary care hospital in India. Neonates being born at ≥ 34 weeks of gestation after a complicated pregnancy or labor were randomized just before birth to receive resuscitation as per the Neonatal Resuscitation Program algorithm with either an intact cord (intact cord resuscitation or ICR group) or after early cord clamping (early cord clamping-resuscitation or ECR group). The allocated study intervention was administered if the

neonate needed PPV at birth. The primary outcome was 'expanded Apgar score' at 5 minutes after birth.

**Results:** Birth weight, gestation, and incidence of pregnancy complications were similar in the two study groups. Proportion of neonates who received PPV was lower in the ICR group (28.7% vs 36.5%,  $P=0.05$ , RR: 0.79; 95% CI: 0.61 to 1.01). Among neonates who received PPV, expanded Apgar score at 5 minutes was significantly higher in the ICR group (median: 15; IQR: 14 to 15 vs 14; 13 to 15;  $P < 0.001$ ). Expanded Apgar score at 10 minutes, Apgar scores at 5- and 10-minutes, and oxygen saturation at 1, 5, and 10 minutes were also higher in the ICR group.

**Conclusion:** In late preterm and term neonates, resuscitation with an intact cord results in better postnatal physiological transition than the standard practice of resuscitation after immediate cord clamping.

Resusc Plus. 2022 Sep 17;12:100298.

doi: 10.1016/j.resplu.2022.100298. eCollection 2022 Dec.

### [Suctioning of clear amniotic fluid at birth: A systematic review](#)

[Joe Fawke<sup>1</sup>](#), [Jonathan Wyllie<sup>2</sup>](#), [Enrique Udaeta<sup>3</sup>](#), [Mario Rüdiger<sup>4</sup>](#), [Hege Ersdal<sup>5,6</sup>](#), [Mary-Doug Wright<sup>7</sup>](#), [Myra H Wyckoff<sup>8</sup>](#), [Helen G Liley<sup>9</sup>](#), [Yacob Rabi<sup>10</sup>](#), [Gary M Weiner<sup>11</sup>](#), [International Liaison Committee On Resuscitation Neonatal Life Support Task Force](#)

#### **Abstract**

**Context:** Upper airway suctioning at birth was considered standard procedure and is still commonly practiced. Negative effects could exceed benefits of suction.

**Question:** In infants born through clear amniotic fluid (P) does suctioning of the mouth and nose (I) vs no suctioning (C) improve outcomes (O).

**Data sources:** Information specialist conducted literature search (12th September 2021, re-run 17th June 2022) using Medline, Embase, Cochrane Databases, Database of Abstracts of Reviews of Effects, and CINAHL. RCTs, non-RCTs and observational studies with a defined selection strategy were included. Unpublished studies, reviews, editorials, animal and manikin studies were excluded.

**Data extraction:** Two authors independently extracted data, risk of bias was assessed using the Cochrane ROB2 and ROBINS-I tools. Certainty of evidence was assessed using the GRADE framework. Review Manager was used to analyse data and GRADEPro to develop summary of evidence tables. Meta-analyses were performed if  $\geq 2$  RCTs were available.

**Outcomes:** Primary: assisted ventilation. Secondary: advanced resuscitation, oxygen supplementation, adverse effects of suctioning, unanticipated NICU admission.

**Results:** Nine RCTs ( $n = 1096$ ) and 2 observational studies ( $n = 418$ ) were identified. Two RCTs ( $n = 280$ ) with data concerns were excluded post-hoc. Meta-analysis of 3 RCTs, ( $n = 702$ ) showed no difference in primary outcome. Two RCTs ( $n = 200$ ) and 2 prospective observational studies ( $n = 418$ ) found lower oxygen saturations in first 10 minutes of life with suctioning. Two RCTs ( $n = 200$ ) showed suctioned newborns took longer to achieve target saturations.

**Limitations:** Certainty of evidence was low or very low for all outcomes. Most studies selected healthy newborns limiting generalisability and insufficient data was available for planned subgroup analyses.

**Conclusions:** Despite low certainty evidence, this review suggests no clinical benefit from suctioning clear amniotic fluid from infants following birth, with some evidence suggesting a resulting desaturation. These findings support current guideline recommendations that this practice is not used as a routine step in birth.

Indian J Pediatr. 2022 Aug;89(8):793-800.

doi: 10.1007/s12098-022-04124-0. Epub 2022 Apr 9.

**[Delivery Room Respiratory Stabilization of Preterm Neonates: A Randomized, Controlled Trial](#)**

[Rajat Grover](#)<sup>1</sup>, [Poonam Singh](#)<sup>1</sup>, [Shantanu Shubham](#)<sup>1</sup>, [Mayank Priyadarshi](#)<sup>1</sup>, [Suman Chaurasia](#)<sup>1</sup>, [Sriparna Basu](#)<sup>2</sup>

**Abstract**

**Objective:** To determine whether heated humidified high-flow nasal cannula (HHHFNC) is noninferior to NCPAP to provide DR respiratory support to preterm neonates of gestational age (GA) 28-36 wk.

**Methods:** This randomized, controlled, noninferiority trial included 124 spontaneously breathing preterm neonates who developed respiratory distress soon after birth and/or had a FiO<sub>2</sub> requirement > 0.3. Primary outcome measure was treatment failure within 24 h. The absolute risk difference with 95% confidence interval (CI) were calculated with a noninferiority margin of 10%. Secondary outcome variables were temperature at admission, time to treatment failure, treatment failure at 72 h, need for surfactant, intubation, duration of respiratory support, and incidences of adverse events including mortality. Intention-to-treat analysis was done in Stata software.

**Results:** Both the groups were similar in baseline characteristics. There was no statistically significant difference between the treatment failure rates with HHHFNC (13.1%, n = 61) and NCPAP (11.1%, n = 63) (risk difference 2.0%, 95% CI - 9.9% to 14.07%, p = 0.73). However, noninferiority of HHHFNC to NCPAP could not be conclusively proved as the 95% CI crossed both 0 and the noninferiority margin of 10%. There were no significant differences in secondary outcomes.

**Conclusions:** HHHFNC showed similar efficacy and safety as NCPAP irrespective of gestational age, though its noninferiority to NCPAP remained inconclusive.

Resuscitation. 2023 May 15;109840.

doi: 10.1016/j.resuscitation.2023.109840. Online ahead of print.

**[Immediate skin-to-skin contact versus care under radiant warmer at birth in moderate to late preterm neonates - A randomized controlled trial](#)**

[Kuldeep Singh](#)<sup>1</sup>, [Deepak Chawla](#)<sup>2</sup>, [Suksham Jain](#)<sup>1</sup>, [Supreet Khurana](#)<sup>1</sup>, [Navneet Takkar](#)<sup>3</sup>

**Abstract**

**Objective:** To compare the effect of immediate care at birth in skin-to-skin contact (SSC) or under a radiant warmer on cardiorespiratory stability at 60 minutes of age in moderate-to-late preterm neonates.

**Methods:** In this open-label, parallel-group, randomized controlled trial, neonates born at 33<sup>0/7</sup> to 36<sup>6/7</sup> weeks of gestation by vaginal delivery and breathing or crying were randomized to receive care at birth in SSC (n = 50) or under a radiant warmer (n = 50). In the SSC group, immediate care at birth including drying and clearing of the airway was provided in SSC over

the mother's abdomen. SSC was maintained for an observational period of 60 minutes after birth. In the radiant warmer group, care at birth and post-birth observation was performed under an overhead radiant warmer. The primary outcome of the study was the stability of the cardio-respiratory system in late preterm infants (SCRIP) score at 60 minutes of age.

**Results:** Baseline variables were similar in the two study groups. The SCRIP score at 60 minutes of age was similar in the two study groups (median: 5.0, IQR: 5-6 vs. 5.0, 5-6). The mean axillary temperature at 60 minutes of age was significantly lower in the SSC group ( $^{\circ}\text{C}$ ;  $36.4 \pm 0.4$  vs.  $36.6 \pm 0.4$ ,  $P = 0.004$ ).

**Conclusion:** It was feasible to provide immediate care at birth in moderate and late preterm neonates while being positioned in SSC with the mother. However, in comparison to care under a radiant warmer, this did not lead to better cardiorespiratory stability at 60 minutes of age.

Am J Perinatol. 2022 Aug 30.

doi: 10.1055/a-1933-7235. Online ahead of print.

**[Providing Positive End Expiratory Pressure during Neonatal Resuscitation: A Meta-analysis](#)**

[I Bellos](#)<sup>1</sup>, [Anish Pillai](#)<sup>2</sup>, [Aakash Pandita](#)<sup>3</sup>

**Abstract**

**Objective:** To conduct a systematic review and metanalysis evaluating the effects of administering positive end-expiratory pressure (PEEP) during neonatal resuscitation at birth.

**Data sources:** Medline, Web of Science, Scopus, CENTRAL and Clinicaltrials.gov databases were systematically searched from inception to 15 December 2020.

**Study selection:** Randomized controlled trials and cohort studies were held eligible. Studies were included if they compared the administration of PEEP using either a T-piece resuscitator or a self-inflating bag with a PEEP valve with the resuscitation via a self-inflating bag without a PEEP valve.

**Data extraction and synthesis:** Data was extracted by two reviewers independently. The credibility of evidence was appraised with the Grading of Recommendations, Assessment, Development and Evaluations approach. Random-effects models were fitted to provide pooled estimates of risk ratio (RR) and 95% confidence intervals (CI).

**Results:** Overall, 10 studies were included, comprising 4,149 neonates. This included 5 RCTs, 1 quasi-randomized trial and 4 cohort studies. The administration of PEEP was associated with significantly lower rates of mortality till discharge (odds ratio-OR: 0.60, 95% confidence intervals-CI: 0.49-0.74, moderate quality of evidence). The association was significant in preterm (OR: 0.57, 95% CI: 0.46-0.69) but not in term (OR: 1.03, 95% CI: 0.52-2.02) neonates.

**Conclusions:** Providing PEEP during neonatal resuscitation associated with lower rates of mortality, in preterm neonates. Evidence regarding term neonates is limited and inconclusive. Future research is needed to determine the optimal device and shed more light on the long-term effects of PEEP administration during neonatal resuscitation

JMIR Med Educ. 2022 Sep 12;8(3):e37297.

doi: 10.2196/37297.



**Using Mobile Virtual Reality Simulation to Prepare for In-Person Helping Babies Breathe Training: Secondary Analysis of a Randomized Controlled Trial (the eHBB/mHBS Trial)**

[Beatrice Nkolika Ezenwa](#) <sup>#1</sup>, [Rachel Umoren](#) <sup>#2</sup>, [Iretiola Bamikeolu Fajolu](#) <sup>#1</sup>, [Daniel S Hippe](#) <sup>3</sup>, [Sherri Bucher](#) <sup>4</sup>, [Saptarshi Purkayastha](#) <sup>5</sup>, [Felicitas Okwako](#) <sup>6</sup>, [Fabian Esamai](#) <sup>6</sup>, [John B Feltner](#) <sup>2</sup>, [Olubukola Olawuyi](#) <sup>1</sup>, [Annet Mmboga](#) <sup>6</sup>, [Mary Concepta Nafula](#) <sup>6</sup>, [Chris Paton](#) <sup>7</sup>, [Veronica Chinyere Ezeaka](#) <sup>1</sup>

**Abstract**

**Background:** Neonatal mortality accounts for approximately 46% of global under-5 child mortality. The widespread access to mobile devices in low- and middle-income countries has enabled innovations, such as mobile virtual reality (VR), to be leveraged in simulation education for health care workers.

**Objective:** This study explores the feasibility and educational efficacy of using mobile VR for the precourse preparation of health care professionals in neonatal resuscitation training.

**Methods:** Health care professionals in obstetrics and newborn care units at 20 secondary and tertiary health care facilities in Lagos, Nigeria, and Busia, Western Kenya, who had not received training in Helping Babies Breathe (HBB) within the past 1 year were randomized to access the electronic HBB VR simulation and digitized HBB Provider's Guide (VR group) or the digitized HBB Provider's Guide only (control group). A sample size of 91 participants per group was calculated based on the main study protocol that was previously published. Participants were directed to use the electronic HBB VR simulation and digitized HBB Provider's Guide or the digitized HBB Provider's Guide alone for a minimum of 20 minutes. HBB knowledge and skills assessments were then conducted, which were immediately followed by a standard, in-person HBB training course that was led by study staff and used standard HBB evaluation tools and the Neonatalie Live manikin (Laerdal Medical).

**Results:** A total of 179 nurses and midwives participated (VR group: n=91; control group: n=88). The overall performance scores on the knowledge check (P=.29), bag and mask ventilation skills check (P=.34), and Objective Structured Clinical Examination A checklist (P=.43) were similar between groups, with low overall pass rates (6/178, 3.4% of participants). During the Objective Structured Clinical Examination A test, participants in the VR group performed better on the critical step of positioning the head and clearing the airway (VR group: 77/90, 86%; control group: 57/88, 65%; P=.002). The median percentage of ventilations that were performed via head tilt, as recorded by the Neonatalie Live manikin, was also numerically higher in the VR group (75%, IQR 9%-98%) than in the control group (62%, IQR 13%-97%), though not statistically significantly different (P=.35). Participants in the control group performed better on the identifying a helper and reviewing the emergency plan step (VR group: 7/90, 8%; control group: 16/88, 18%; P=.045) and the washing hands step (VR group: 20/90, 22%; control group: 32/88, 36%; P=.048).

**Conclusions:** The use of digital interventions, such as mobile VR simulations, may be a viable approach to precourse preparation in neonatal resuscitation training for health care professionals in low- and middle-income countries.

## Perinatal asphyxia

Eur J Pediatr. 2023 Apr 4.

doi: 10.1007/s00431-023-04950-0. Online ahead of print.

**To feed or not to feed during therapeutic hypothermia in asphyxiated neonates: a systematic review and meta-analysis**

[Jogender Kumar<sup>1</sup>](#), [Rajendra Prasad Anne<sup>2</sup>](#), [Jitendra Meena<sup>3</sup>](#), [Venkateshan Sundaram<sup>1</sup>](#), [Sourabh Dutta<sup>1</sup>](#), [Praveen Kumar<sup>4</sup>](#)

**Abstract**

The practice of withholding feed during therapeutic hypothermia (TH) in neonates with hypoxic ischemic encephalopathy (HIE) is based on conventions rather than evidence. Recent studies suggest that enteral feeding might be safe during TH. We systematically compared the benefits and harms of enteral feeding in infants undergoing TH for HIE. We searched electronic databases and trial registries (MEDLINE, CINAHL, Embase, Web of Science, and CENTRAL) until December 15, 2022, for studies comparing enteral feeding and non-feeding strategies. We performed a random-effects meta-analysis using RevMan 5.4 software. The primary outcome was the incidence of stage II/III necrotizing enterocolitis (NEC). Other outcomes included the incidence of any stage NEC, mortality, sepsis, feed intolerance, time to full enteral feeds, and hospital stay. Six studies ((two randomized controlled trials (RCTs) and four nonrandomized studies of intervention (NRSIs)) enrolling 3693 participants were included. The overall incidence of stage II/III NEC was very low (0.6%). There was no significant difference in the incidence of stage II/III NEC in RCTs (2 trials, 192 participants; RR, 1.20; 95% CI: 0.53 to 2.71,  $I^2$ , 0%) and NRSIs (3 studies, no events in either group). In the NRSIs, infants in the enteral feeding group had significantly lower sepsis rates (four studies, 3500 participants, RR, 0.59; 95% CI: 0.51 to 0.67,  $I^2$ -0%) and lower all-cause mortality (three studies, 3465 participants, RR: 0.43; 95% CI: 0.33 to 0.57,  $I^2$ -0%) than the infants in the "no feeding" group. However, no significant difference in mortality was observed in RCTs (RR: 0.70; 95% CI: 0.28 to 1.74,  $I^2$ -0%). Infants in the enteral feeding group achieved full enteral feeding earlier, had higher breastfeeding rates at discharge, received parenteral nutrition for a shorter duration, and had shorter hospital stays than the control group. Conclusion: In late preterm and term infants with HIE, enteral feeding appears safe and feasible during the cooling phase of TH. However, there is insufficient evidence to guide the timing of initiation, volume, and feed advancement.

Many neonatal units withhold enteral feeding during therapeutic hypothermia, fearing an increased risk of complications (feed intolerance and necrotizing enterocolitis).

The overall risk of necrotizing enterocolitis in late-preterm and term infants is extremely low (<1%).

Enteral feeding during therapeutic hypothermia is safe and does not increase the risk of necrotizing enterocolitis, hypoglycemia, or feed intolerance. It may reduce the incidence of sepsis and all-cause mortality until discharge.

JAMA Netw Open. 2023 May 1;6(5):e2312152.

doi: 10.1001/jamanetworkopen.2023.12152.

**Whole-Body Hypothermia, Cerebral Magnetic Resonance Biomarkers, and Outcomes in Neonates With Moderate or Severe Hypoxic-Ischemic Encephalopathy Born at Tertiary Care Centers vs Other Facilities: A Nested Study Within a Randomized Clinical Trial**

[Sudhin Thayyil<sup>1</sup>](#), [Paolo Montaldo<sup>1,2</sup>](#), [Vaisakh Krishnan<sup>1</sup>](#), [Phoebe Ivain<sup>1</sup>](#), [Stuti Pant<sup>1</sup>](#), [Peter J Lally<sup>1</sup>](#), [Prathik Bandiya<sup>3</sup>](#), [Naveen Benkappa<sup>3</sup>](#), [Chinnathambi N Kamalaratnam<sup>4</sup>](#), [Rema Chandramohan<sup>4</sup>](#), [Swati Manerkar<sup>5</sup>](#), [Jayshree Mondkar<sup>5</sup>](#), [Ismat Jahan<sup>6</sup>](#), [Sadeka C Moni<sup>6</sup>](#), [Mohammad Shahidullah<sup>6</sup>](#), [Ranmali Rodrigo<sup>7</sup>](#), [Samanmali Sumanasena<sup>7</sup>](#), [Radhika](#)

[Sujatha<sup>8</sup>](#), [Constance Burgod<sup>1</sup>](#), [Reema Garegrat<sup>1</sup>](#), [Munirah Mazlan<sup>1</sup>](#), [Ismita Chettri<sup>1</sup>](#), [Sathyanathan Babu Peter<sup>9</sup>](#), [Anagha R Joshi<sup>10</sup>](#), [Ravi Swamy<sup>1</sup>](#), [Kling Chong<sup>11</sup>](#), [Ronit R Pressler<sup>12</sup>](#), [Paul Bassett<sup>13</sup>](#), [Seetha Shankaran<sup>14</sup>](#)

## Abstract

**Importance:** The association between place of birth and hypothermic neuroprotection after hypoxic-ischemic encephalopathy (HIE) in low- and middle-income countries (LMICs) is unknown.

**Objective:** To ascertain the association between place of birth and the efficacy of whole-body hypothermia for protection against brain injury measured by magnetic resonance (MR) biomarkers among neonates born at a tertiary care center (inborn) or other facilities (outborn).

**Design, setting, and participants:** This nested cohort study within a randomized clinical trial involved neonates at 7 tertiary neonatal intensive care units in India, Sri Lanka, and Bangladesh between August 15, 2015, and February 15, 2019. A total of 408 neonates born at or after 36 weeks' gestation with moderate or severe HIE were randomized to receive whole-body hypothermia (reduction of rectal temperatures to between 33.0 °C and 34.0 °C; hypothermia group) for 72 hours or no whole-body hypothermia (rectal temperatures maintained between 36.0 °C and 37.0 °C; control group) within 6 hours of birth, with follow-up until September 27, 2020.

**Exposure:** 3T MR imaging, MR spectroscopy, and diffusion tensor imaging.

**Main outcomes and measures:** Thalamic N-acetyl aspartate (NAA) mmol/kg wet weight, thalamic lactate to NAA peak area ratios, brain injury scores, and white matter fractional anisotropy at 1 to 2 weeks and death or moderate or severe disability at 18 to 22 months.

**Results:** Among 408 neonates, the mean (SD) gestational age was 38.7 (1.3) weeks; 267 (65.4%) were male. A total of 123 neonates were inborn and 285 were outborn. Inborn neonates were smaller (mean [SD], 2.8 [0.5] kg vs 2.9 [0.4] kg;  $P = .02$ ), more likely to have instrumental or cesarean deliveries (43.1% vs 24.7%;  $P = .01$ ), and more likely to be intubated at birth (78.9% vs 29.1%;  $P = .001$ ) than outborn neonates, although the rate of severe HIE was not different (23.6% vs 17.9%;  $P = .22$ ). Magnetic resonance data from 267 neonates (80 inborn and 187 outborn) were analyzed. In the hypothermia vs control groups, the mean (SD) thalamic NAA levels were 8.04 (1.98) vs 8.31 (1.13) among inborn neonates (odds ratio [OR], -0.28; 95% CI, -1.62 to 1.07;  $P = .68$ ) and 8.03 (1.89) vs 7.99 (1.72) among outborn neonates (OR, 0.05; 95% CI, -0.62 to 0.71;  $P = .89$ ); the median (IQR) thalamic lactate to NAA peak area ratios were 0.13 (0.10-0.20) vs 0.12 (0.09-0.18) among inborn neonates (OR, 1.02; 95% CI, 0.96-1.08;  $P = .59$ ) and 0.14 (0.11-0.20) vs 0.14 (0.10-0.17) among outborn neonates (OR, 1.03; 95% CI, 0.98-1.09;  $P = .18$ ). There was no difference in brain injury scores or white matter fractional anisotropy between the hypothermia and control groups among inborn or outborn neonates. Whole-body hypothermia was not associated with reductions in death or disability, either among 123 inborn neonates (hypothermia vs control group: 34 neonates [58.6%] vs 34 [56.7%]; risk ratio, 1.03; 95% CI, 0.76-1.41), or 285 outborn neonates (hypothermia vs control group: 64 neonates [46.7%] vs 60 [43.2%]; risk ratio, 1.08; 95% CI, 0.83-1.41).

**Conclusions and relevance:** In this nested cohort study, whole-body hypothermia was not associated with reductions in brain injury after HIE among neonates in South Asia, irrespective of place of birth. These findings do not support the use of whole-body hypothermia for HIE among neonates in LMICs.

## Neonatal seizures

Eur J Pediatr. 2023 Feb 24;1-6.

doi: 10.1007/s00431-023-04864-x. Online ahead of print.

### [Comparison between Phenobarbitone and Levetiracetam as the initial anticonvulsant in preterm neonatal seizures - a pilot randomized control trial in developing country setup](#)

[Gummalla Gyandeep](#)<sup>1</sup>, [Sushree Smita Behura](#)<sup>1</sup>, [Sanjay Kumar Sahu](#)<sup>1</sup>, [Santosh Kumar Panda](#)<sup>2</sup>

#### Abstract

This study aimed to compare the efficacy and safety of intravenous Levetiracetam and Phenobarbitone in the treatment of seizures in preterm neonates. It was an open-labeled, parallel randomized controlled trial conducted in a tertiary Neonatal Intensive Care Unit, India. Total 48 preterm neonates (28-36<sup>+6</sup> weeks) with clinical seizures were randomized to receive either Levetiracetam (LEV; 40 mg/kg, then 20 mg/kg) or Phenobarbitone (PB; 15 mg/kg, then 10 mg/kg) intravenously as first loading dose in ratio 1:1; second loading was given for persistent seizure. Efficacy was denoted by cessation of clinical seizures with first or second doses of the allotted antiepileptic, and remaining seizure-free for the next 24 h. The demographic characteristics of preterm neonates and seizure types were comparable between both groups. Clinical seizure was controlled in 19 (79%) neonates in LEV group and 17 (70%) neonates in PB group, RR 1.12 (95% CI: 0.80 to 1.55),  $p = 0.504$ . There was increased respiratory support in PB group 9 (38%) vs. 3 (13%) in LEV group, RR 3.0 (95% CI: 0.92 to 9.74),  $p = 0.06$ . Conclusion: Levetiracetam and Phenobarbitone were equally efficacious for clinical neonatal seizure control, but increased respiratory support was found with Phenobarbitone use.

J Matern Fetal Neonatal Med. 2022 Oct;35(20):3923-3930.

doi: 10.1080/14767058.2020.1844651. Epub 2020 Nov 10.

### [Efficacy of Levetiracetam in neonatal seizures: a systematic review](#)

[Deepak Sharma](#)<sup>1</sup>, [Ansar Murtuza Hussain](#)<sup>2</sup>, [Sweta Shastri Sharma](#)<sup>3</sup>

#### Abstract

**Background:** Neonatal seizures represent the most frequent presenting sign of any neurological abnormality secondary to various etiologies in the neonatal period. Phenobarbitone (PB) has been used as first-line anti-epileptic drug in the treatment of seizures but concerns have been raised regarding its neuro-apoptotic effects over the developing brain. Levetiracetam (LEV) is a newer anti-epileptic drug with neuroprotective property and has been used in adults and pediatric patient but its use in neonates have very limited experience. Recently many neonatal studies have sought the role of LEV in the management of neonatal seizures.

**Aims and objective:** To evaluate the efficacy of Levetiracetam in the management of neonatal seizures.

**Search methods:** The literature search was done for this systematic review by searching the Cochrane Central Register of Controlled Trials (CENTRAL), and other various electronic databases including PubMed and various sites for ongoing trials and abstracts of conferences.

**Results:** Two eligible studies were analyzed that fulfilled the inclusion criteria of the systematic review. Fifteen studies were excluded due to the non-fulfillment of inclusion criteria. The primary outcome of both studies was to see the efficiency of LEV in controlling neonatal seizures when compared to PB. Better seizure control after a single loading dose of LEV was seen. Rates of seizure cessation at 24 h was also better in the LEV arm. Neonatal seizures secondary to hypoxic-ischemic encephalopathy (HIE) and receiving therapeutic hypothermia were better controlled with LEV. The side effect of LEV was significantly less when compared to PB.

**Conclusion:** Levetiracetam has shown to have promising anti-epileptic properties for the management of neonatal seizure with better efficacy and less or no side effects. There is a need to conduct more randomized controlled trials seeking the role of LEV in the acute management of neonatal seizures and also for assessing its neuroprotective role and neurodevelopmental outcome in these neonates.

## Neonatal sepsis

EClinicalMedicine. 2023 May 18;60:102006.

doi: 10.1016/j.eclinm.2023.102006. eCollection 2023 Jun.

### [Effect on neonatal sepsis following immediate kangaroo mother care in a newborn intensive care unit: a post-hoc analysis of a multicentre, open-label, randomised controlled trial](#)

[Sugandha Arya<sup>1</sup>](#), [Suhail Chhabra<sup>1</sup>](#), [Richa Singhal<sup>1</sup>](#), [Archana Kumari<sup>1</sup>](#), [Nitya Wadhwa<sup>2</sup>](#), [Pratima Anand<sup>1</sup>](#), [Helga Naburi<sup>3</sup>](#), [Kondwani Kawaza<sup>4</sup>](#), [Sam Newton<sup>5</sup>](#), [Ebunoluwa Adejuyigbe<sup>6</sup>](#), [Bjorn Westrup<sup>7</sup>](#), [Nils Bergman<sup>7</sup>](#), [Siren Rettedal<sup>8</sup>](#), [Agnes Linner<sup>9</sup>](#), [Rahul Chauhan<sup>1</sup>](#), [Nisha Rani<sup>1</sup>](#), [Nicole Minckas<sup>10</sup>](#), [Sachiyo Yoshida<sup>10</sup>](#), [Suman Rao<sup>10,11</sup>](#), [Harish Chellani<sup>1</sup>](#)

#### Abstract

**Background:** To implement the immediate Kangaroo mother care (iKMC) intervention in the previous multicentre, open-label, randomised controlled trial, the mother or a surrogate caregiver and neonate needed to be together continuously, which led to the concept of the Mother-Newborn Care Unit (MNCU). Health-care providers and administrators were concerned of the potential increase in infections caused by the continuous presence of mothers or surrogates in the MNCU. We aimed to assess the incidence of neonatal sepsis in sub-groups and the bacterial profile among intervention and control neonates in the study population.

**Methods:** This is a post-hoc analysis of the previous iKMC trial, which was conducted in five level 2 Newborn Intensive Care Units (NICUs) one each in Ghana, India, Malawi, Nigeria, and Tanzania, in neonates with birth weight 1 to <1.8 kg. The intervention was KMC initiated immediately after birth and continued until discharge and compared to conventional care with KMC initiated after meeting stability criteria. The primary outcomes of this report were the incidence of neonatal sepsis in sub-groups, sepsis-related mortality and bacterial profile

of isolates during hospital stay. The original trial is registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12618001880235) and the Clinical Trials Registry-India (CTRI/2018/08/01536).

**Findings:** Between November 30, 2017, and January 20, 2020, 1609 newborns in the intervention group and in the control group 1602 newborns were enrolled in iKMC study. 1575 newborns in the intervention group and 1561 in the control group were clinically evaluated for sepsis. Suspected sepsis was 14% lower in intervention group in sub-group of neonates with birth weight 1.0-<1.5 kg; RR 0.86 (CI 0.75, 0.99). Among neonates with birth weight 1.5-<1.8 kg, suspected sepsis was reduced by 24%; RR 0.76 (CI 0.62, 0.93). Suspected sepsis rates were lower in intervention group than in the control group across all sites. Sepsis related mortality was 37% less in intervention group than the control group; RR 0.63 (CI 0.47-0.85) which was statistically significant. The intervention group had fewer cases of Gram-negative isolates (n = 9) than Gram positive isolates (n = 16). The control group had more cases of Gram-negative isolates (n = 18) than Gram positive (n = 12).

**Interpretation:** Immediate Kangaroo Mother care is an effective intervention to prevent neonatal sepsis and sepsis related mortality.

## Jaundice

J Matern Fetal Neonatal Med. 2022 Nov;35(21):4075-4080.

doi: 10.1080/14767058.2020.1846705. Epub 2020 Nov 22.

### [The effect of ursodeoxycholic acid on indirect hyperbilirubinemia in neonates treated with phototherapy: a randomized clinical trial](#)

[Rona Akefi](#)<sup>1</sup>, [Seyed Mojtaba Hashemi](#)<sup>2</sup>, [Saeed Alinejad](#)<sup>2</sup>, [Amir Almasi-Hashiani](#)<sup>3</sup>

#### Abstract

**Objectives:** Indirect hyperbilirubinemia during neonatal period is a common problem, and most preterm and more than half of the term neonates find this problem. Ursodeoxycholic acid (UDCA) protects the liver against oxidative stresses and prevents cellular apoptosis. In addition, it causes stimulation of bile flow, is well tolerated by the patient, and has limited side effects. Thus, the aim of this study was to investigate the effect of UDCA in treating neonates with unconjugated hyperbilirubinemia undergoing phototherapy.

**Methods:** In this randomized clinical trial, 220 neonates with unconjugated hyperbilirubinemia who referred to Amir-Kabir Hospital, Arak, Iran in 2017-2018, were randomly assigned to phototherapy group (Control group) and phototherapy plus UDCA group (Intervention group) as 10 mg/kg/day. The level of total bilirubin was measured at the baseline, and after 12, and 24 h using spectrophotometric, and the duration of receiving phototherapy was also measured in both groups.

**Results:** The mean age of included neonates in the control and intervention group was 5.3 and 4.9 days, respectively. The results revealed that after 12 h of treatment, the total bilirubin level in the control group had diminished by 2.70 mg/dL on average while, in the intervention group, the reduction was 3.7 md/dL ( $p = .001$ ) and after 24 h of treatment, the total bilirubin level in the control group had diminished by 5.22 mg/dL on average and in the intervention group, the reduction was 6.54 md/dL ( $p = .001$ ). It was also observed that there



is no significant difference between groups in terms of the mean of the duration required for phototherapy ( $p = .63$ ).

**Conclusions:** UDCA combined with phototherapy enhances TSB decrease, but this effect is not relevant from a clinical point of view because it does not decrease phototherapy and hospital stay duration. Thus, this study does not support the UDCA use in the clinical practice.

## Nutrition

(see also Anaemia and iron deficiency, Zinc, Maternal nutrition, Vitamin A, Tuberculosis, Helminths and other gastrointestinal infections, HIV case management)

### Nutrition assessment and education

BMC Nutr. 2022 Oct 31;8(1):125.

doi: 10.1186/s40795-022-00618-4.

#### [Validation of a new scoring approach of a child dietary questionnaire for use in early childhood among low-income, Latino populations](#)

[Laura E Adams](#)<sup>1</sup>, [Evan C Sommer](#)<sup>1</sup>, [Kimberly P Truesdale](#)<sup>2</sup>, [Shari L Barkin](#)<sup>1</sup>, [William J Heerman](#)<sup>3</sup>

#### Abstract

**Background:** Measuring diet quality in early childhood requires time-intensive and costly measurements (e.g., 24-hour diet recall) that are especially burdensome for low-income, minority populations. This study aimed to validate a new method for calculating overall diet quality among low-income, Latino preschoolers.

**Methods:** This study was an observational study using data from a randomized controlled trial. Participants included parents of Latino preschoolers who reported child diet quality at baseline, 4-month, 7-month, 12-month, and 13-month follow-up. At each timepoint parents responded to a 28-item child dietary questionnaire (CDQ), based on the National Health and Nutrition Examination Survey (NHANES) dietary module, which generated the number of times/day that a child ate each of 28 foods in the past month. These 28 items were then used to create a total standardized child diet quality index (possible range 0-100), using a percent of maximum method. Parents were asked to complete three 24-hour diet recalls at the 13-month follow-up, from which the 2015 Healthy Eating Index (HEI) was derived. Construct validity was evaluated by Spearman's rank correlations between the new child diet quality index and the 2015 HEI at the 13-month follow-up. Test-retest reliability was assessed by intraclass correlation coefficients (ICC) for sequential pairs of time points.

**Results:** Among 71 eligible parent-child pairs, mean child age was 4.2 (SD = 0.8) years, 50.7% of children were female, and mean child body mass index (BMI) was 17.8 (SD = 2.0) kg/m<sup>2</sup>. Mean Child Diet Quality Index was 45.2 (SD = 3.2) and mean HEI was 68.4 (SD = 10.5). Child Diet Quality Index and HEI total scores were significantly correlated ( $r = 0.37$ ;  $p = 0.001$ ). Test-retest ICCs were statistically significant between all sequential pairs of time points.

**Conclusion:** The new approach for calculating a measure of overall diet quality from the previously-validated 28-item dietary questionnaire demonstrated modest construct validity.

When time and resources are limited, this new measure of overall diet quality may be an appropriate choice among low-income, Latino preschoolers.

PLoS One. 2022 Dec 8;17(12):e0277137.

doi: 10.1371/journal.pone.0277137. eCollection 2022.

**[Impacts of a social and behavior change communication program implemented at scale on infant and young feeding practices in Nigeria: Results of a cluster-randomized evaluation](#)**

[Valerie L Flax](#)<sup>1</sup>, [Mariam Fagbemi](#)<sup>2</sup>, [Courtney H Schnefke](#)<sup>1</sup>, [Auwalu A Kawu](#)<sup>3</sup>, [Susan Edwards](#)<sup>1</sup>, [Jennifer Unangst](#)<sup>1</sup>, [Sujata Bose](#)<sup>4</sup>

**Abstract**

**Background:** Infant and young child feeding (IYCF) practices are important for child survival and healthy growth, but IYCF practices remain suboptimal in Nigeria. The objective of this study was to measure the impact of Alive & Thrive's IYCF social and behavior change communication intervention on early initiation of breastfeeding, exclusive breastfeeding, and minimum dietary diversity in Kaduna and Lagos States.

**Methods:** Local government areas were randomly allocated to intervention or comparison. Cross-sectional surveys of households with children aged 0-23 months were conducted [N = 6,266 baseline (2017), N = 7,320 endline (2020)]. Logistic regression was used to calculate difference-in-differences estimates (DDEs) of impact on IYCF practices and to assess within group changes from baseline to endline. Associations between intervention exposures and IYCF practices were tested in both study groups combined.

**Results:** In Kaduna, a positive differential effect of the intervention was found for exclusive breastfeeding (adjusted DDE 8.9 pp, P<0.099). Increases in both study groups from baseline to endline were observed in Kaduna for early initiation of breastfeeding (intervention 12.2 pp, P = 0.010; comparison 6.4 pp, P = 0.118) and minimum dietary diversity (intervention 20.0 pp, P<0.001; comparison 19.7 pp, P<0.001), which eliminated differential effects. In Lagos, no differential intervention impacts were found on IYCF practices because changes in early initiation of breastfeeding from baseline to endline were small in both study groups and increases in both study groups from baseline to endline were observed for exclusive breastfeeding (intervention 8.9 pp, P = 0.05; comparison 6.6 pp, P<0.001) and minimum dietary diversity (intervention 18.9 pp, P<0.001; comparison 24.3 pp, P<0.001). Odds of all three IYCF practices increased with exposure to facility-based interpersonal communication in both states and with community mobilization or mass media exposure in Kaduna.

**Conclusions:** This evaluation found weak impacts of the Alive & Thrive intervention on IYCF practices in the difference-in-differences analysis because of suspected intervention spillover to the comparison group. Substantial within group increases in IYCF practices from baseline to endline are likely attributable to the intervention, which was the major IYCF promotion activity in both states. This is supported by the association between intervention exposures and IYCF practices.

doi: 10.1002/fsn3.2960. eCollection 2022 Nov.

**[Using preschoolers to improve caregivers' knowledge, attitude, and practices relating to biofortified crops: Evidence from a randomized nutrition education trial in Kenya](#)**

[Sylvester Okoth Ojwang'<sup>1,2</sup>](#), [Julius Juma Okello<sup>3</sup>](#), [David Jakinda Otieno<sup>1</sup>](#), [Rose Adhiambo Nyikal<sup>1</sup>](#), [Penina Ngusye Muoki<sup>2,4</sup>](#)

**Abstract**

This 2018 randomized controlled trial examined the role behavioral nudges can play in improving caregivers' knowledge, attitude, and practices (KAP) relating to biofortified orange-fleshed sweetpotato (OFSP). The experiment involved 431 preschooler-caregiver pairs in 15 villages. The preschoolers were enrolled in public-run Early Childhood Development and Education (ECDE) centers in the respective villages. Caregivers were first exposed to the routine OFSP promotion activities in the area - invited to cooking demonstration workshops and issued with free OFSP vines to plant. A baseline survey followed. Next, the 15 villages were randomized into four study groups (a control and three treatments). The interventions were deployed for 30 days as follows: Treatment 1 - preschoolers issued OFSP-branded exercise books, class posters, and poems; Treatment 2 - caregivers received phone-mediated text messages; and Treatment 3 - received the full suite of interventions. This study analyzed the endline and baseline data and finds that, in general, changes in KAP scores were negatively associated with control group ( $p = .005$ ) and positively associated with Treatment 3 ( $p = .02$ ). Specifically, Treatment 3 significantly increased caregivers' knowledge of OFSP production, consumption, and vitamin A. Treatment 2 significantly improved their attitude too. It concludes that an integrated complementary nutrition education approach targeting preschooler-caregiver pairs is more effective in increasing knowledge of cultivation and consumption of OFSP. It discusses the implications for the design of more effective nutrition programs targeting households with preschoolers to accelerate the fight against vitamin A deficiency (VAD).

Nutrients. 2022 Jul 29;14(15):3128.

doi: 10.3390/nu14153128.

**[Front-of-Package Labels on Unhealthy Packaged Foods in India: Evidence from a Randomized Field Experiment](#)**

[S K Singh<sup>1</sup>](#), [Lindsey Smith Taillie<sup>2</sup>](#), [Ashish Gupta<sup>3</sup>](#), [Maxime Bercholz<sup>4</sup>](#), [Barry Popkin<sup>2</sup>](#), [Nandita Murukutla<sup>3</sup>](#)

**Abstract**

Policies to require front-of-package labels (FOPLs) on packaged foods may help Indian consumers to better identify foods high in nutrients of concern, including sugar, saturated fat, and sodium, and discourage their consumption, which are outcomes that are critical for preventing rises in diet-related non-communicable disease. The objective was to test whether FOPLs helped Indian consumers identify "high-in" packaged foods and reduce intentions to purchase them. We conducted an in-person randomized experiment ( $n = 2869$  adults between ages 18 and 60 years old) in six states of India in 2022. Participants were randomized to one of five FOPLs: a control label (barcode), warning label (octagon with "High in [nutrient]"), Health Star Rating (HSR), Guideline Daily Amount (GDA), or traffic light label. Participants then viewed a series of packaged foods high in sugar, saturated fat, or sodium with the assigned FOPL, and rated product perceptions and label reactions. Fewer than half of participants in the control group (39.1%) correctly identified all products high in

nutrient(s) of concern. All FOPLs led to an increase in this outcome, with the biggest differences observed for the warning label (60.8%,  $p < 0.001$ ), followed by the traffic light label (54.8%,  $p < 0.001$ ), GDA (55.0%,  $p < 0.001$ ), and HSR (45.0%,  $p < 0.01$ ). While no FOPLs led to a reduction in intentions to purchase the packaged foods, the overall pattern of results suggested that warning labels are the most effective FOPL to help Indian consumers identify unhealthy foods.

Matern Child Nutr. 2023 Apr;19(2):e13460.

doi: 10.1111/mcn.13460. Epub 2022 Dec 8.

**[Engaging men in maternal, infant and young child nutrition in rural Tanzania: Outcomes from a cluster randomized control trial and qualitative study](#)**

[Jessica D Rothstein](#)<sup>1,2</sup>, [Rolf D W Klemm](#)<sup>1,3</sup>, [Yunhee Kang](#)<sup>3</sup>, [Debora Niyeha](#)<sup>4</sup>, [Erin Smith](#)<sup>5</sup>, [Stella Nordhagen](#)<sup>6</sup>

**Abstract**

There is growing recognition that engaging men in maternal, infant and young child nutrition (MIYCN) interventions can benefit child health and disrupt harmful gender norms. We conducted a cluster-randomized controlled trial in Tanzania, which engaged men and women in behaviour change via mobile messaging (short message service [SMS]) and traditional interpersonal communication (IPC), separately and in combination. Here, we evaluate intervention effects on individual-level men's MIYCN knowledge and discuss barriers to male engagement. Eligible clusters were dispensary catchment areas with >3000 residents. Forty clusters were stratified by population size and randomly allocated to the four study arms, with 10 clusters per arm. Data on knowledge and intervention exposure were collected from 1394 men through baseline and endline surveys (March-April 2018 and July-September 2019). A process evaluation conducted partway through the 15-18-month intervention period included focus group discussions and interviews. Data were analysed for key trends and themes using Stata and ATLAS.ti software. Male participants in the short message service + interpersonal communication (SMS + IPC) group reported higher exposure to IPC discussions than IPC-only men (43.8% and 21.9%, respectively). Knowledge scores increased significantly across all three intervention groups, with the greatest impact in the SMS + IPC group. Qualitative findings indicated that the main barriers to male participation were a lack of interest in health/nutrition and perceptions that these topics were a woman's responsibility. Other challenges included meeting logistics, prioritizing income-earning activities and insufficient efforts to engage men. The use of a combined approach fusing IPC with SMS is promising, yet countering gender norms and encouraging stronger male engagement may require additional strategies.

## Growth monitoring

Am J Public Health. 2023 Jan;113(1):105-114.

doi: 10.2105/AJPH.2022.307111.

**[A Community Health Worker-Based Intervention on Anthropometric Outcomes of Children Aged 3 to 21 Months in Urban Pakistan, 2019-2021](#)**

[Abu S Shonchoy<sup>1</sup>](#), [Agha A Akram<sup>1</sup>](#), [Mahrukh Khan<sup>1</sup>](#), [Hina Khalid<sup>1</sup>](#), [Sidra Mazhar<sup>1</sup>](#), [Akib Khan<sup>1</sup>](#), [Takashi Kurosaki<sup>1</sup>](#)

## Abstract

**Objectives.** To evaluate the impact of a community health worker-based "in-home growth monitoring with counseling" (IHGMC) intervention on anthropometric outcomes in Pakistan, where 38% of children younger than 5 years are stunted. **Methods.** We used an individual, single-blind, step-wedge randomized controlled trial and a pure control group recruited at endline. We based the analysis on an intention-to-treat estimation using the coarsened exact matching (CEM) method for sample selection among treatments and the control. We conducted the baseline in July 2019 and completed endline in September-October 2021. We recruited 1639 households (treated: 1188; control: 451) with children aged 3 to 21 months who were residing in an urban informal settlement area. The CEM sample used for analysis numbered 1046 (treated: 636; control: 410). The intervention continued for 6 months. **Results.** Compared with the control group, the height-for-age z-score in the IHGMC group increased by 0.58 SD (95% confidence interval [CI] = 0.33, 0.83;  $P = .001$ ) and the weight-for-age z-score by 0.43 SD (95% CI = 0.20, 0.67;  $P < .01$ ), measured at endline. **Conclusions.** IHGMC substantially improved child anthropometric outcomes in disadvantaged localities, and this impact persisted during the COVID-19 pandemic.

## Micronutrients, multivitamins, and food fortification

(See also Vitamin A, Vitamin D)

Br J Nutr. 2022 Jul 25;1-22.

doi: 10.1017/S0007114522002343. Online ahead of print.

### [Vitamin B12 and/or folic acid supplementation on linear growth; a 6 years follow-up study of a randomised controlled trial in early childhood in North India](#)

[Sunita Taneja<sup>1</sup>](#), [Ranadip Chowdhury<sup>1</sup>](#), [Ingrid Kvestad<sup>2,3</sup>](#), [Nita Bhandari<sup>1</sup>](#), [Tor A Strand<sup>3</sup>](#)

## Abstract

Folate and vitamin B12 are essential for growth. Our objective was to estimate their long-term effects on linear growth in North Indian children. This is a follow-up study of a factorial designed, double-blind, randomized placebo-controlled trial in 1,000 young children. Starting at 6-30 months of age, we gave folic acid (~2 RDAs), vitamin B12 (~2 RDAs), both vitamins, or a placebo daily for six months. Six years after the end of supplementation, we measured height in 791 children. We used the plasma concentrations of cobalamin, folate, and total homocysteine to estimate vitamin status. The effect of the interventions, the association between height-for-age z-scores (HAZ) and baseline vitamin status, and the interactions between supplementation and baseline status were estimated in multiple regression models. Mean (SD) age at follow-up was 7.4 (0.7) years (range 6 to 9 years). There was a small, non-significant effect of vitamin B12 on linear growth and no effect of folic acid. We observed a subgroup-effect of vitamin B12 supplementation in those with plasma cobalamin concentration < 200 pmol/L ( $P$  interaction = 0.01). The effect of vitamin B12 supplementation in this group was 0.34 HAZ (95% CI: 0.11-0.58). We found an association between cobalamin status and HAZ in children not given vitamin B12 ( $P$  interaction = 0.001).

In this group, each doubling of the cobalamin concentration was associated with 0.26 (95% CI: 0.15 to 0.38) higher HAZ. Suboptimal B12 status in early childhood seemingly limits linear growth in North Indian Children.

J Nutr. 2023 Mar 6;S0022-3166(23)35282-9.

doi: 10.1016/j.tjnut.2023.03.003. Online ahead of print.

**Daily folic acid and/or vitamin B12 supplementation between 6 to 30 months of age and cardiometabolic risk markers after 6 to 7 years, a follow-up of a randomized controlled trial**

[Rukman Manapurath<sup>1</sup>](#), [Tor A Strand<sup>2</sup>](#), [Ranadip Chowdhury<sup>3</sup>](#), [Ingrid Kvestad<sup>4</sup>](#), [Chittaranjan S Yajnik<sup>5</sup>](#), [Nita Bhandari<sup>3</sup>](#), [Sunita Taneja<sup>3</sup>](#)

**Abstract**

**Background:** Deficiencies of vitamin B12 and folate are associated with elevated levels of metabolic markers related to cardiovascular diseases.

**Objectives:** We investigated the effect of supplementation of vitamin B12 with or without folic acid for six months in early childhood on cardio-metabolic risk markers after 6 to 7 years.

**Design:** This is a follow-up study of a 2X2 factorial, double-blind, randomized controlled trial of vitamin B12 and/or folic acid supplementation in 6 to 30 months old children. The supplement contained 1.8 µg of vitamin B12 or 150 µg of folic acid or both, constituting more than one adequate intake or recommended daily allowances for a period of 6 months. Enrolled children were contacted again after 6 years (September 2016 to November 2017), and plasma concentrations of total homocysteine (tHcy), leptin, high molecular weight adiponectin, and total adiponectin were measured (N=791).

**Results:** At baseline, 32% of children had a deficiency of either vitamin B12 (<200 pmol/L) or folate (<7.5 nmol/L). Combined supplementation of vitamin B12 and folic acid resulted in 1.19 µmol/L (95% confidence interval: 0.09, 2.30 µmol/L) lower tHcy concentration 6 years later compared to placebo. We also found that vitamin B12 supplementation was associated with a lower leptin adiponectin ratio in subgroups based on their nutritional status.

**Conclusions:** Supplementation with vitamin B12 and folic acid in early childhood was associated with a decrease in plasma tHcy levels after 6 years. The results from our study provide some evidence of persistent beneficial metabolic effects of vitamin B12 and folic acid supplementation in impoverished populations.

Eur J Nutr. 2022 Oct;61(7):3423-3435.

doi: 10.1007/s00394-022-02890-3. Epub 2022 May 9.

**Daily supplementation of a multiple micronutrient powder improves folate but not thiamine, riboflavin, or vitamin B<sub>12</sub> status among young Laotian children: a randomized controlled trial**

[Guy-Marino Hinnouho<sup>1,2</sup>](#), [Daniela Hampel<sup>3,4</sup>](#), [Setareh Shahab-Ferdows<sup>4</sup>](#), [Maxwell A Barffour<sup>3,5,6</sup>](#), [Liadhan McAnena<sup>7</sup>](#), [Charles D Arnold<sup>3</sup>](#), [K Ryan Wessells<sup>3</sup>](#), [Sengchanh Kounnavong<sup>8</sup>](#), [Lindsay H Allen<sup>3,4</sup>](#), [Helene McNulty<sup>7</sup>](#), [Sonja Y Hess<sup>3</sup>](#)

**Abstract**



**Purpose:** To assess the effects of intervention with a daily multiple micronutrient powder (MNP) on thiamine, riboflavin, folate, and B<sub>12</sub> status among young Laotian children.

**Methods:** Children (n = 1704) aged 6-23 mo, participating in a double-blind placebo-controlled randomized trial were individually randomized to receive daily either MNP (containing 0.5 mg of thiamine, 0.5 mg riboflavin, 150 µg folic acid, and 0.9 µg vitamin B<sub>12</sub> along with 11 other micronutrients) or placebo and followed for ~ 36 weeks. In a randomly selected sub-sample of 260 children, erythrocyte thiamine diphosphate (eThDP), plasma folate and B<sub>12</sub> concentrations, and erythrocyte glutathione reductase activation coefficient (EGRac; riboflavin biomarker) were assessed at baseline and endline.

**Results:** There was no treatment effect on endline eThDP concentrations (110.6 ± 8.9 nmol/L in MNP vs. 109.4 ± 8.9 nmol/L in placebo group; p = 0.924), EGRac (1.46 ± 0.3 vs. 1.49 ± 0.3; p = 0.184) and B<sub>12</sub> concentrations (523.3 ± 24.6 pmol/L vs. 515.9 ± 24.8 pmol/L; p = 0.678). Likewise, the prevalence of thiamine, riboflavin, and B<sub>12</sub> deficiencies did not differ significantly between the two groups. However, endline folate concentration was significantly higher in the MNP compared to the placebo group (28.2 ± 0.8 nmol/L vs 19.9 ± 0.8 nmol/L, respectively; p < 0.001), and correspondingly, the prevalence of folate deficiency was significantly lower in the MNP group (1.6% vs 17.4%; p = 0.015).

**Conclusions:** Compared to a placebo, daily MNP for 9 months increased only folate but not thiamine, riboflavin, or B<sub>12</sub> status in young Laotian children.

Int J Epidemiol. 2022 Dec 13;51(6):1761-1774.

doi: 10.1093/ije/dyab117.

[Effects of prenatal and postnatal maternal multiple micronutrient supplementation on child growth and morbidity in Tanzania: a double-blind, randomized-controlled trial](#)

[Dongqing Wang](#)<sup>1</sup>, [Uma Chandra Mouli Natchu](#)<sup>2</sup>, [Anne Marie Darling](#)<sup>1</sup>, [Ramadhani A Noor](#)<sup>3</sup>, [Ellen Hertzmark](#)<sup>1</sup>, [Willy Urassa](#)<sup>4</sup>, [Wafaie W Fawzi](#)<sup>1,5,6</sup>

#### Abstract

**Background:** Maternal micronutrient status is critical for child growth and nutrition. It is unclear whether maternal multiple micronutrient supplementation (MMS) during pregnancy and lactation improves child growth and prevents child morbidity.

**Methods:** This study aimed to determine the effects of prenatal and postnatal maternal MMS on child growth and morbidity. In this double-blind, randomized-controlled trial, 8428 HIV-negative pregnant women were enrolled from Dar es Salaam, Tanzania, between 2001 and 2004. From pregnancy (12-27 weeks of gestation) through to 6 weeks postpartum, participants were randomized to receive daily oral MMS or placebo. All women received daily iron and folic acid during pregnancy. From 6 weeks postpartum through to 18 months postpartum, 3100 women were re-randomized to MMS or placebo. Child-growth measures, haemoglobin concentrations and infectious morbidities were assessed longitudinally from birth to ≤18 months.

**Results:** Prenatal MMS led to modest increases in weight-for-age z-scores (mean difference: 0.050; 95% confidence interval: 0.002, 0.099; p = 0.04) and length-for-age z-score (mean difference: 0.062; 95% confidence interval: 0.013, 0.111; p = 0.01) during the first 6 months of life but not thereafter. Prenatal or postnatal MMS did not have benefits for other child outcomes.

**Conclusions:** Whereas maternal MMS is a proven strategy to prevent adverse birth outcomes, other approaches may also need to be considered to curb the high burdens of child morbidity and growth faltering.

Wellcome Open Res. 2023 Feb 20;5:238.

doi: 10.12688/wellcomeopenres.16282.2. eCollection 2020.

[\*\*Acknowledging the gap: a systematic review of micronutrient supplementation in infants under six months of age\*\*](#)

[Isabella Stelle<sup>1</sup>](#), [Sruthi Venkatesan<sup>1</sup>](#), [Karen Edmond<sup>1</sup>](#), [Sophie E Moore<sup>1,2</sup>](#)

**Abstract**

**Background:** Micronutrient deficiencies remain common worldwide, but the consequences to growth and development in early infancy (under six months of age) are not fully understood. We present a systematic review of micronutrient interventions in term infants under six months of age, with a specific focus on iron supplementation. **Methods:** We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid) and Embase (Ovid) from January 1980 through December 2019. Interventions included iron or multiple micronutrients (MMNs). **Results:** Of 11,109 records identified, 33 publications from 24 trials were included (19 iron and five MMN supplementation trials). All but one trial (evaluating only morbidity and mortality) evaluated the effect of supplementation on biochemical outcomes, ten reported on growth, 15 on morbidity and/or mortality and six on neuro-behavioural development. Low- and middle- income countries made up 88% (22/25) of the total trial locations. Meta-analysis was not possible due to extensive heterogeneity in both exposure and outcome measures. However, these trials indicated that infants less than six months of age benefit biochemically from early supplementation with iron, but the effect of additional nutrients or MMNs, along with the impacts on growth, morbidity and/or mortality, and neuro-behavioural outcomes remain unclear. **Conclusions:** Infants less than six months of age appear to benefit biochemically from micronutrient supplementation. However, well-powered randomised controlled trials are required to determine whether routine supplementation with iron or MMNs containing iron should commence before six months of life in exclusively breast-fed infants in low-resource settings.

## Lipid-based nutrition supplements

Matern Child Nutr. 2022 Jul;18(3):e13331.

doi: 10.1111/mcn.13331. Epub 2022 Feb 7.

[\*\*Provision of small-quantity lipid-based nutrient supplements does not improve intestinal health among rural Malawian children\*\*](#)

[Zhifei Liu<sup>1</sup>](#), [Ulla Ashorn<sup>1</sup>](#), [Chilungamo Chingwanda<sup>2</sup>](#), [Kenneth Maleta<sup>2</sup>](#), [Lotta Hallamaa<sup>1</sup>](#), [Andrew Matchado<sup>2</sup>](#), [Emma Kortekangas<sup>1</sup>](#), [Kathryn G Dewey<sup>3</sup>](#), [Per Ashorn<sup>1,4</sup>](#), [Yue-Mei Fan<sup>1</sup>](#)

**Abstract**

Lipid-based nutrient supplements (LNS) have been found to improve child growth and reduce child mortality. However, the mechanistic pathways for these improvements warrant

exploration. One potential pathway is linked to improvement in intestinal health. Our study aimed to test a hypothesis that small-quantity LNS (SQ-LNS) could reduce the levels of intestinal inflammation, repair and permeability of children. As intestinal health markers we measured fecal calprotectin, regenerating 1B protein (REG1B) and alpha-1-antitrypsin concentrations at 18 months of age (after 12 months of supplementation) and 1 year later (12 months after cessation of supplementation). In this analysis, we included data of 735 children who participated in a randomised dietary supplementation trial in rural Malawi; 243 children who received 20 g/day SQ-LNS from 6 to 18 months of age were in the SQ-LNS group, while the others who received no dietary supplementation during this period were in the control group. At 18 months of age, the mean concentrations of calprotectin, REG1B and alpha-1-antitrypsin were 241, 105 µg/g and 7.1 mg/dl, respectively, in the SQ-LNS group, and 224, 105 µg/g and 7.4 mg/dl, respectively, in the control group, and did not differ between the SQ-LNS and control groups. We conclude that SQ-LNS provision did not have an impact on children's intestinal health in rural Malawi.

Am J Clin Nutr. 2022 Aug 31;nqac232.

doi: 10.1093/ajcn/nqac232. Online ahead of print.

**[Preventive small-quantity lipid-based nutrient supplements reduce severe wasting and severe stunting among young children: an individual participant data meta-analysis of randomized controlled trials](#)**

[Kathryn G Dewey](#)<sup>1</sup>, [Charles D Arnold](#)<sup>1</sup>, [K Ryan Wessells](#)<sup>1</sup>, [Elizabeth L Prado](#)<sup>1</sup>, [Souheila Abbeddou](#)<sup>2</sup>, [Seth Adu-Afarwuah](#)<sup>3</sup>, [Hasmot Ali](#)<sup>4</sup>, [Benjamin F Arnold](#)<sup>5</sup>, [Per Ashorn](#)<sup>6,7</sup>, [Ulla Ashorn](#)<sup>6</sup>, [Sania Ashraf](#)<sup>8</sup>, [Elodie Becquey](#)<sup>9</sup>, [Kenneth H Brown](#)<sup>1,10</sup>, [Parul Christian](#)<sup>11</sup>, [John M Colford](#)<sup>12</sup>, [Sherlie J L Duliencie](#)<sup>13</sup>, [Lia C H Fernald](#)<sup>12</sup>, [Emanuela Galasso](#)<sup>14</sup>, [Lotta Hallamaa](#)<sup>6,9</sup>, [Sonja Y Hess](#)<sup>1</sup>, [Jean H Humphrey](#)<sup>11,15</sup>, [Lieven Huybregts](#)<sup>9</sup>, [Lora L Iannottie](#)<sup>13</sup>, [Kaniz Jannat](#)<sup>16</sup>, [Anna Lartey](#)<sup>3</sup>, [Agnes Le Port](#)<sup>17</sup>, [Jef L Leroy](#)<sup>9</sup>, [Stephen P Luby](#)<sup>18</sup>, [Kenneth Maleta](#)<sup>19</sup>, [Susana L Matias](#)<sup>20</sup>, [Mduduzi N N Mbuya](#)<sup>15,21,22</sup>, [Malay K Mridha](#)<sup>21</sup>, [Minyanga Nkhoma](#)<sup>19</sup>, [Clair Null](#)<sup>23</sup>, [Rina R Paul](#)<sup>21</sup>, [Harriet Okronipa](#)<sup>24</sup>, [Jean-Bosco Ouédraogo](#)<sup>25</sup>, [Amy J Pickering](#)<sup>26</sup>, [Andrew J Prendergast](#)<sup>15,27</sup>, [Marie Ruel](#)<sup>9</sup>, [Saijuddin Shaikh](#)<sup>4</sup>, [Ann M Weber](#)<sup>28</sup>, [Patricia Wolff](#)<sup>29</sup>, [Amanda Zongrone](#)<sup>30</sup>, [Christine P Stewart](#)<sup>1</sup>

**Abstract**

**Background:** Meta-analyses show that small-quantity lipid-based nutrient supplements (SQ-LNS) reduce child wasting and stunting. There is little information regarding effects on severe wasting or stunting.

**Objective:** We aimed to identify the effect of SQ-LNS on prevalence of severe wasting (weight-for-length z-score < -3) and severe stunting (length-for-age z-score < -3).

**Methods:** We conducted a two-stage meta-analysis of individual participant data from 14 randomized controlled trials of SQ-LNS provided to children 6 to 24 mo of age. We generated study-specific and subgroup estimates of SQ-LNS vs. control and pooled the estimates using fixed-effects models. We used random effects meta-regression to examine study-level effect modifiers. In sensitivity analyses, we examined whether results differed depending on study arm inclusion criteria and types of comparisons.

**Results:** SQ-LNS provision led to a relative reduction of 31% in severe wasting (Prevalence Ratio, PR 0.69 (0.55, 0.86), n=34,373) and 17% in severe stunting (PR 0.83 (95% CI: 0.78, 0.90), n=36,795) at endline. Results were similar in most of the sensitivity analyses but somewhat

attenuated when comparisons using passive control arms were excluded: PR 0.74 (0.57, 0.96), n=26,327 for severe wasting and PR 0.88 (0.81, 0.95), n=28,742 for severe stunting. Study-level characteristics generally did not significantly modify the effects of SQ-LNS, but results suggested greater effects of SQ-LNS in sites with greater burdens of wasting or stunting, or with poorer water quality or sanitation.

**Conclusions:** Including SQ-LNS in preventive interventions to promote healthy child growth and development is likely to reduce rates of severe wasting and stunting

## Macronutrient nutrition and complementary feeding

(See also Vitamin A)

J Nutr. 2023 Feb 16;S0022-3166(23)09593-7.

doi: 10.1016/j.tjnut.2023.02.004. Online ahead of print.

### [An Egg Intervention Improves Dietary Intakes but Does Not Fill Intake Gaps for Multiple Micronutrients among Infants in Rural Bangladesh](#)

[Monica M Pasqualino](#)<sup>1</sup>, [Saijuddin Shaikh](#)<sup>2</sup>, [John McGready](#)<sup>3</sup>, [Md Tanvir Islam](#)<sup>2</sup>, [Hasmot Ali](#)<sup>2</sup>, [Tahmeed Ahmed](#)<sup>4</sup>, [Keith P West Jr](#)<sup>5</sup>, [Munirul Alam](#)<sup>4</sup>, [Md Iqbal Hossain](#)<sup>4</sup>, [Alain B Labrique](#)<sup>3</sup>, [Amanda C Palmer](#)<sup>3</sup>

#### Abstract

**Background:** Eggs are nutrient-rich. Strengthening evidence of the impact of egg consumption on dietary quality can inform complementary feeding guidance.

**Objectives:** We aimed to assess the effect of an egg intervention on dietary intakes among infants aged 6-12 mo in rural Bangladesh.

**Methods:** We conducted a cluster-randomized controlled trial allocating clusters (n = 566) to enteric pathogen control or placebo treatment, with daily provision of a protein-rich meal, isocaloric meal, egg, or control. Nutrition education was provided to all arms. Our focus here is on the egg and control arms. Infants were enrolled at 3 mo. From 6 mo, we visited households weekly to distribute eggs and measure compliance. A semistructured feeding questionnaire assessed 24-h intake at 6, 9, and 12 mo. Assessments were repeated in ~10% of subjects 2-29 d later. Using NCI SAS macros, we estimated usual intake distributions for energy, protein, fat, and 18 micronutrients and the proportion meeting intake recommendations. We compared the outcomes between the arms using clustered bootstrapping.

**Results:** Data were available from 757 infants (137 clusters) and 943 infants (141 clusters) in the egg and control arms, respectively. In the egg arm compared with the control arm, the mean usual intakes were higher for energy (610 compared with 602 kcal/d, 9 mo; 669 compared with 658 kcal/d, 12 mo), crude protein (2.2 compared with 1.7 g/(kg·d), 9 mo; 2.4 compared with 1.9 g/(kg·d), 12 mo), available protein (2.0 compared with 1.6 g/(kg·d), 9 mo; 2.1 compared with 1.8 g/(kg·d), 12 mo), and for 13 and 14 micronutrients at 9 and 12 mo, respectively. The proportion meeting intake recommendations for most micronutrients was higher in the egg arm but remained <50% for 15 and 13 micronutrients at 9 and 12 mo, respectively.

**Conclusions:** Daily egg consumption improved dietary intakes among Bangladeshi infants, but was insufficient to meet multiple micronutrient intake recommendations, demonstrating the need to be coupled with other strategies.

Br J Nutr. 2022 Dec 21;1-26.

doi: 10.1017/S0007114522003944. Online ahead of print.

**[Milk-cereal mix supplementation during infancy and impact on neurodevelopmental outcomes at 12 and 24 months of age: a randomized controlled trial in India](#)**

[Ravi Prakash Upadhyay](#)<sup>1,2</sup>, [Sunita Taneja](#)<sup>1</sup>, [Tor A Strand](#)<sup>3</sup>, [Mari Hysing](#)<sup>4</sup>, [Beena Koshy](#)<sup>5</sup>, [Nita Bhandari](#)<sup>1</sup>, [Rajiv Bahl](#)<sup>6</sup>

**Abstract**

Inadequate protein intake and lack of micronutrients may affect neurodevelopment in infants. This randomized controlled trial was conducted to measure the effect of two milk-cereal mixes with modest and high amounts of protein and enriched with multiple micronutrients (MMN), given between 6-12 months, on cognitive, language, motor and behavioural scores at 12 and 24 months of age, compared to no-supplementation. The two supplements were also compared with each other. The study was conducted in urban Delhi, India and the infants were randomized in a 1:1:1 ratio to the three study groups. At 12 and 24 months of age, 1134 and 1214 children were available, respectively. At 12 months of age, compared to no supplement group, an increase in the motor scores (mean difference, MD 1.52, 95% CI: 0.28, 2.75) and a decrease in the infant temperament scores (mean difference, MD -2.76, 95% CI: -4.23, -1.29) in the modest protein group was observed. Those in the high protein group had lower socio-emotional scores (MD -1.40, 95% CI: -2.43, -0.37) and higher scores on infant temperament scale (MD 2.05, 95% CI: 0.62, 3.48) when compared to modest protein group. At 24 months, no significant differences in any of the neurodevelopment scores between the three study groups was found. In conclusion, supplementation with modest amount of protein and MMN may lead to short term small improvements in motor function and infant temperament. There appears no advantage of supplementing with high protein, rather negative effects on infant behaviour were observed.

J Food Sci. 2022 Jul;87(7):3163-3172.

doi: 10.1111/1750-3841.16225. Epub 2022 Jun 15.

**[Acceptability of orange corn-common bean as an alternative to corn-soybean complementary porridge in Malawi](#)**

[Aggrey Pemba Gama](#)<sup>1</sup>, [Limbikani Matumba](#)<sup>2</sup>, [Justice Munthali](#)<sup>3</sup>, [Sydney Namaumbo](#)<sup>2</sup>, [Monica Chimbaza](#)<sup>2</sup>, [Theresa Ngoma](#)<sup>2</sup>, [Kondwani Kammwamba](#)<sup>2</sup>, [Gift Chisapo](#)<sup>2</sup>, [Madalitso Chilembo](#)<sup>2</sup>, [Nyadani Meleke](#)<sup>2</sup>, [Rowland Chirwa](#)<sup>3</sup>, [Robert Fungo](#)<sup>4</sup>

**Abstract**

This study assessed the acceptability of porridge from a corn-common bean flour blend to increase the diversity of complementary foods in Malawi. Porridges prepared using commercial corn-soybean flour (C-CSB), homemade orange corn-soybean flour (H-CSB), and orange corn-common bean flour (CCBB) were evaluated by 101 pairs of mothers and their respective children aged from 6 to 24 months. A home use test (HUT) setup was used in this study, and the flours were given sequentially to participating households following a

randomized complete block design. Each sample type was evaluated for 3 days in a row followed by a 1-day break (washout period) between sample types. Based on aggregate mean scores, all the samples were liked by both the children and their mothers. However, clustering results revealed two distinct consumer segments for mothers as well as for children. Most of the mothers (59.4% in cluster 1) liked all the samples, while the minority (cluster 2) were neutral (neither like nor dislike) regarding the H-CSB porridge. Likewise, most children (66.3% in cluster 2) liked all the samples, while the rest in cluster 1 did not like CCBB porridge. Infants ( $\leq 12$  months) and those from food-insecure households, respectively, were 5.42 and 6.75 times more likely to like the CCBB porridge than their counterparts. The study has demonstrated the potential of introducing CCBB complementary porridge in Malawi and possibly in other countries with similar food preferences and socioeconomic stature. **PRACTICAL APPLICATION:** The study provides a solution to the limited diversity of complementary foods in sub-Saharan Africa and Malawi in particular. The findings can help food scientists, nutritionists, marketers, and policymakers develop strategies for promoting the consumption of orange corn-common bean porridge. Furthermore, the findings can inform decisions on commercializing orange corn-common bean flour by flour processors.

BMC Nutr. 2022 Aug 2;8(1):73.

doi: 10.1186/s40795-022-00565-0.

**[Effect of short-term educational intervention on complementary feeding index among infants in rural Bangladesh: a randomized control trial](#)**

[Aminur Rahman](#)<sup>1</sup>, [Mohammad Badrul Bhuiyan](#)<sup>2</sup>, [Sumon Kumar Das](#)<sup>3</sup>

**Abstract**

**Background:** Timely, adequate and appropriate Complementary Feeding (CF) is essential for the growth and cognitive development of infants, but until today, evidence-based information is scarce in terms of impact evaluation of CF index (CFI). The study aimed to examine the effect of the short-term intervention of promoting CF practices on the nutritional status of infants in rural Bangladesh.

**Methods:** An educational-intervention study followed a randomized controlled trial (RCT) design ([NCT03024710](#)). Mothers and family members in the intervention arm received intensive counselling on CF through community health workers (CHWs), whereas existing healthcare services were received in the comparison arm. The study was carried out in the rural Matlab sub-district of Bangladesh between April 2011 and March 2013. In the specified study areas among 360 mother-infant pairs systematically assigned into intervention group and comparison group. Short-term educational intervention on CF was provided for the intervention group and existing services were un-intervened for the comparison group. The outcome of interventions was evaluated after the implementation period using Generalized equation estimation model.

**Results:** At baseline, the study participants were not different except mean height ( $p = 0.04$ ), weight-for-age Z score (WAZ) ( $p = 0.03$ ) and religion ( $p = 0.04$ ) in between two groups. The mean CFI was significantly higher at intervention area than the comparison and higher category of CFI (score 10 or more) was significantly higher at intervention area than comparison. After adjustment, one-unit CFI increased height-for-age z score by 0.07 units and decreased WAZ by 0.13 units in the intervention group but not significantly changed observed at comparison group.



**Conclusion:** Guided short-term nutritional intervention and developed CFI indicated a significantly better score in intervention area than comparison groups and would be a well adaptable tool for future studies.

BMC Nutr. 2023 Mar 8;9(1):42.

doi: 10.1186/s40795-023-00700-5.

**[Identifying positive and negative deviants and factors associated with healthy dietary practices among young schoolchildren in Nepal: a mixed methods study](#)**

[Prasant Vikram Shahi](#)<sup>1</sup>, [Rachana Manandhar Shrestha](#)<sup>1</sup>, [Pepijn Schreinemachers](#)<sup>2</sup>, [Akira Shibanuma](#)<sup>1</sup>, [Junko Kiriya](#)<sup>1</sup>, [Ken Ing Cherng Ong](#)<sup>3</sup>, [Masamine Jimba](#)<sup>1</sup>

**Abstract**

**Background:** School-based interventions have been implemented in resource-limited settings to promote healthy dietary habits, but their sustainability remains a challenge. This study identified positive deviants (PDs) and negative deviants (NDs) from the control and treatment groups in a nutrition-sensitive agricultural intervention in Nepal to identify factors associated with healthy dietary practices.

**Methods:** This is an explanatory mixed methods study. Quantitative data come from the endline survey of a cluster randomized controlled trial of a school and home garden intervention in Nepal. Data were analyzed from 332 and 317 schoolchildren (grades 4 and 5) in the control and treatment group, respectively. From the control group, PDs were identified as schoolchildren with a minimum dietary diversity score (DDS)  $\geq 4$  and coming from low wealth index households. From the treatment group, NDs were identified as schoolchildren with a DDS  $< 4$  and coming from high wealth index households. Logistic regression analyses were conducted to identify factors associated with PDs and NDs. Qualitative data were collected through in-depth phone interviews with nine pairs of parents and schoolchildren in each PD and ND group. Qualitative data were analyzed thematically and integrated with quantitative data in the analysis.

**Results:** Twenty-three schoolchildren were identified as PDs, and 73 schoolchildren as NDs. Schoolchildren eating more frequently a day (AOR = 2.25; 95% CI:1.07-5.68) and whose parents had a higher agricultural knowledge level (AOR = 1.62; 95% CI:1.11-2.34) were more likely to be PDs. On the other hand, schoolchildren who consumed diverse types of vegetables (AOR = 0.56; 95% CI: 0.38-0.81), whose parents had higher vegetable preference (AOR = 0.72; 95% CI: 0.53-0.97) and bought food more often (AOR = 0.71; 95% CI: 0.56-0.88) were less likely to be NDs. Yet, schoolchildren from households with a grandmother (AOR = 1.98; 95% CI: 1.03-3.81) were more likely to be NDs. Integrated results identified four themes that influenced schoolchildren's DDS: the availability of diverse food, the involvement of children in meal preparation, parental procedural knowledge, and the grandmother's presence.

**Conclusion:** Healthy dietary habit can be promoted among schoolchildren in Nepal by encouraging parents to involve their children in meal preparation and increasing the awareness of family members.

## Breastfeeding

\*\*\* Am J Clin Nutr. 2023 Mar;117(3):518-528.

doi: 10.1016/j.ajcnut.2023.01.003. Epub 2023 Jan 10.

### [Tailored text messages to improve breastfeeding practices in Yangon, Myanmar: the M528 individually randomized controlled trial](#)

[Myat Pan Hmone<sup>1</sup>](#), [Mu Li<sup>2</sup>](#), [Kingsley Emwinyore Agho<sup>3</sup>](#), [Neeloy Ashraful Alam<sup>2</sup>](#), [Nina Chad<sup>2</sup>](#), [Michael J Dibley<sup>4</sup>](#)

#### Abstract

**Background:** Text messages are a feasible delivery channel for breastfeeding promotion, but only a few articles have examined their effectiveness.

**Objective:** To evaluate the impact of mobile phone text messages on breastfeeding practices.

**Design:** We implemented a 2-arm, parallel, individually randomized controlled trial with 353 pregnant participants at the Central Women's Hospital, Yangon. The intervention group (n = 179) received breastfeeding-promotion text messages, and the control group (n = 174) received other maternal and child health care messages. The primary outcome was the exclusive breastfeeding rate at 1-6 mo postpartum. Secondary outcomes were other breastfeeding indicators, breastfeeding self-efficacy, and child morbidity. Using the intention-to-treat approach, the available outcome data were analyzed with generalized estimation equation Poisson regression models to estimate RR and 95% CIs, adjusted for within-person correlation and time, and tested for treatment group-by-time interactions.

**Results:** Exclusive breastfeeding prevalence was significantly higher in the intervention than in the control group for the 6 follow-up visits combined (RR: 1.48; 95%CI: 1.35, 1.63; P < 0.001) and at each monthly follow-up visit. At 6 mo, exclusive breastfeeding was 43.4% in the intervention compared with 15.3% in the control group (RR: 2.74; 95%CI: 1.79, 4.19; P < 0.001). Also, at 6 mo, the intervention increased current breastfeeding (RR: 1.17; 95%CI: 1.07, 1.26; P < 0.001) and reduced bottle feeding (RR: 0.30; 95%CI: 0.17, 0.54; P < 0.001). Exclusive breastfeeding was progressively higher in the intervention group than in the control group at each follow-up (P for interaction < 0.001) and similarly for current breastfeeding. The intervention increased the mean breastfeeding self-efficacy score (adjusted mean difference 4.0; 95%CI: 1.36, 6.64; P = 0.030). Over the 6-month follow-up, the intervention significantly reduced diarrhea risk by 55% (RR: 0.45; 95%CI: 0.24, 0.82; P < 0.009).

**Conclusions:** Regular, targeted text messages delivered to urban pregnant women and mothers via mobile phones significantly improve breastfeeding practices and reduce infant morbidity during the first 6 mo of life.

Public Health Nutr. 2022 Nov;25(11):3067-3078.

doi: 10.1017/S1368980022001732. Epub 2022 Aug 19.

### [A theory-based behavioural change communication intervention to decrease the provision of water to infants under 6 months of age in the Republic of Guinea](#)

[Nèmanan R Ninamou<sup>1</sup>](#), [Jérémie B Dupuis<sup>2</sup>](#), [Noël-Marie Zagré<sup>3</sup>](#), [Mamady Daffé<sup>4</sup>](#), [Sonia Blaney<sup>1</sup>](#)

#### Abstract

**Objective:** In many countries, the provision of water in the early months of a baby's life jeopardises exclusive breast-feeding (EBF). Using a behavioural theory, this study assessed the impact of a behaviour change intervention on mothers' intention to act and, in turn, on the water provision in addition to breast milk to their infants under 6 months of age (IU6M) in two regions of Guinea.

**Design:** A quasi-experimental design. Data on individual and environmental factors of the theoretical framework, sociodemographic and outcomes were collected using validated questionnaires before and after the intervention. The outcomes examined were the intention to provide water to IU6M, the provision of water and EBF. Path analyses were performed to investigate pathways by which psychosocial and environmental factors influenced the water provision in addition to breast milk.

**Setting:** Four health centres were assigned randomly to each study's arm (one control/CG and one intervention group/IG per region).

**Participants:** The sample included 300 mothers of IU6M: 150 per group.

**Results:** In IG, the proportion of mothers providing water decreased from 61 % to 29 % before and after the intervention ( $P < 0.001$ ), while no difference was observed in CG ( $P = 0.097$ ). The EBF rate increased in IG (from 24.0 % to 53.8 %,  $P < 0.001$ ) as opposed to CG (36.7 % to 45.9 %,  $P = 0.107$ ). An association ( $P < 0.001$ ) between the intention and the behaviour was observed in both groups.

**Conclusions:** An intervention developed using a sound framework reduces the provision of water among IU6M and improves EBF.

Cochrane Database Syst Rev. 2022 Oct 25;10(10):CD001141.

doi: 10.1002/14651858.CD001141.pub6.

### [Support for healthy breastfeeding mothers with healthy term babies](#)

[Anna Gavine<sup>1</sup>](#), [Shona C Shinwell<sup>1</sup>](#), [Phyll Buchanan<sup>2</sup>](#), [Albert Farre<sup>1</sup>](#), [Angela Wade<sup>3</sup>](#), [Fiona Lynn<sup>4</sup>](#), [Joyce Marshall<sup>5</sup>](#), [Sara E Cumming<sup>1,6</sup>](#), [Shadrach Dare<sup>1</sup>](#), [Alison McFadden<sup>1</sup>](#)

#### **Abstract**

**Background:** There is extensive evidence of important health risks for infants and mothers related to not breastfeeding. In 2003, the World Health Organization recommended that infants be breastfed exclusively until six months of age, with breastfeeding continuing as an important part of the infant's diet until at least two years of age. However, current breastfeeding rates in many countries do not reflect this recommendation.

**Objectives:** 1. To describe types of breastfeeding support for healthy breastfeeding mothers with healthy term babies. 2. To examine the effectiveness of different types of breastfeeding support interventions in terms of whether they offered only breastfeeding support or breastfeeding support in combination with a wider maternal and child health intervention ('breastfeeding plus' support). 3. To examine the effectiveness of the following intervention characteristics on breastfeeding support: a. type of support (e.g. face-to-face, telephone, digital technologies, group or individual support, proactive or reactive); b. intensity of support (i.e. number of postnatal contacts); c. person delivering the intervention (e.g. healthcare professional, lay person); d. to examine whether the impact of support varied between high- and low- and middle-income countries.

**Search methods:** We searched Cochrane Pregnancy and Childbirth's Trials Register (which includes results of searches of CENTRAL, MEDLINE, Embase, CINAHL, ClinicalTrials.gov, WHO

International Clinical Trials Registry Platform (ICTRP)) (11 May 2021) and reference lists of retrieved studies.

**Selection criteria:** Randomised or quasi-randomised controlled trials comparing extra support for healthy breastfeeding mothers of healthy term babies with usual maternity care. Support could be provided face-to-face, over the phone or via digital technologies. All studies had to meet the trustworthiness criteria. **DATA COLLECTION AND ANALYSIS:** We used standard Cochrane Pregnancy and Childbirth methods. Two review authors independently selected trials, extracted data, and assessed risk of bias and study trustworthiness. The certainty of the evidence was assessed using the GRADE approach.

**Main results:** This updated review includes 116 trials of which 103 contribute data to the analyses. In total more than 98,816 mother-infant pairs were included. Moderate-certainty evidence indicated that 'breastfeeding only' support probably reduced the number of women stopping breastfeeding for all primary outcomes: stopping any breastfeeding at six months (Risk Ratio (RR) 0.93, 95% Confidence Interval (CI) 0.89 to 0.97); stopping exclusive breastfeeding at six months (RR 0.90, 95% CI 0.88 to 0.93); stopping any breastfeeding at 4-6 weeks (RR 0.88, 95% CI 0.79 to 0.97); and stopping exclusive breastfeeding at 4-6 (RR 0.83 95% CI 0.76 to 0.90). Similar findings were reported for the secondary breastfeeding outcomes except for any breastfeeding at two months and 12 months when the evidence was uncertain if 'breastfeeding only' support helped reduce the number of women stopping breastfeeding. The evidence for 'breastfeeding plus' was less consistent. For primary outcomes there was some evidence that 'breastfeeding plus' support probably reduced the number of women stopping any breastfeeding (RR 0.94, 95% CI 0.91 to 0.97, moderate-certainty evidence) or exclusive breastfeeding at six months (RR 0.79, 95% CI 0.70 to 0.90). 'Breastfeeding plus' interventions may have a beneficial effect on reducing the number of women stopping exclusive breastfeeding at 4-6 weeks, but the evidence is very uncertain (RR 0.73, 95% CI 0.57 to 0.95). The evidence suggests that 'breastfeeding plus' support probably results in little to no difference in the number of women stopping any breastfeeding at 4-6 weeks (RR 0.94, 95% CI 0.82 to 1.08, moderate-certainty evidence). For the secondary outcomes, it was uncertain if 'breastfeeding plus' support helped reduce the number of women stopping any or exclusive breastfeeding at any time points. There were no consistent findings emerging from the narrative synthesis of the non-breastfeeding outcomes (maternal satisfaction with care, maternal satisfaction with feeding method, infant morbidity, and maternal mental health), except for a possible reduction of diarrhoea in intervention infants. We considered the overall risk of bias of trials included in the review was mixed. Blinding of participants and personnel is not feasible in such interventions and as studies utilised self-report breastfeeding data, there is also a risk of bias in outcome assessment. We conducted meta-regression to explore substantial heterogeneity for the primary outcomes using the following categories: person providing care; mode of delivery; intensity of support; and income status of country. It is possible that moderate levels (defined as 4-8 visits) of 'breastfeeding only' support may be associated with a more beneficial effect on exclusive breastfeeding at 4-6 weeks and six months. 'Breastfeeding only' support may also be more effective in reducing women in low- and middle-income countries (LMICs) stopping exclusive breastfeeding at six months compared to women in high-income countries (HICs). However, no other differential effects were found and thus heterogeneity remains largely unexplained. The meta-regression suggested that there were no differential effects regarding person providing support or mode of delivery, however, power was limited. **AUTHORS' CONCLUSIONS:** When 'breastfeeding only' support is offered to women, the duration and in

particular, the exclusivity of breastfeeding is likely to be increased. Support may also be more effective in reducing the number of women stopping breastfeeding at three to four months compared to later time points. For 'breastfeeding plus' interventions the evidence is less certain. Support may be offered either by professional or lay/peer supporters, or a combination of both. Support can also be offered face-to-face, via telephone or digital technologies, or a combination and may be more effective when delivered on a schedule of four to eight visits. Further work is needed to identify components of the effective interventions and to deliver interventions on a larger scale.

Matern Child Nutr. 2022 Jul;18(3):e13362.

doi: 10.1111/mcn.13362. Epub 2022 Apr 29.

### [\*\*The impact of a package of behaviour change interventions on breastfeeding practices in East Java Province, Indonesia\*\*](#)

[Christiana Rialine Titaley<sup>1</sup>](#), [Michael J Dibley<sup>2</sup>](#), [Iwan Ariawan<sup>3</sup>](#), [Anifatun Mu'asyaroh<sup>4</sup>](#), [Bunga Astria Paramashanti<sup>2,5</sup>](#), [Ashrafal Alam<sup>2</sup>](#), [Rita Damayanti<sup>3</sup>](#), [Tran Thanh Do<sup>6</sup>](#), [Elaine Ferguson<sup>7</sup>](#), [Min Kyaw Htet<sup>2,8</sup>](#), [Mu Li<sup>2</sup>](#), [Aang Sutrisna<sup>9</sup>](#), [Umi Fahmida<sup>8</sup>](#)

#### **Abstract**

Suboptimal infant young child feeding practices are frequently reported globally, including in Indonesia. This analysis examined the impact of a package of behaviour change interventions on breastfeeding practices in Malang and Sidoarjo Districts, East Java Province, Indonesia. The BADUTA study (which in the Indonesian Language is an acronym for BAawah DUa TAHun, or children aged less than 2 years) was an impact evaluation using a cluster-randomized controlled trial with two parallel treatment arms. We conducted household surveys in 12 subdistricts from Malang and Sidoarjo. We collected information from 5175 mothers of children aged 0-23 months: 2435 mothers at baseline (February 2015) and 2740 mothers at endline (January to February 2017). This analysis used two indicators for fever and diarrhoea and seven breastfeeding indicators (early initiation of breastfeeding, prelacteal feeding, exclusive breastfeeding under 6 months, predominant breastfeeding, continued breastfeeding, age-appropriate breastfeeding and bottle-feeding). We used multilevel logistic regression analysis to assess the effect of the intervention. After 2 years of implementation of interventions, we observed an increased odds of exclusive breastfeeding under 6 months (adjusted odds ratio [aOR] = 1.85; 95% confidence interval [CI]: 1.35-2.53) and age-appropriate breastfeeding (aOR = 1.39; 95% CI: 1.07-1.79) in the intervention group than in the comparison group, at the endline survey. We found significantly lower odds for prelacteal feeding (aOR = 0.52; 95% CI: 0.41-0.65) in the intervention than in the comparison group. Our findings confirmed the benefits of integrated, multilayer behaviour change interventions to promote breastfeeding practices. Further research is required to develop effective interventions to reduce bottle use and improve other breastfeeding indicators that did not change with the BADUTA intervention.

Matern Child Nutr. 2022 Jul;18(3):e13377.

doi: 10.1111/mcn.13377. Epub 2022 May 19.

### [\*\*The effect of electronic job aid assisted one-to-one counselling to support exclusive breastfeeding among 0-5-month-old infants in rural Bangladesh\*\*](#)

[Sk Masum Billah<sup>1,2</sup>](#), [Tarana E Ferdous<sup>1</sup>](#), [Abu Bakkar Siddique<sup>1</sup>](#), [Camille Raynes-Greenow<sup>2</sup>](#), [Patrick Kelly<sup>2</sup>](#), [Nuzhat Choudhury<sup>3</sup>](#), [Tahmeed Ahmed<sup>3</sup>](#), [Stuart Gillespie<sup>4</sup>](#), [John Hoddinott<sup>4,5</sup>](#), [Rukhsana Haider<sup>6</sup>](#), [Purnima Menon<sup>4</sup>](#), [Shams El Arifeen<sup>1</sup>](#), [Michael J Dibley<sup>2</sup>](#)

### Abstract

Exclusive breastfeeding (EBF) for the first 6 months has established benefits, yet had slow improvements globally. Little is known about electronic job aid-assisted counselling to support EBF. As a secondary outcome of a cluster randomized controlled trial in Bangladesh, we assessed the effect of electronic job aid-supported nutrition counselling and practical demonstration on EBF. We randomized pregnant women to one of five study arms in the trial and followed mother-child dyads until 2 years of age. Community health workers (CHWs) provided breastfeeding counselling with or without prenatal and complementary nutrient supplements in all four intervention arms. The comparison arm continued with the usual practice where mothers could receive nutrition counselling at routine antenatal and postnatal care, and during careseeking for childhood illnesses. We assessed breastfeeding indicators at birth and monthly until the child was 6 months old, in both intervention and comparison arms. To evaluate the effect of nutrition counselling on breastfeeding, we combined all four intervention arms and compared them with the comparison arm. Intervention newborns had half the risk (relative risk [RR]: 0.54, 95% confidence interval [CI]: 0.39, 0.76) of receiving prelacteal feeds than those in the comparison arm. EBF declined steeply in the comparison arm after 3 months of age. EBF was 16% higher in the intervention than the comparison arm at 4 months (RR: 1.16, 95% CI: 1.08, 1.23) and 22% higher at 5 months of age (RR: 1.22, 95% CI: 1.12, 1.33). Maternal background and household characteristics did not modify the intervention effect, and we observed no difference in EBF among caesarean versus vaginal births. Breastfeeding counselling and practical demonstration using an electronic job aid by CHWs are promising interventions to improve EBF and are scalable into existing community-based programmes.

PLoS One. 2022 Dec 30;17(12):e0279941.

doi: 10.1371/journal.pone.0279941. eCollection 2022.

### [Breastfeeding knowledge, attitude, and self-efficacy among mothers with infant and young child in rural Ethiopia](#)

[Abraham Tamirat Gizaw<sup>1</sup>](#), [Pradeep Sopory<sup>2</sup>](#), [Sudhakar Morankar<sup>1</sup>](#)

### Abstract

**Background:** Breastfeeding has several benefits for both mothers and their children. Despite strong evidence in support of the practice, its prevalence has remained low worldwide, particularly in Ethiopia. Therefore, this study is aimed to assess breastfeeding knowledge, attitude, and self-efficacy among mothers with index infants and young children in the rural community of Southwest Ethiopia.

**Methods:** A community-based cross-sectional study was conducted between March and April 2022 as baseline data for a cluster of randomized control trials. Multistage sample techniques followed by systematic random sampling techniques were employed. The Chi-square and Fisher's exact probability tests were used to assess the baseline differences in the socio-demographic characteristics of the two groups. An independent sample t-test was used to determine the mean differences. Multivariate logistic regression analysis was used to



evaluate the association. All tests were two-tailed, and a statistically significant association was declared at a p-value  $\leq 0.05$ .

**Results:** A total of 516 mothers (258 from the intervention and 258 from the control group) were interviewed. A total of 516 mothers (258 from the intervention group and 258 from the control group) were interviewed. Except for the child's sex and age, no significant difference was observed between the intervention and control groups in terms of socio-demographic variables ( $p > 0.05$ ). Independent t-tests found no significant difference between the two groups ( $p > 0.05$ ) in terms of the mean score of maternal breastfeeding knowledge, attitude and self-efficacy at baseline. After adjusting for other covariates, maternal age (AOR = 1.44, 95% CI: 0.69, 3.07), educational status (AOR = 1.87, 95% CI: 0.56, 2.33), occupation (AOR = 1.79, 95% CI, 1.04, 3.69), ANC (antenatal care) (AOR = 1.88, 95% CI, 1.11, 4.09), received breastfeeding information (AOR = 1.69, 95% CI, 1.33, 5.04), postnatal care (PNC) (AOR = 3.85, 95% CI, 2.01, 5.77) and parity (AOR = 2.49, 95% CI, 1.08, 4.19) were significantly associated with high level breastfeeding knowledge. The positive attitude was associated with maternal age (AOR = 2.41, 95% CI, 1.18, 5.67), education status (AOR = 1.79, 95% CI, 0.99, 4.03), ANC (AOR = 2.07, 95% CI, 1.44, 5.13), last child breastfeeding history (AOR = 1.77, 95% CI, 1.21, 4.88) and high level of breastfeeding knowledge (AOR = 2.02, 95% CI, 1.56, 4.04). Finally, high breastfeeding self-efficacy was associated with ANC (AOR = 1.88, 95% CI 1.04, 3.83), parity (AOR = 4.05, 95% CI, 1.49, 5.03) and high knowledge level (AOR = 1.69, 95% CI, 0.89, 2.85).

**Conclusions:** The study concluded that mothers in both the intervention and control groups have a low level of breastfeeding knowledge, a neutral attitude, and medium self-efficacy. Therefore, nutrition education interventions using tailored messages appropriate to the sociocultural context in the rural setting should be developed and evaluated continuously.

J Hum Lact. 2022 Aug;38(3):466-476.

doi: 10.1177/08903344221097689. Epub 2022 Jun 9.

### [The Influence of Breastfeeding Promotion Programs on Exclusive Breastfeeding Rates in Sub-Saharan Africa: A Systematic Review and Meta-Analysis](#)

[Roselyn Chipojola<sup>1,2</sup>](#), [Madalitso Khwepeya<sup>3</sup>](#), [Kaboni Whitney Gondwe<sup>4</sup>](#), [Yohanes Andy Rias<sup>2,5</sup>](#), [Mega Hasanul Huda<sup>2</sup>](#)

#### **Abstract**

**Background:** The benefits of breastfeeding in promoting child survival are well recognized. As one of the nutritional interventions for children, exclusive breastfeeding protects babies from various diseases that contribute to infant morbidity and mortality. However, no systematic review and meta-analysis has examined the influence of breastfeeding promotion programs on exclusive breastfeeding rates in sub-Saharan Africa.

**Research aim:** We examined the influence of breastfeeding promotion programs on exclusive breastfeeding rates at  $< 1$  month, and at 1-5 months of breastfeeding in sub-Saharan countries including Ghana, Burkina Faso, Uganda, South Africa, Guinea-Bissau, Kenya, Tanzania, and the Democratic Republic of Congo.

**Methods:** A systematic review and meta-analyses study of randomized controlled trials and quasi-experimental studies was conducted by searching in electronic databases and articles' reference lists. Two investigators independently evaluated and extracted the data. A total of 131 studies were identified using five databases. Of the 10 studies meeting the inclusion

criteria for systematic review, seven studies were included in the meta-analysis. We used a random-effects model to pool studies together and performed a subgroup analysis.

**Results:** Breastfeeding promotion programs resulted in significantly higher exclusive breastfeeding rates at < 1 month (OR = 1.60, 95% CI [1.36,1.86]). However, there was no significant effect observed for exclusive breastfeeding at 1-5 months. Combined interventions were more effective in improving exclusive breastfeeding rates than individual counseling or home-based counseling alone.

**Conclusion:** Breastfeeding promotion programs in sub-Saharan Africa are effective in increasing exclusive breastfeeding rates at 6 months after birth.

## Community and home nutrition programs

Matern Child Nutr. 2023 Jul;19(3):e13505.

doi: 10.1111/mcn.13505. Epub 2023 Mar 24.

### [Impact of a Homestead Food Production program on poultry rearing and egg consumption: A cluster-randomized controlled trial in Bangladesh](#)

[Nathalie J Lambrecht](#)<sup>1,2</sup>, [Jillian L Waid](#)<sup>2,3</sup>, [Amanda S Wendt](#)<sup>2</sup>, [Shafinaz Sobhan](#)<sup>1,2</sup>, [Abdul Kader](#)<sup>4</sup>, [Sabine Gabrysch](#)<sup>1,2,3</sup>

#### Abstract

Women and children in Bangladesh face high levels of micronutrient deficiencies from inadequate diets. We evaluated the impact of a Homestead Food Production (HFP) intervention on poultry production, as a pathway outcome, and women's and children's egg consumption, as secondary outcomes, as part of the Food and Agricultural Approaches to Reducing Malnutrition cluster-randomized trial in Sylhet division, Bangladesh. The 3-year intervention (2015-2018) promoted home gardening, poultry rearing, and nutrition counseling. We randomly allocated 96 clusters to intervention (48 clusters; 1337 women) or control (48 clusters; 1368 women). Children < 3 years old born to participants were enrolled during the trial. We analyzed poultry production indicators, measured annually, and any egg consumption (24-h recall), measured every 2-6 months for women and their children. We conducted intention-to-treat analyses using mixed-effects logistic regression models with repeat measures, with minimal adjustment to increase precision. Poultry ownership increased by 16% points (pp) and egg production by 13 pp in the final intervention year. The intervention doubled women's odds of egg consumption in the final year (Odds Ratio [OR]: 2.31, 95% CI: 1.68-3.18), with positive effects sustained 1-year post-intervention (OR: 1.58, 95% CI: 1.16-2.15). Children's odds of egg consumption were increased in the final year (OR: 3.04, 95% CI: 1.87-4.95). Poultry ownership was associated with women's egg consumption, accounting for 12% of the total intervention effect, but not with children's egg consumption. Our findings demonstrate that an HFP program can have longer-term positive effects on poultry production and women's and children's diets.

Matern Child Nutr. 2023 Apr;19(2):e13467.

doi: 10.1111/mcn.13467. Epub 2022 Dec 12.

### **Factors associated with nutrition intervention adherence: Evidence from a cluster-randomised controlled trial in Kenya**

[Kim Siegal<sup>1</sup>](#), [Kelvin Musau<sup>1</sup>](#), [Bradley A Woodruff<sup>2</sup>](#), [Emily Custer<sup>1</sup>](#), [Lucie Vergari<sup>1</sup>](#), [Hellen Anyango<sup>1</sup>](#), [William Donkor<sup>2</sup>](#), [Marion Kiprotich<sup>1</sup>](#), [Fabian Rohner<sup>2</sup>](#), [Rita Wegmüller<sup>2</sup>](#)

#### **Abstract**

Nutrition experts point to the importance of a multipronged approach to address high stunting rates in rural areas. This can include nutrition-specific and -sensitive interventions, such as the provision of micronutrient powder, eggs, and chlorine, and nutrition training to improve feeding practices. In 2018, an agricultural nongovernmental organisation initiated a multipronged approach as part of a randomised trial. However, adherence to a programme with so many components can be challenging for participants. The aim of this study is to understand which factors are associated with high adherence in complex multifaceted nutrition-sensitive agricultural programmes. We used a mixed method approach in which we used bivariate and multivariable analyses to estimate the relationship between child and caregiver demographic factors with product adherence. We analyzed data from six focus groups and 120 feedback sessions on barriers to product adherence. We found that the age and sex of the child did not influence product adherence, but caregivers were more likely to adhere to all products if they were not the child's biological mother (most often grandmothers) (0.28 higher adherence score;  $p < 0.001$ ) and if caregivers were older (0.34 higher adherence score,  $p < 0.001$ ). A higher monthly training attendance, combining product distribution and interactive training, predicted stronger product adherence. Participants noted that adherence was supported by the early demonstration of positive results, regular reminders, interactive trainings, and the encouragement of family members. These findings underscore the importance of combining product distribution with training and include potentially targeting grandmothers and other caregivers who may demonstrate higher product adherence.

Matern Child Nutr. 2023 Jul;19(3):e13495.

doi: 10.1111/mcn.13495. Epub 2023 Mar 31.

### **Household animal ownership is associated with infant animal source food consumption in Bangladesh**

[Monica M Pasqualino<sup>1</sup>](#), [Saijuddin Shaikh<sup>2</sup>](#), [Md Tanvir Islam<sup>2</sup>](#), [Shahnaj Parvin<sup>2</sup>](#), [Hasmot Ali<sup>2</sup>](#), [John McGready<sup>3</sup>](#), [Alain B Labrique<sup>1</sup>](#), [Md Iqbal Hossain<sup>4</sup>](#), [Amanda C Palmer<sup>1</sup>](#)

#### **Abstract**

Context-specific research is needed on the relationship between household animal production and nutrition outcomes to inform programmes intervening in small-scale animal production. We examined associations between household animal/fishpond ownership and animal source food (ASF) consumption among 6- to 12-month-old infants enrolled in the control arm of a cluster-randomised controlled trial in rural Bangladesh. We measured ASF consumption using a 7-day food frequency questionnaire at 6, 9 and 12 months and assessed household animal/fishpond ownership at 12 months. We developed negative binomial regression models with random intercepts for infant and cluster, controlling for infant age and sex, maternal age, socioeconomic status and season. Models were stratified by a dichotomised maternal decision-making score. Compared with infants in households without each animal type, those with 4-10 and  $\geq 11$  poultry consumed eggs 1.3 (95%

confidence interval [CI]: 1.1, 1.6) and 1.6 (95% CI: 1.3, 2.0) times more, respectively; 2-3 and  $\geq 4$  dairy-producing animals consumed dairy 1.9 (95% CI: 1.3, 2.7) and 2.0 (95% CI: 1.3, 3.1) times more, respectively; and  $\geq 12$  meat-producing animals consumed meat 1.4 (95% CI: 1.0, 1.8) times more. It was unclear whether there was an association between fishpond ownership and fish consumption. Our results did not suggest that maternal decision-making power was a modifier in the relationship between animal/fishpond ownership and ASF consumption. In this South Asian context, strategies intervening in household animal production may increase infant consumption of eggs, dairy and meat, but not necessarily fish. Research is needed on the role of market access and other dimensions of women's empowerment.

J Trop Pediatr. 2022 Oct 6;68(6):fmac096.

doi: 10.1093/tropej/fmac096.

**Cash transfers and nutrition education to improve dietary diversity among children aged 6-23 months in Grand Gedeh County, Liberia: a cluster-randomized trial**

[Chris A Rees](#)<sup>1,2</sup>, [Dadah Cleon](#)<sup>3</sup>, [Annette B Davis](#)<sup>4</sup>, [Andrew M Sammy](#)<sup>5</sup>, [Carl D Britto](#)<sup>6</sup>, [Wesley Massaquoi](#)<sup>7</sup>, [Oretha W Forkpa](#)<sup>4</sup>, [Andrew J Johnson](#)<sup>8</sup>, [Varla F Hook](#)<sup>8</sup>, [Jane A MaCauley](#)<sup>8</sup>, [Garbie F Pewu](#)<sup>8</sup>, [Mercy Gorpue](#)<sup>8</sup>, [Amos Gborie](#)<sup>8</sup>, [Trokon T Brown](#)<sup>8</sup>, [Augustine Fannieh](#)<sup>9</sup>, [Teeline Dweh](#)<sup>9</sup>, [Ruth B Marley](#)<sup>9</sup>, [Massaboi K Baysah](#)<sup>9</sup>, [Netus N Nowine](#)<sup>9</sup>, [Michelle Niescierenko](#)<sup>10</sup>, [Leela Zaizay](#)<sup>7</sup>

**Abstract**

**Objectives:** To evaluate the efficacy of a cash transfer and nutrition education program on dietary diversity among children in Liberia. We hypothesized that a multi-pronged intervention would result in improved dietary diversity among children.

**Methods:** We conducted a three-armed, cluster-randomized study in 42 communities (12 children per community) in Grand Gedeh County, Liberia, over a 12-month period. We randomly assigned communities to control (n = 14 communities), those that received both bimonthly cash transfers and a structured nutrition education program (n = 14 communities) and those that received bimonthly cash transfers alone (n = 14 communities). Community health assistants conducted bimonthly assessments in participants' homes. The primary outcome was the proportion of children aged 6-23 months who met minimum dietary diversity score (i.e.,  $\geq 4$  food groups consumed per day). Secondary outcomes included meal frequency and healthcare utilization for illnesses ([NCT04101487](#)).

**Results:** There were 599 children enrolled; 533 (88.9%) were retained through the trial period. The proportion of children who consumed  $\geq 4$  food groups per day did not differ among the three arms. However, children randomized to receive cash transfers had higher dietary diversity scores than the control group. Children in communities that received cash transfers alone and with nutrition education consumed significantly more meals per day and were less likely to have visits to clinics or hospitals for illnesses than children in control communities.

**Conclusion:** Bimonthly, unconditional cash transfers and nutrition education were associated with higher dietary diversity scores, greater meal frequency, and fewer healthcare visits for illnesses among children aged 6-23 months.

doi: 10.1093/aje/kwac165.

## [A Causal Mediation Analysis for Investigating the Effect of a Randomized Cash-Transfer Program in Nicaragua](#)

[Thomas J Charters](#), [Jay S Kaufman](#), [Arijit Nandi](#)

### **Abstract**

Mediation analysis can be applied to data from randomized trials of health and social interventions to draw causal inference concerning their mechanisms. We used data from a cluster-randomized trial in Nicaragua, fielded between 2000 and 2002, to investigate whether the impact of providing access to a conditional cash-transfer program on child nutritional outcomes was mediated by child health check-ups and household dietary diversity. In a sample of 443 children 6-35 months old, we estimated the controlled direct (CDE) effect of random assignment on measured height-for-age z scores had we intervened so that all children received a health check-up and had the same level of household dietary diversity, using inverse-probability weighted marginal structural models to account for mediator-outcome confounding. Sensitivity analyses corrected the CDE for potential nondifferential error in the measurement of dietary diversity. Treatment assignment increased height-for-age z score by 0.37 (95% CI: 0.05, 0.69) standard deviations. The CDE was 0.20 (95% CI: -0.17, 0.57) standard deviations, suggesting nearly one-half of the program's impact on child nutrition would be eliminated had we intervened on these factors, although estimates were relatively imprecise. This study provides an illustration of how causal mediation analysis can be applied to examine the mechanisms of multifaceted interventions.

Soc Sci Med. 2023 Mar 27;324:115869.

doi: 10.1016/j.socscimed.2023.115869. Online ahead of print.

## [Effects of engaging fathers and bundling nutrition and parenting interventions on household gender equality and women's empowerment in rural Tanzania: Results from EFFECTS, a five-arm cluster-randomized controlled trial](#)

[Lauren Galvin](#)<sup>1</sup>, [Cristiana K Verissimo](#)<sup>2</sup>, [Ramya Ambikapathi](#)<sup>3</sup>, [Nilupa S Gunaratna](#)<sup>4</sup>, [Paula Rudnicka](#)<sup>5</sup>, [Amy Sunseri](#)<sup>6</sup>, [Joshua Jeong](#)<sup>7</sup>, [Savannah Froese O'Malley](#)<sup>8</sup>, [Aisha K Yousafzai](#)<sup>9</sup>, [Mary Mwanyika Sando](#)<sup>10</sup>, [Dominic Mosha](#)<sup>11</sup>, [Elfrida Kumaliya](#)<sup>12</sup>, [Hannah Connolly](#)<sup>13</sup>, [George PrayGod](#)<sup>14</sup>, [Cara Endyke-Doran](#)<sup>15</sup>, [Mary Pat Kieffer](#)<sup>16</sup>

### **Abstract**

Advancing gender equality and women's empowerment (GE/WE) may contribute to better child nutrition and development in low-resource settings. However, few empirical studies have generated evidence on GE/WE and examined the potential of engaging men to transform gender norms and power relations in the context of nutrition and parenting programs. We tested the independent and combined effects of engaging couples and bundling nutrition and parenting interventions on GE/WE in Mara, Tanzania. EFFECTS (ClinicalTrials.gov, [NCT03759821](#)) was a cluster-randomized 2 × 2 factorial trial plus control. Eighty village clusters were randomly assigned to one of five intervention conditions: standard of care, mothers nutrition, couples nutrition, mothers bundled nutrition and parenting, or couples bundled nutrition and parenting. Between October 2018-May 2019, 960 households were enrolled with children under 18 months of age residing with their mother and father. Community health workers (CHWs) delivered a bi-weekly 24-session hybrid peer group/home visit gender-transformative behavior change program to either mothers or couples. GE/WE outcomes were analyzed as intention-to-treat and included time use, gender

attitudes, social support, couples' communication frequency and quality, decision-making power, intimate partner violence (IPV), and women's dietary diversity (WDD). Data were collected from 957 to 815 mothers and 913 and 733 fathers at baseline and endline, respectively. Engaging couples compared to mothers only significantly increased paternal and maternal gender-equitable attitudes, paternal time spent on domestic chores, and maternal decision-making power. Bundling increased maternal leisure time, decreased maternal exposure to any IPV, and increased WDD over 7 days. A combination of engaging couples and bundling was most effective for paternal gender attitudes, couples communication frequency, and WDD over 24 h and 7 days. Our findings generate novel evidence that CHWs can deliver bundled nutrition and parenting interventions to couples in low-resource community settings that advance GE/WE more than nutrition interventions targeting only women.

BMC Public Health. 2023 Jan 7;23(1):51.

doi: 10.1186/s12889-022-14900-4.

**[Impact of a home-based nutritional intervention program on nutritional status of preschool children: a cluster randomized controlled trial](#)**

[Ansuya B<sup>1</sup>](#), [Baby S Nayak<sup>2</sup>](#), [Unnikrishnan B<sup>3</sup>](#), [Ravishankar N<sup>4</sup>](#), [Shashidhara Y N<sup>1</sup>](#), [Suneel C Mundkur<sup>5</sup>](#)

**Abstract**

**Background:** Undernutrition in under-five children remains a worldwide health issue and is considered one of the leading causes of increased morbidity and mortality. This study aims to assess the impact of home-based nutritional intervention on the nutritional status of preschool children living in rural areas of South India.

**Methods:** A single-blinded cluster randomized controlled trial evaluated the impact of the intervention, with weight gain as the primary outcome. A cluster of 12 villages was randomized to intervention or control arms. A total of 253 underweight preschool children from 12 clusters (villages) were randomized to intervention (n = 127) and control arm (n = 126). The intervention was composed of a health-teaching program and a demonstration of nutritious food preparation in addition to the regular services provided at the Anganwadi centers. The control arm received only standard routine care provided in the Anganwadi centre. The anthropometric assessment was carried out at the baseline and every month for a year.

**Result:** A significant increase in the mean weight kilograms was noted in the intervention group ( $11.9 \pm 0.98$  to  $13.78 \pm 0.89$ ) compared to the control group ( $11.8 \pm 1.03$  to  $12.96 \pm 0.88$ ). In the intervention group, at the baseline, 41.5% were moderately malnourished (> -2SD-3SD), which decreased to 24% at the end of the year. Similarly, severe malnutrition decreased from 8.69 to 3.16%, while 20.5% of malnourished children achieved normal nutritional status. In the control group, undernourished children demonstrated minimal changes in nutritional status. Analysis of repeated measures of ANOVA results between the intervention and control groups on weight measurements ( $F(1, 251) = 15.42, p .001$ ) and height measurements ( $F(2, 1258) = 1.540, p .001$ ) revealed statistical significance.

**Conclusion:** The nutritional status of preschool children is found to be improved by home-based intervention, which includes training mothers or caregivers in planning and preparing



healthy nutritious diets, providing timely care, and gaining an understanding and knowledge of the nutritional status along with regular home-based diet preparation.

J Nutr. 2022 Oct 6;152(10):2255-2268.

doi: 10.1093/jn/nxac132.

**Economic Evaluation of Nutrition-Sensitive Agricultural Interventions to Increase Maternal and Child Dietary Diversity and Nutritional Status in Rural Odisha, India**

Hassan Haghparast-Bidgoli<sup>1</sup>, Helen Harris-Fry<sup>2</sup>, Abhinav Kumar<sup>3</sup>, Ronali Pradhan<sup>3</sup>, Naba Kishore Mishra<sup>4</sup>, Shibananth Padhan<sup>4</sup>, Amit Kumar Ojha<sup>5</sup>, Sailendra Narayan Mishra<sup>4</sup>, Emily Fivian<sup>2</sup>, Philip James<sup>2</sup>, Sarah Ferguson<sup>6</sup>, Sneha Krishnan<sup>7</sup>, Meghan O'Hearn<sup>8</sup>, Tom Palmer<sup>1</sup>, Peggy Koniz-Booher<sup>9</sup>, Heather Danton<sup>9</sup>, Sandee Minovi<sup>9</sup>, Satyanarayan Mohanty<sup>10</sup>, Shibanand Rath<sup>5</sup>, Suchitra Rath<sup>5</sup>, Nirmala Nair<sup>5</sup>, Prasanta Tripathy<sup>5</sup>, Audrey Prost<sup>1</sup>, Elizabeth Allen<sup>2</sup>, Jolene Skordis<sup>1</sup>, Suneetha Kadiyala<sup>2</sup>

**Abstract**

**Background:** Economic evaluations of nutrition-sensitive agriculture (NSA) interventions are scarce, limiting assessment of their potential affordability and scalability.

**Objectives:** We conducted cost-consequence analyses of 3 participatory video-based interventions of fortnightly women's group meetings using the following platforms: 1) NSA videos; 2) NSA and nutrition-specific videos; or 3) NSA videos with a nutrition-specific participatory learning and action (PLA) cycle.

**Methods:** Interventions were tested in a 32-mo, 4-arm cluster-randomized controlled trial, Upscaling Participatory Action and Videos for Agriculture and Nutrition (UPAVAN) in the Keonjhar district, Odisha, India. Impacts were evaluated in children aged 0-23 mo and their mothers. We estimated program costs using data collected prospectively from expenditure records of implementing and technical partners and societal costs using expenditure assessment data collected from households with a child aged 0-23 mo and key informant interviews. Costs were adjusted for inflation, discounted, and converted to 2019 US\$.

**Results:** Total program costs of each intervention ranged from US\$272,121 to US\$386,907. Program costs per pregnant woman or mother of a child aged 0-23 mo were US\$62 for NSA videos, US\$84 for NSA and nutrition-specific videos, and US\$78 for NSA videos with PLA (societal costs: US\$125, US\$143, and US\$122, respectively). Substantial shares of total costs were attributable to development and delivery of the videos and PLA (52-69%) and quality assurance (25-41%). Relative to control, minimum dietary diversity was higher in the children who underwent the interventions incorporating nutrition-specific videos and PLA (adjusted RRs: 1.19 and 1.27; 95% CIs: 1.03-1.37 and 1.11, 1.46, respectively). Relative to control, minimum dietary diversity in mothers was higher in those who underwent NSA video (1.21 [1.01, 1.45]) and NSA with PLA (1.30 [1.10, 1.53]) interventions.

**Conclusion:** NSA videos with PLA can increase both maternal and child dietary diversity and have the lowest cost per unit increase in diet diversity. Building on investments made in developing UPAVAN, cost-efficiency at scale could be increased with less intensive monitoring, reduced startup costs, and integration within existing government programs. This trial was registered at clinicaltrials.gov as ISRCTN65922679.

## Obesity

Lancet Glob Health. 2023 Mar;11 Suppl 1:S16.

doi: 10.1016/S2214-109X(23)00099-2.

### [Interventions to reduce and prevent childhood obesity in low-income and middle-income countries: a systematic review and meta-analysis](#)

[Isaac Olufadewa](#)<sup>1</sup>, [Miracle Adesina](#)<sup>2</sup>, [Ruth Oladele](#)<sup>2</sup>, [Toluwase Olufadewa](#)<sup>2</sup>, [Abimbola Solagbade](#)<sup>2</sup>, [Olajumoke Ogundele](#)<sup>2</sup>, [Oluwadara Asaolu](#)<sup>3</sup>, [Tejumade Adene](#)<sup>4</sup>, [Omotayo Oladesu](#)<sup>3</sup>, [Eyitayo Lawal](#)<sup>2</sup>, [Joshua Nnatus](#)<sup>2</sup>, [Deborah Akinrinde](#)<sup>5</sup>, [Esther Opone](#)<sup>2</sup>

#### Abstract

**Background:** 70% of children with obesity and overweight live in low-income and middle-income countries. Several interventions have been done to reduce the prevalence of childhood obesity and prevent incident cases. Hence, we did a systematic review and meta-analysis to determine the effectiveness of these interventions in reducing and preventing childhood obesity.

**Methods:** We conducted a search for randomised controlled trials and quantitative non-randomised studies published on MEDLINE, Embase, Web of Science, and PsycINFO databases between Jan 1, 2010, and Nov 1, 2022. We included interventional studies on the prevention and control of obesity in children up to age 12 years in low-income and middle-income countries. Quality appraisal was performed using Cochrane's risk-of-bias tools. We did three-level random-effects meta-analyses and explored the heterogeneity of studies included. We excluded critical risk-of-bias studies from primary analyses. We assessed the certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation.

**Findings:** The search generated 12 104 studies, of which eight studies were included involving 5734 children. Six studies were based on obesity prevention, most of which targeted behavioural changes with a focus on counselling and diet, and a significant reduction in BMI was observed (standardised mean difference 2.04 [95% CI 1.01-3.08];  $p < 0.001$ ). In contrast, only two studies focused on the control of childhood obesity; the overall effect of the interventions in these studies was not significant ( $p = 0.38$ ). The combined studies of prevention and control had a significant overall effect, with study-specific estimates ranging between 0.23 and 3.10, albeit with a high statistical heterogeneity ( $I^2 > 75\%$ ).

**Interpretation:** Preventive interventions, such as behavioural change and diet modification, are more effective than control interventions in reducing and preventing childhood obesity.

Am J Hum Biol. 2022 Aug;34(8):e23745.

doi: 10.1002/ajhb.23745. Epub 2022 Mar 16.

### [Insulin sensitivity as a predictor of longitudinal changes on body mass index in Brazilian adolescents](#)

[Valéria Lima da Cruz](#)<sup>1</sup>, [Mauro Felipe Felix Mediano](#)<sup>2,3</sup>, [Vitor Barreto Paravidino](#)<sup>1,4</sup>, [Fabiana Alves Neves](#)<sup>5</sup>, [Tayanne de Oliveira Malafaia](#)<sup>5</sup>, [Luiz Fernando Rodrigues Junior](#)<sup>3</sup>, [Anibal Sanchez Moura](#)<sup>5</sup>, [Rosely Sichieri](#)<sup>1</sup>

#### Abstract

**Objectives:** We aimed to investigate the effect of insulin sensitivity and insulin resistance status at baseline on longitudinal body mass index, and the possible effect modification by sex.

**Methods:** This is a secondary analysis of a randomized intervention community trial, in which a subgroup of 84 adolescents, aged between 10 and 12 years, were analyzed. Body weight, height, and body mass index (BMI) were determined before and after 8 months of follow-up. Glucose and serum insulin were examined at baseline and IR was defined based on the homeostasis model assessment-insulin resistance (HOMA-IR), with a cutoff  $>2.5$  for both genders. Linear mixed-effects models were performed to evaluate the influence of HOMA-IR at baseline on BMI changes over time. Models were adjusted for age, pubertal stage, and stratified by sex.

**Results:** The sample comprised 65.4% of girls and the prevalence of overweight/obesity was 54.7% among girls and 50.0% among boys. The overall prevalence of IR was 75.3%, of which 60.7% for boys and 83.0% for girls. We found an interaction effect by sex ( $p = .004$ ) for HOMA-IR as a continuous variable, with a decreased BMI rate of change among boys ( $\beta = -0.13$ ;  $p = .03$ ) but not for girls ( $\beta = +0.03$ ;  $p = .36$ ). Longitudinal BMI changes considering IR status at baseline (IR vs. non-IR) did not demonstrate any statistically significant difference for both boys ( $-0.1$  vs.  $+0.4$ ;  $p = .28$ ) and girls ( $+0.7$  vs.  $+1.0$ ;  $p = .44$ ).

**Conclusion:** Increased HOMA-IR values at baseline were associated with greater BMI reduction over time among boys but not girls, with no influence of IR status.

## Oncology

Cancer Chemother Pharmacol. 2023 Apr;91(4):331-336.

doi: 10.1007/s00280-023-04525-8. Epub 2023 Mar 23.

[Impact of pre-hydration duration on high-dose methotrexate induced nephrotoxicity in childhood acute lymphoblastic leukaemia in resource constraint centers: a randomized crossover study](#)

[Sanjeev Khera](#)<sup>1</sup>, [Deepti Mahajan](#)<sup>2</sup>, [Kapil Barbind](#)<sup>3</sup>, [Sandeep Dhingra](#)<sup>2</sup>

### Abstract

**Purpose:** Hydration before starting high-dose methotrexate (HD-MTX) ensures good renal perfusion and alkaline urinary pH. The duration of pre-hydration is not uniform across protocols. We compared 6-h versus 12-h of pre-hydration for HD-MTX therapy in childhood acute lymphoblastic leukaemia (ALL) at our centre where serial MTX level monitoring is not feasible.

**Methods:** This randomised cross-over study consecutively enrolled children  $< 12$  years with ALL receiving HD-MTX. Children with pre-existing renal disease or those exposed to nephrotoxic drugs were excluded. Two groups receiving 6-h versus 12-h pre-hydration on alternate basis in same patient (each exposed to four cycles of 2-5 g/m<sup>2</sup> of HD-MTX) were compared for HD-MTX induced nephrotoxicity (primary outcome) and other HD-MTX toxicities (HMT) as per common terminology criteria for adverse events (CTCAE-4.0). HD-MTX was administered over 24 h as per BFM-protocol-2009. Solitary MTX levels at 36-h (MTX36) were outsourced and leucovorin (LV) was started at 36 h at 15 mg/m<sup>2</sup>/dose for 6-8 doses 6-

hourly depending on MTX36. Hydration fluid was dextrose normal saline with sodium-bicarbonate and administered till last LV dose.

**Results:** Total 136 HD-MTX cycles in 34 patients (age range 5-144 months) were evaluated. Nephrotoxicity [2/68 (2.9%) in 6-h versus 1/68 (1.5%) in 12-h] and HMT incidence was comparable in two pre-hydration groups. Median MTX36 levels were not affected by duration of hydration irrespective of administered dose of HD-MTX. Median serum creatinine at baseline, post-pre-hydration and at 36-h post start of HD-MTX were comparable.

**Conclusion:** Reduction of pre-hydration duration does not affect HD-MTX induced nephrotoxicity and MTX36 levels in children < 12 years.

J Pediatr Nurs. 2023 Feb 13;S0882-5963(22)00318-9.

doi: 10.1016/j.pedn.2022.12.003. Online ahead of print.

**[The efficacy of honey or olive oil on the severity of oral mucositis and pain compared to placebo \(standard care\) in children with leukemia receiving intensive chemotherapy: A randomized controlled trial \(RCT\)](#)**

[Lina Kurdahi Badr<sup>1</sup>](#), [Rebecca El Asmar<sup>2</sup>](#), [Sarah Hakim<sup>3</sup>](#), [Rima Saad<sup>4</sup>](#), [Roni Merhi<sup>5</sup>](#), [Ammar Zahreddine<sup>6</sup>](#), [Samar Muwakkit<sup>7</sup>](#)

**Abstract**

**Background:** Oral mucositis (OM) is a significant complication occurring in approximately 40 to 80% of patients receiving chemotherapy regimens. Although a wide variety of agents have been tested to prevent OM or reduce its severity, none have provided conclusive evidence.

**Objectives:** To determine the efficacy of honey or olive oil on the severity and OM pain in children with leukemia and suffering from OM compared to placebo (standard care) and, to assess which of the two interventions is more beneficial.

**Methods:** A single blind randomized controlled study (RCT) was used to evaluate the effect of Manuka honey or olive oil, in the treatment of chemotherapy-related OM in 42 children with leukemia. The primary outcome was the severity of mucositis, using the World Health Organization (WHO) scale and the secondary outcome was the pain assessed using the Visual analogue scale (VAS).

**Results:** Children who received the honey had less severe OM (assessed on the (WHO) scale),  $p = 0.00$  and less pain (assessed on the VAS scale),  $p = 0.00$ , compared to the control group. Children who received the olive oil had less pain than the control group,  $p = 0.00$ , although not lower than the honey group.

**Conclusion:** Manuka honey or olive oil can be used as alternative therapies by nurses to children with leukemia and suffering from OM, especially in low and middle-income countries where more expensive therapies may not be available or economical.

Pediatr Blood Cancer. 2023 Jul;70(7):e30309.

doi: 10.1002/pbc.30309. Epub 2023 Apr 14.

**[Efficacy and safety of zinc in the prevention of oral mucositis in children with cancer receiving intensified chemotherapy: A randomized double-blind placebo-controlled trial](#)**

[Dinesh Shah<sup>1</sup>](#), [Aditya Gupta<sup>2</sup>](#), [Jagdish Prasad Meena<sup>2</sup>](#), [Aditya Kumar Gupta<sup>2</sup>](#), [Thirumurthy Velpandian<sup>3</sup>](#), [Ravindra Mohan Pandey<sup>4</sup>](#), [Harshita Makkar<sup>1</sup>](#), [Rachna Seth<sup>2</sup>](#)

## Abstract

**Background and aims:** A limited number of safe and effective preventive options for oral mucositis (OM) are available. This randomized, double-blind, placebo-controlled trial aimed to evaluate the efficacy and safety of zinc in preventing OM in children with cancer receiving intensified chemotherapy.

**Methods:** Children aged 3-18 years were randomized to receive oral zinc at 1 mg/kg/dose daily for 14 days or a placebo at the same doses and schedule. The primary outcome of this study was to determine the effect of oral zinc in the prevention of OM, and secondary outcomes included any adverse effect of oral zinc, the severity and duration of OM, and the need for hospitalizations.

**Results:** A total of 90 children were randomized to either the oral zinc (n = 44) or placebo group (n = 46). The incidence of OM in the zinc group was 20.5%, while that in the placebo group was 19.6% (p = .91; risk ratio: 1.04, 95% CI 0.45-2.30). There were no significant adverse events of the drug observed. There were no significant differences between the two groups in the severity (p = .79), the mean time of onset (p = .09), the mean duration of OM (p = .18), and the need for hospitalizations (p = 1.0).

**Conclusions:** Among children on cancer chemotherapy, there was no decrease in the incidence of OM observed with oral zinc at a dose of 1 mg/kg/day. No significant adverse events were observed with administering oral zinc. Further research is warranted to test higher doses of oral zinc with longer duration for a clinically significant effect.

Blood Cancer J. 2022 Sep 6;12(9):131.

doi: 10.1038/s41408-022-00726-1.

## [Two-drug versus three-drug induction chemotherapy in pediatric acute myeloid leukemia: a randomized controlled trial](#)

[Venkatraman Radhakrishnan<sup>1</sup>](#), [Sameer Bakhshi<sup>2</sup>](#), [Smita Kayal<sup>3</sup>](#), [Cherian Thampy<sup>4</sup>](#), [Ankit Batra<sup>4</sup>](#), [Praveen Kumar Shenoy<sup>4</sup>](#), [Hemanth Kumar<sup>4</sup>](#), [Swaminathan Rajaraman<sup>5</sup>](#), [Shilpi Chaudhary<sup>2</sup>](#), [Reema Bisht<sup>2</sup>](#), [Biswajit Dubashi<sup>3</sup>](#), [Trivadi S Ganesan<sup>4</sup>](#)

## Abstract

The benefit of three-drug induction chemotherapy over a two-drug induction has not been evaluated in pediatric acute myeloid leukemia (AML). We, therefore, conducted a randomized controlled trial to ascertain the benefit of a three-drug induction regimen. Patients aged 1-18 years with newly diagnosed AML were randomized to two cycles of induction chemotherapy with daunorubicin and ara-C (DA) or two cycles of ara-C, daunorubicin, and etoposide (ADE). After induction, patients in both arms received consolidation with two cycles of high-dose ara-C. The study's primary objective was to compare the event-free survival (EFS) between the two arms. The secondary objectives included comparing the composite complete remission (cCR) rates, overall survival (OS), and toxicities. The study randomized 149 patients, 77 in the DA and 72 in the ADE arm. The median age was 8.7 years, and 92 (62%) patients were males. The median follow-up was 50.9 months. The cCR rate in the DA and ADE arm were 82% and 79% (p = 0.68) after the second induction. There were 13 (17%) induction deaths in the DA arm and 12 (17%) in the ADE arm (p = 0.97). The 5-year EFS in the DA and ADE arm was 34.4% and 34.5%, respectively (p =

0.66). The 5-year OS in the DA and ADE arms was 41.4% and 42.09%, respectively ( $p = 0.74$ ). There were no significant differences in toxicities between the regimens. There was no statistically significant difference in EFS, OS, CR, or toxicity between ADE and DA regimens in pediatric AML.

Cancer Chemother Pharmacol. 2022 Dec;90(6):445-453.

doi: 10.1007/s00280-022-04482-8. Epub 2022 Oct 17.

**[A prospective, open-label, randomised, parallel design study of 4 generic formulations of intramuscular L-asparaginase in childhood precursor B-cell acute lymphoblastic leukaemia \(ALL\)](#)**

[Suja Johnson](#)<sup>1</sup>, [Chetan Dhamne](#)<sup>2,3</sup>, [Hari Sankaran](#)<sup>2</sup>, [Khushboo A Gandhi](#)<sup>1</sup>, [Pallavi Rane](#)<sup>1</sup>, [Nirmaly Roy Moulik](#)<sup>1,2</sup>, [Shraddha Mahesh Jadhav](#)<sup>1</sup>, [Murari Gurjar](#)<sup>1</sup>, [Gaurav Narula](#)<sup>2,3</sup>, [Shripad Banavali](#)<sup>2,3</sup>, [Vikram Gota](#)<sup>4,5</sup>

**Abstract**

**Aims:** L-asparaginase is an essential medicine for childhood ALL. The quality of generic L-asparaginase available in India is a matter of concern. We compared four commonly used generic formulations of L-asparaginase in India.

**Materials and methods:** We conducted a prospective, open-label, randomised trial of four generic formulations of asparaginase for the treatment of patients with newly diagnosed intermediate-risk B-ALL. Patients were randomly assigned in a 1:1:1:1 ratio to receive generic asparaginase at a dose of at 10,000 IU/m<sup>2</sup> on days 9, 12, 15, and 18 of a 35-day cycle (Induction treatment). The primary end points were to determine the difference in the asparaginase activity and asparagine depletion. Historical patients who received L-asparaginase Medac (innovator) served as controls.

**Results:** A total of 48 patients underwent randomization; 12 patients each in the four arms. Failure to achieve predefined activity threshold of 100 IU/L was observed in 9/40 samples of Generic A (22.5%), 23/40 of Generic B (57.5%), and 43/44 (98%) each of Generic C and D. All 27 samples from seven historical patients who were administered Medac had activity  $\geq$  100 IU/L. The average activity was significantly higher for Generic A, 154 (70.3, 285.4) IU/L followed by Generic B 84.5(44.2, 289.1) IU/L, Generic C 45(14.4, 58.4) IU/L, and Generic D 20.4(13, 35) IU/L. Only 6 patients had asparaginase activity  $\geq$  100 IU/L on each of the four occasions (Generic A = 5; Generic B = 1), and none of them developed Anti-Asparaginase Antibodies (AAA). On the other hand, AAA was observed in 12/36 patients who had at least one level  $\leq$  100 IU/L ( $P \leq$  0.05): Generic A 3/5, Generic B = 3/9, Generic D (4/11), and Generic C (5/11).

**Conclusion:** Generic A and B had better trough asparaginase activity compared to Generic D and C. Overall, generic formulations had lower asparaginase activity which raises serious clinical concerns regarding their quality. Until strict regulatory enforcement improves the quality of these generics, dose adaptive approaches coupled with therapeutic drug monitoring need to be considered.

BMJ Support Palliat Care. 2022 Dec;12(4):421-430.

doi: 10.1136/spcare-2022-003833. Epub 2022 Jul 8.



**Neutropenic versus regular diet for acute leukaemia induction chemotherapy: randomised controlled trial**

[Venkatraman Radhakrishnan](#)<sup>#1</sup>, [Perraju Bhaskar Bhuvan Lagudu](#)<sup>#2</sup>, [Devleena Gangopadhyay](#)<sup>2</sup>, [Varalakshmi Vijaykumar](#)<sup>2</sup>, [Swaminathan Rajaraman](#)<sup>3</sup>, [Jayachandran Perumal Kalaiyarasi](#)<sup>2</sup>, [Prasanth Ganesan](#)<sup>4</sup>, [Trivadi S Ganesan](#)<sup>5</sup>

**Abstract**

**Objectives:** Restriction of raw fruits and vegetables (neutropenic diet) is advised for patients receiving treatment for acute leukaemia in low-income and middle-income countries (LMICs) to reduce infections despite evidence to the contrary from high-income countries. We, therefore, conducted a randomised controlled trial to ascertain the efficacy of the neutropenic diet in an LMIC setting.

**Methods:** Patients aged 1-60 years receiving induction chemotherapy for acute leukaemia were randomised to a regular or neutropenic diet. The study's primary objective was to compare the incidence of major infections among patients receiving the two diets during induction chemotherapy. The secondary objectives were to compare stool microbial flora and induction mortality rates.

**Results:** We randomised 200 patients, 98 patients to the regular diet arm and 102 to the neutropenic diet arm. Major infections occurred in 32 (32%) patients in the regular diet arm and 26 (25%) patients in the neutropenic diet arm ( $p=0.26$ ). There were no statistically significant differences between patients receiving a regular diet versus neutropenic diet for blood culture positivity ( $n=6$  vs  $9$ ), inotropic support ( $17$  vs  $12$ ), mechanical ventilation ( $8$  vs  $5$ ), third-line antibiotic use ( $28$  vs  $20$ ), minor infections ( $12$  vs  $9$ ), induction mortality ( $9$  vs  $4$ ) and remission status ( $94\%$  vs  $94\%$ ). The stool culture on day 15 of induction grew multidrug-resistant bacteria in  $38\%$  of patients in the regular diet arm and  $35\%$  in the neutropenic diet arm ( $p=0.67$ ).

**Conclusions:** A neutropenic diet did not prevent infections, reduce mortality or change stool microbial flora in patients with acute leukaemia.

Pediatr Blood Cancer. 2023 May 27;e30444.

doi: 10.1002/pbc.30444. Online ahead of print.

**A single-blinded, randomized controlled trial of standard versus higher dose carboplatin-based intravenous chemotherapy for group D and E retinoblastoma**

[Pritam Singha Roy](#)<sup>1</sup>, [Safal Muhammed](#)<sup>1,2</sup>, [Usha Singh](#)<sup>3</sup>, [Sameeksha Gowravajhala](#)<sup>3</sup>, [Richa Jain](#)<sup>1</sup>, [Amita Trehan](#)<sup>1</sup>, [Deepak Bansal](#)<sup>1</sup>

**Abstract**

**Background:** Access to intra-arterial chemotherapy for retinoblastoma in low- and middle-income countries (LMICs) is limited. There is a need to optimize the efficacy of systemic chemotherapy for advanced intraocular retinoblastoma, particularly in LMICs. The aim was to compare the efficacy of standard versus higher dose carboplatin-based intravenous chemotherapy for group D and E retinoblastoma.

**Methods:** The single-center, single-blinded, randomized study was conducted during 2019-2021. Patients with newly diagnosed group D or E retinoblastoma were randomized to receive vincristine, etoposide, and standard versus higher dose ( $<36$  months:  $18.6$  vs.  $28$  mg/kg;  $\geq 36$  months:  $560$  vs.  $840$  mg/m<sup>2</sup>) carboplatin. Examination under anesthesia and ultrasonography was performed at diagnosis and following three cycles of chemotherapy. Group E eyes with poor likelihood of globe/vision salvage at diagnosis were excluded.

**Results:** Thirty-two eyes of 30 patients were analyzed: 17 group D and 15 group E eyes. The tumor response to chemotherapy with regards to regression pattern ( $p = .72$ ), tumor shrinkage (diameter:  $p = .11$ , height:  $p = .96$ ), subretinal seeds ( $p = .91$ ), and vitreous seeds ( $p = .9$ ) were comparable between the two treatment arms. The globe salvage (group D [82% vs. 67%;  $p = .58$ ]; group E [12.5% vs. 29%;  $p = .57$ ]) and salvage of meaningful vision (group D [100% vs. 75%;  $p = .13$ ]; group E [100% vs. 50%;  $p = .48$ ]) were comparable between standard and higher dose arms. No excess treatment-related toxicity was observed in the higher dose arm.

**Conclusions:** Higher dose carboplatin-based intravenous chemotherapy did not result in superior globe or vision salvage in group D or E retinoblastoma.

Int J Radiat Oncol Biol Phys. 2022 Aug 1;113(5):996-1002.

doi: 10.1016/j.ijrobp.2022.04.024. Epub 2022 May 11.

### **Radiation Therapy Dose Escalation in Unresectable Ewing Sarcoma: Final Results of a Phase 3 Randomized Controlled Trial**

[Siddhartha Laskar](#)<sup>1</sup>, [Shwetabh Sinha](#)<sup>2</sup>, [Abhishek Chatterjee](#)<sup>2</sup>, [Nehal Khanna](#)<sup>2</sup>, [Jifmi Jose Manjali](#)<sup>2</sup>, [Ajay Puri](#)<sup>3</sup>, [Ashish Gulia](#)<sup>3</sup>, [Prakash Nayak](#)<sup>3</sup>, [Tushar Vora](#)<sup>4</sup>, [Girish Chinnaswamy](#)<sup>4</sup>, [Maya Prasad](#)<sup>4</sup>, [Jyoti Bajpai](#)<sup>5</sup>, [Shashikant Juvekar](#)<sup>6</sup>, [Subhash Desai](#)<sup>6</sup>, [Amit Janu](#)<sup>6</sup>, [Venkatesh Rangarajan](#)<sup>7</sup>, [Nilendu Purandare](#)<sup>7</sup>, [Sneha Shah](#)<sup>7</sup>, [Bharat Rekhi](#)<sup>8</sup>, [Nirmala Jambhekar](#)<sup>8</sup>, [Mary Ann Muckaden](#)<sup>2</sup>, [Purna Kurkure](#)<sup>4</sup>

#### **Abstract**

**Purpose:** Our aim was to assess the effect of radiation therapy (RT) dose escalation on outcomes in surgically unresectable Ewing sarcoma (ES)/primitive neuroectodermal tumor (PNET).

**Methods and materials:** Patients with nonmetastatic unresectable ES/PNET (excluding intracranial/chest wall) receiving vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide chemotherapy, planned for definitive RT, were accrued in this single-institution, open-label, phase 3 randomized controlled trial. Randomization was between standard dose RT (SDRT; 55.8 Gy/31 fractions/5 days a week) versus escalated dose RT (EDRT; 70.2 Gy/39 fractions/5 days a week) with a primary objective of improving local control (LC) by 17% (65%-82%). Secondary outcomes included disease-free survival (DFS), overall survival (OS), and functional outcomes by Musculoskeletal Tumor Society score.

**Results:** Between April 2005 and December 2015, 95 patients (SDRT 47 and EDRT 48) with a median age of 17 years (interquartile range, 13-23 years) were accrued. The majority of patients were male (59%). Pelvis was the most common site of primary disease ( $n = 60$ ; 63%). The median largest tumor dimension (9.7 cm) and the median maximum standardized uptake value (8.2) on pretreatment fluorodeoxyglucose positron emission tomography-computed tomography were similar. At a median follow-up of 67 months, the 5-year LC, DFS, and OS for the entire cohort was 62.4%, 41.3%, and 51.9%, respectively. The 5-year LC was significantly better in EDRT compared with SDRT (76.4% vs 49.4%;  $P = .02$ ). The differences in DFS and OS at 5 years (for EDRT vs SDRT) did not achieve statistical significance (DFS 46.7% vs 31.8%;  $P = .22$  and OS 58.8% vs 45.4%;  $P = .08$ ). There was a higher incidence of Radiation Therapy Oncology Group grade >2 skin toxic effects (acute) in the EDRT arm (10.4% vs 2.1%;  $P = .08$ ) with excellent functional outcomes (median Musculoskeletal Tumor Society score = 29) in both arms.

**Conclusions:** EDRT results in improved LC with good functional outcomes without a significant increase in toxic effects. Radiation dose escalation should be considered for surgically unresectable nonmetastatic ES/PNET.

J Pediatr Hematol Oncol. 2022 Nov 1;44(8):446-453.

doi: 10.1097/MPH.0000000000002408. Epub 2022 Jan 28.

**Efficacy and Safety of Olanzapine in Children Receiving Highly Emetogenic Chemotherapy: A Randomized, Double-blind Placebo-controlled Phase 3 Trial**

Abdul W Moothedath<sup>1</sup>, Jagdish P Meena<sup>1</sup>, Aditya K Gupta<sup>1</sup>, Thirumurthy Velpandian<sup>2</sup>, Ravindra M Pandey<sup>3</sup>, Rachna Seth<sup>1</sup>

**Abstract**

**Background:** In this trial, we evaluated the safety and efficacy of olanzapine in children receiving highly emetogenic chemotherapy.

**Materials and methods:** In this study, patients aged 3 to 18 years were randomly assigned to either the olanzapine group or the placebo group. All patients received intravenous ondansetron and dexamethasone 30 minutes before highly emetogenic chemotherapy, followed by oral ondansetron for 48 hours. Participants in the olanzapine group received olanzapine once daily on days 1 and 2, while those in the control group received a placebo in the same dosage and schedule. The primary objective was: (a) to compare the complete control rates of vomiting in the delayed phase and (b) to compare the complete control rates of vomiting in acute and overall phases. The secondary objective was to evaluate the safety of olanzapine and the need for rescue medications.

**Results:** A total of 128 patients were randomly assigned either to the olanzapine group (n=63) or the control group (n=65). Complete control of vomiting between olanzapine and placebo group was 73% versus 48% ( P =0.005) in the delayed phase, 60% versus 54% ( P =0.46) in the acute phase, and 48% versus 34% ( P =0.117) in the overall phase, respectively. Grades 1 and 2 sedation was greater in the olanzapine group (46% vs. 14%; P <0.001). A significantly higher proportion of patients in the placebo group required rescue medications for vomiting compared with in the olanzapine group ( P =0.025).

**Conclusions:** Olanzapine significantly improved complete control of vomiting in the delayed phase. A considerably lesser proportion of patients in the olanzapine group needed rescue medications.

## Ophthalmology and optometry

Curr Eye Res. 2022 Dec 29;1-6.

doi: 10.1080/02713683.2022.2162925. Online ahead of print.

**Low Dose Atropine in Preventing the Progression of Childhood Myopia: A Randomised Controlled Trial**

Isha Sharma<sup>1</sup>, Gopal K Das<sup>1</sup>, Jolly Rohatgi<sup>1</sup>, Pramod K Sahu<sup>1</sup>, Pragti Chhabra<sup>2</sup>, Rahul Bhatia<sup>1</sup>

**Abstract**

**Purpose:** To study the efficacy of low dose atropine (0.01%) eye drops in preventing myopia progression in children by comparing the mean change in spherical equivalent (diopter) and axial length (mm) over a period of one year to a control group and study its effect on near vision, pupil size, keratometry and pachymetry.

**Methods:** 200 eyes of 100 myopic children were randomized into two groups based on a computer-generated random number table. The treatment group was administered 0.01% atropine eye drop once at bedtime and control group was administered a placebo. The follow up was done 3-monthly for 12 months by assessing the mean change in spherical equivalent and mean change in axial length. Other parameters like near vision, pupil size, keratometry and pachymetry were assessed at each follow up.

**Result:** The study was age and sex matched. The mean change in spherical equivalent refraction and axial length was significantly lower in the treatment group ( $0.31 \pm 0.55$  D;  $0.11 \pm 0.22$  mm) than the placebo group ( $0.80 \pm 1.65$  D;  $0.23 \pm 0.44$  D) ( $p$ -value: 0.003). Less steepening of the corneal curvature was observed in the treatment group ( $0.16 \pm 0.28$  D vs  $0.29 \pm 0.3$  D;  $p < 0.001$ ) and the mean change in pachymetry was comparable between the groups ( $0.00 \pm 0.01$ ) ( $p$ -value 0.489). No significant change was seen in near vision (96% of the eyes with atropine had no change in near vision; 2% of the eyes had a change of near vision by one line ( $p$ -value 0.500); 2% had a change by 3 lines ( $p$ -value: 0.07) or pupil size following treatment.

**Conclusion:** The use of 0.01% atropine eye drop reduced the progression of myopia over the study period of one year with no significant changes in near vision, pupil size. No patient reported any systemic and local side effects with administration of 0.01% atropine eye drop.

Cochrane Database Syst Rev. 2022 Dec 12;12(12):CD010790.

doi: 10.1002/14651858.CD010790.pub3.

### [Laser therapy for retinopathy in sickle cell disease](#)

[Kay Thi Myint](#)<sup>1</sup>, [Soumendra Sahoo](#)<sup>2</sup>, [Aung Win Thein](#)<sup>3</sup>, [Soe Moe](#)<sup>4</sup>, [Han Ni](#)<sup>5</sup>

#### **Abstract**

**Background:** Sickle cell disease (SCD) includes a group of inherited haemoglobinopathies affecting multiple organs including the eyes. Some people with SCD develop ocular manifestations. Vision-threatening complications are mainly due to proliferative sickle retinopathy, which is characterised by proliferation of new blood vessels. Laser photocoagulation is widely applicable in proliferative retinopathies. It is important to evaluate the efficacy and safety of laser photocoagulation in the treatment of proliferative sickle retinopathy (PSR) to prevent sight-threatening complications.

**Objectives:** To evaluate the effectiveness of various techniques of laser photocoagulation therapy in SCD-related proliferative retinopathy.

**Search methods:** We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books. Date of last search: 4 July 2022. We also searched the following resources (26 June 2022): Latin American and Caribbean Health Science Literature Database (LILACS); WHO International Clinical Trials Registry Platforms (ICTRP); and ClinicalTrials.gov.

**Selection criteria:** Randomised controlled trials comparing laser photocoagulation to no treatment in children and adults with SCD.

**Data collection and analysis:** Two review authors independently assessed eligibility and risk of bias of the included trials; we extracted and analysed data, contacting trial authors for additional information. We assessed the certainty of the evidence using the GRADE criteria.

**Main results:** We included three trials (414 eyes of 339 children and adults) comparing the efficacy and safety of laser photocoagulation to no therapy in people with PSR. There were 160 males and 179 females ranging in age from 13 to 67 years. The trials used different laser photocoagulation techniques; one single-centre trial employed sectoral scatter laser photocoagulation using an argon laser; a two-centre trial employed feeder vessel coagulation using argon laser in one centre and xenon arc in the second centre; while a third trial employed focal scatter laser photocoagulation using argon laser. The mean follow-up periods were 21 to 32 months in one trial, 42 to 47 months in a second, and 48 months in the third. Two trials had a high risk of allocation bias due to the randomisation method for participants with bilateral disease; the third trial had an unclear risk of selection bias. One trial was at risk of reporting bias. Given the unit of analysis is the eye rather than the individual, we chose to report the data narratively. Using sectoral scatter laser photocoagulation, one trial (174 eyes) reported no difference between groups for complete regression of PSR: 30.2% in the laser group and 22.4% in the control group. The same trial also reported no difference between groups in the development of new PSR: 34.3% of lasered eyes and 41.3% of control eyes (very low-certainty evidence). The two-centre trial using feeder vessel coagulation, only presented data at follow-up for one centre (mean period of nine years) and reported the development of new sea fan in 48.0% in the treated and 45.0% in the control group; no statistical significance ( $P = 0.64$ ). A third trial reported regression in 55% of the laser group versus 28.6% of controls and progression of PSR in 10.5% of treated versus 25.7% of control eyes. We graded the evidence for these two primary outcomes as very low-certainty evidence. The sectoral scatter laser photocoagulation trial reported visual loss in 3.0% of treated eyes (mean follow-up 47 months) versus 12.0% of controlled eyes (mean follow-up 42 months) ( $P = 0.019$ ). The feeder vessel coagulation trial reported visual loss in 1.14% of the laser group and 7.5% of the control group (mean follow-up 26 months at one site and 32 months in another) ( $P = 0.07$ ). The focal scatter laser photocoagulation trial (mean follow-up of four years) reported that 72/73 eyes had the same visual acuity, while visual loss was seen in only one eye from the control group. We graded the certainty of the evidence as very low. The sectoral scatter laser trial detected vitreous haemorrhage in 12.0% of the laser group and 25.3% of control with a mean follow-up of 42 (control) to 47 months (treated) ( $P \leq 0.5$ ). The two-centre feeder vessel coagulation trial observed vitreous haemorrhage in 3.4% treated eyes (mean follow-up 26 months) versus 27.5% control eyes (mean follow-up 32 months); one centre (mean follow-up nine years) reported vitreous haemorrhage in 1/25 eyes (4.0%) in the treatment group and 9/20 eyes (45.0%) in the control group ( $P = 0.002$ ). The scatter laser photocoagulation trial reported that vitreous haemorrhage was not seen in the treated group compared to 6/35 (17.1%) eyes in the control group and appeared only in the grades B and (PSR) stage III) ( $P < 0.05$ ). We graded evidence for this outcome as low-certainty. Regarding adverse effects, only one occurrence of retinal tear was reported. All three trials reported on retinal detachment, with no significance across the treatment and control groups (low-certainty evidence). One trial reported on choroidal neovascularization, with treatment with xenon arc found to be associated with a significantly higher risk, but visual loss related to this complication is uncommon with long-term follow-up of three years or more. The included trials did not report on other adverse effects or quality of life.

**Authors' conclusions:** Our conclusions are based on the data from three trials (two of which were conducted over 30 years ago). Given the limited evidence available, which we assessed to be of low- or very low-certainty, we are uncertain whether laser therapy for sickle cell retinopathy improves the outcomes measured in this review. This treatment does not appear to have an effect on clinical outcomes such as regression of PSR and development of new incidences. No evidence is available assessing efficacy in relation to patient-important outcomes (such as quality of life or the loss of a driving licence). Further research is needed to examine the safety of laser treatment compared to other interventions such as intravitreal injection of anti-vascular endothelial growth factors (VEGFs). Patient-important outcomes as well as cost-effectiveness should be addressed.

## Trachoma

JAMA Netw Open. 2022 Aug 1;5(8):e2228244.

doi: 10.1001/jamanetworkopen.2022.28244.

### [Effect of Biannual Mass Azithromycin Distributions to Preschool-Aged Children on Trachoma Prevalence in Niger: A Cluster Randomized Clinical Trial](#)

[Ahmed M Arzika](#)<sup>1,2</sup>, [Dallas Mindo-Panasis](#)<sup>3</sup>, [Amza Abdou](#)<sup>4</sup>, [Boubacar Kadri](#)<sup>4</sup>, [Beido Nassirou](#)<sup>4</sup>, [Ramatou Maliki](#)<sup>1,2</sup>, [Amer F Alsoudi](#)<sup>3</sup>, [Tianyi Zhang](#)<sup>3</sup>, [Sun Y Cotter](#)<sup>3</sup>, [Elodie Lebas](#)<sup>3</sup>, [Kieran S O'Brien](#)<sup>3</sup>, [E Kelly Callahan](#)<sup>5</sup>, [Robin L Bailey](#)<sup>6</sup>, [Sheila K West](#)<sup>7</sup>, [E Brook Goodhew](#)<sup>8</sup>, [Diana L Martin](#)<sup>8</sup>, [Benjamin F Arnold](#)<sup>3,9</sup>, [Travis C Porco](#)<sup>3,9,10</sup>, [Thomas M Lietman](#)<sup>3,9,10,11</sup>, [Jeremy D Keenan](#)<sup>3,9</sup>, [Macrolides Oraux pour Réduire les Décès Avec un Oeil sur la Résistance \(MORDOR\)–Niger Study Group](#)

#### Abstract

**Importance:** Because transmission of ocular strains of *Chlamydia trachomatis* is greatest among preschool-aged children, limiting azithromycin distributions to this age group may conserve resources and result in less antimicrobial resistance, which is a potential advantage in areas with hypoendemic trachoma and limited resources.

**Objective:** To determine the efficacy of mass azithromycin distributions to preschool-aged children as a strategy for trachoma elimination in areas with hypoendemic disease.

**Design, setting, and participants:** In this cluster randomized clinical trial performed from November 23, 2014, until July 31, 2017, thirty rural communities in Niger were randomized at a 1:1 ratio to biannual mass distributions of either azithromycin or placebo to children aged 1 to 59 months. Participants and study personnel were masked to treatment allocation. Data analyses for trachoma outcomes were performed from October 19, 2021, through June 10, 2022.

**Interventions:** Every 6 months, a single dose of either oral azithromycin (20 mg/kg using height-based approximation for children who could stand or weight calculation for small children) or oral placebo was provided to all children aged 1 to 59 months.

**Main outcomes and measures:** Trachoma was a prespecified outcome of the trial, assessed as the community-level prevalence of trachomatous inflammation-follicular and trachomatous inflammation-intense through masked grading of conjunctival photographs from a random sample of 40 children per community each year during the 2-year study period. A secondary outcome was the seroprevalence of antibodies to *C trachomatis* antigens.



**Results:** At baseline, 4726 children in 30 communities were included; 1695 children were enrolled in 15 azithromycin communities and 3031 children were enrolled in 15 placebo communities (mean [SD] proportions of boys, 51.8% [4.7%] vs 52.0% [4.2%]; mean [SD] age, 30.8 [2.8] vs 30.6 [2.6] months). The mean coverage of study drug for the 4 treatments was 79% (95% CI, 75%-83%) in the azithromycin group and 82% (95% CI, 79%-85%) in the placebo group. The mean prevalence of trachomatous inflammation-follicular at baseline was 1.9% (95% CI, 0.5%-3.5%) in the azithromycin group and 0.9% (95% CI, 0-1.9%) in the placebo group. At 24 months, trachomatous inflammation-follicular prevalence was 0.2% (95% CI, 0-0.5%) in the azithromycin group and 0.8% (95% CI, 0.2%-1.6%) in the placebo group (incidence rate ratio adjusted for baseline: 0.18 [95% CI, 0.01-1.20]; permutation P = .07).

**Conclusions and relevance:** The findings of this trial do not show that biannual mass azithromycin distributions to preschool-aged children were more effective than placebo, although the underlying prevalence of trachoma was low. The sustained absence of trachoma even in the placebo group suggests that trachoma may have been eliminated as a public health problem in this part of Niger.

Am J Trop Med Hyg. 2023 Jan 9;108(2):261-267.

doi: 10.4269/ajtmh.22-0535. Print 2023 Feb 1.

### **Prevalence of Ocular Chlamydia trachomatis Infection in Amhara Region, Ethiopia, after 8 Years of Trachoma Control Interventions**

[Scott D Nash<sup>1</sup>](#), [Ambahun Chernet<sup>2</sup>](#), [Paul Weiss<sup>3</sup>](#), [Andrew W Nute<sup>1</sup>](#), [Mulat Zerihun<sup>2</sup>](#), [Eshetu Sata<sup>2</sup>](#), [Demelash Gessese<sup>2</sup>](#), [Kimberly A Jensen<sup>1</sup>](#), [Zebene Ayele<sup>2</sup>](#), [Berhanu Melak<sup>2</sup>](#), [Taye Zeru<sup>4</sup>](#), [Abdulkerim Mengistu<sup>5</sup>](#), [Adisu Abebe<sup>5</sup>](#), [Fikre Seife<sup>6</sup>](#), [Zerihun Tadesse<sup>2</sup>](#), [E Kelly Callahan<sup>1</sup>](#)

#### **Abstract**

Although trachoma mass drug administration (MDA) programs target ocular Chlamydia trachomatis, the global trachoma control program does not monitor infection as a measure of impact but instead relies on monitoring clinical indicators. This study aimed to monitor the prevalence of ocular C. trachomatis among a population-based sample of children ages 1-5 years throughout Amhara, Ethiopia, a region that has received approximately 8 years of annual MDA as part of trachoma control. Between 2014 and 2021, trachoma impact surveys and surveillance surveys were conducted in all 156 districts of Amhara using a multistage cluster randomized methodology. Certified graders assessed individuals ages  $\geq 1$  year for trachomatous inflammation-follicular (TF), and a random subset of children ages 1-5 years also provided a conjunctival swab. Polymerase chain reaction was used to test for C. trachomatis. A total of 28,410 conjunctival swabs were collected from children ages 1-5 years across Amhara. The regional C. trachomatis infection prevalence was 4.7% (95% uncertainty interval: 4.3-5.1%). Infection was detected in all 10 zones of the region and ranged from 0.2% in Awi Zone to 11.9% in Waghemra Zone. Infection was detected in 17 (26%) districts with a TF prevalence  $< 10\%$  and in 7 (21%) districts with a TF prevalence  $< 5\%$ . Through programmatic monitoring of C. trachomatis infection, this study demonstrated that considerable infection remained throughout Amhara despite approximately 8 years of trachoma interventions and that enhanced interventions such as more frequent than annual MDA will be needed if elimination thresholds are to be reached.

## Oral health / dentistry

BMC Oral Health. 2023 Jun 2;23(1):349.

doi: 10.1186/s12903-023-03045-4.

### [The effectiveness of topical fluoride agents on preventing development of approximal caries in primary teeth: a randomized clinical trial](#)

[Parach Sirivichayakul<sup>1</sup>](#), [Varangkanar Jirarattanasopha<sup>2</sup>](#), [Araya Phonghanyudh<sup>3</sup>](#), [Pitchaya Tunlayadechanont<sup>1</sup>](#), [Ploychompoo Khumsub<sup>4</sup>](#), [Duangporn Duangthip<sup>5</sup>](#)

#### Abstract

**Background:** This 18-month randomized clinical trial aimed to compare the effectiveness of two topical fluoride applications versus placebo control on preventing development of approximal caries in primary teeth.

**Methods:** Preschool children were recruited if they had at least one initial approximal carious lesion at the distal surface of the canines, both approximal surfaces of the first molars, or the mesial surface of the second molars assessed from bitewing radiographs. The participants were randomly allocated into 3 intervention groups: Group 1 (placebo control), Group 2 (5% sodium fluoride [NaF] varnish), and Group 3 (38% silver diamine fluoride [SDF]). All agents were applied semiannually. Two calibrated examiners evaluated the caries development from bitewing radiographs. Caries development was recorded when the baseline sound surface or initial approximal carious lesion surface developed dentin caries (beyond the outer one-third of dentine) at the follow-up examination. The intention-to-treat approach was adopted. The Chi-square test was used to analyze the effectiveness of topical fluoride agents in preventing approximal caries development and the effect of other variables. The multi-level logistic regression analysis was performed to assess the relative effectiveness of topical fluoride agents in preventing approximal caries development at the 18-month follow-up.

**Results:** At baseline, 190 participants with 2,685 sound or initial caries at the approximal surfaces were recruited. No differences in participant demographic backgrounds, oral health related habits, or caries experience were observed among the 3 groups ( $P > 0.05$ ). After 18 months, 155 (82%) participants remained in the study. The rates of developing approximal caries in Groups 1, 2, and 3 were 24.1%, 17.1%, and 27.2%, respectively ( $P < 0.001$ ,  $\chi^2$  test). After adjusting for confounding factors and clustering effect, the multilevel logistic regression analysis showed no differences in caries development rates between the 3 groups ( $P > 0.05$ ). Tooth type and the extent of a carious lesion at baseline were the significant factors for caries development.

**Conclusion:** At 18-month follow-up, after adjusting for confounding factors and clustering effect, there were no statistically significant differences in preventing of approximal caries development between the semiannual application of 5%NaF, 38%SDF, or placebo.

Community Dent Oral Epidemiol. 2022 Dec;50(6):559-569.

doi: 10.1111/cdoe.12710. Epub 2022 Feb 9.

### [\*\*A randomized controlled trial of 6-month dental home visits on 24-month caries incidence in preschool children\*\*](#)

[Muneer Gohar Babar<sup>1</sup>](#), [Niekla Survia Andiesta<sup>1</sup>](#), [Sobia Bilal<sup>1</sup>](#), [Zamros Yuzadi Mohd Yusof<sup>2</sup>](#), [Jennifer Geraldine Doss<sup>2</sup>](#), [Allan Pau<sup>1</sup>](#)

#### **Abstract**

**Objectives:** This paper reports on the effect of 6-month dental home visits compared to no dental home visits on 24-month caries incidence in 5- to 6-year-olds.

**Methods:** 5- to 6-year-olds attending kindergartens were randomized to receive either 6-month dental home visits and education leaflets (Intervention group) or education leaflets alone (Control group) over 24 months. To detect a 15% difference in caries incidence with a significance level of 5% and power of 80%, 88 children were calculated to be needed in the Intervention group and 88 in the Control. Baseline clinical data included oral examinations at the kindergartens. Follow-up visits were made on the 6th, 12th and 18th month. At the end of the 24 months, both the Intervention and Control groups were visited for oral examinations. The primary outcome was caries incidence, measured by the number and proportion of children who developed new caries in the primary molars after 24 months. The secondary outcome was the number of primary molars that developed new caries (d-pms). Frequency distributions of participants by baseline socio-demographic characteristics and caries experience were calculated. The chi-square test was used to test differences between the caries experience in the Intervention and Control groups. The t test was used to compare the mean number of primary molars developing new caries between the Intervention Group and the Control Group. The number of children needed to treat (NNT) was also calculated.

**Results:** At the 24-month follow-up, 19 (14.4%) developed new caries in the Intervention Group, compared to 60 (60.0%) in the Control Group ( $p = .001$ ). On average, 0.2 (95% CI = 0.1-0.3) tooth per child in the Intervention Group was observed to have developed new caries compared to 1.1 (95% CI = 0.8-1.3) tooth per child in the Control Group ( $p = .001$ ). The number of children needed to treat (NNT) to prevent one child from developing new caries was 2.2.

**Conclusions:** The present study has demonstrated that 6-month home visits to families of 5- to 6-year-olds are effective in caries prevention in 5- to 6-year-olds of low-income families in a middle-income country where access to health services, including oral health promotion services, is limited.

Am J Trop Med Hyg. 2022 Sep 6;107(4):939-947.

doi: 10.4269/ajtmh.22-0248. Print 2022 Oct 12.

### [\*\*Long-Term Effects of a Randomized Maternal Education Trial in Rural Uganda: Implications for Child Oral Health\*\*](#)

[Marit S Engh<sup>1</sup>](#), [Grace K M Muhoozi<sup>2</sup>](#), [Moses Ngari<sup>3</sup>](#), [Anne B Skaare<sup>1</sup>](#), [Ane C Westerberg<sup>4,5</sup>](#), [Per Ole Iversen<sup>6,7,8</sup>](#), [Ingvild J Brusevold<sup>1</sup>](#), [Prudence Atukunda<sup>6</sup>](#)

#### **Abstract**

The aim was to examine oral health among 5-6-year-old children whose mothers participated in a 6 months' cluster-randomized education trial in rural Uganda starting when their children were 6-8 months old. The education focused on nutrition, oral hygiene, and child stimulation. In the current follow-up study, 357/511 (70%) children from the original trial were available for data collection (200 in the intervention and 157 in the control group).

Molar caries was assessed on intraoral photographs. Children and/or caregivers answered a WHO health questionnaire for collection of oral data. Dental practices were compared between the intervention and control group using multilevel mixed effect logistic regression accounting for clustering. The children in the intervention group had less caries compared with the control group: 41% versus 60% (odds ratio [OR] 0.46; 95% confidence intervals [CI] 0.24-0.86,  $P = 0.02$ ). The use of toothbrush to clean teeth was more frequent in the intervention than in the control group: 66% versus 38% (OR 3.39; 95% CI 1.54-7.45,  $P = 0.003$ ), as was high teeth-cleaning frequency: 74% versus 62% (OR 1.72; 95% CI 1.09-2.69,  $P = 0.02$ ). Self-reported problems such as toothache (10% versus 19%), difficulty biting (12% versus 24%) and chewing food (8.5% versus 18%) were significantly less frequent among children in the intervention compared with the control group. No significant differences were found in dietary habits. Our data shows that an educational intervention adjusted to a low-resource setting, provided in infancy, resulted in improved oral hygiene and reduced development of dental caries among children aged 5-6 years.

Community Dent Oral Epidemiol. 2023 Apr;51(2):219-227.  
doi: 10.1111/cdoe.12729. Epub 2022 Feb 2.

**[Effectiveness of school-based strategies to prevent tooth decay in Filipino children: A cluster-randomized trial](#)**

[Ryan Richard Ruff](#)<sup>1</sup>, [Bella Monse](#)<sup>2</sup>, [Denise Duijster](#)<sup>3</sup>, [Gina Santos Itchon](#)<sup>4</sup>, [Ella Naliponguit](#)<sup>5</sup>, [Habib Benzian](#)<sup>6</sup>

**Abstract**

**Objectives:** Evidence for affordable and pragmatic programmes to address the burden of untreated tooth decay in children in low- and middle-income settings is limited. This study aimed to (1) assess the effect of a government-run, school-based daily group toothbrushing programme compared to standard school-based oral health education on the incidence of dental caries and odontogenic infections in Filipino children over a period of 3 years; and (2) assess the additional preventive effect of on-demand oral urgent treatment (OUT) and weekly fluoride gel application.

**Methods:** A cluster-randomized trial was conducted in Camiguin, Philippines. Schools in three regions were randomly assigned to one of three intervention groups: The Essential Health Care Programme (EHCP), which includes daily toothbrushing with fluoride toothpaste; EHCP plus twice-yearly access to on-demand urgent oral treatment (EHCP + OUT) and EHCP plus weekly application of high-concentrated fluoride gel (EHCP + Fluoride). Schools in a nearby province with a similar child population were selected as external concurrent control group. Clinical oral examinations were performed by calibrated dentists from a random sample of 682 seven-year-old students who were examined at baseline and over the following 3 years. Outcome variables were the number of decayed primary teeth, the number of decayed, missing and filled permanent teeth (DMFT) and surfaces (DMFS), and the number of permanent teeth with pulpal involvement, ulcerations, fistula or abscess (PUFA). Data were analysed using multilevel mixed-effects negative binomial regression.

**Results:** Three years after implementation, increments in dental caries and odontogenic infections in permanent teeth did not significantly differ between the EHCP and control group, yet the incidence of DMFT was lower by 22% in children receiving EHCP. Compared to controls, children receiving EHCP + Fluoride had a significantly lower increment of DMFT,

DMFS and PUFA by 40%, 40% and 47%, respectively. Children receiving EHCP + OUT had lower incidence rates of DMFT and DMFS than control children by 23% and 28%, respectively. A lower incidence rate was also found for PUFA, but the effect was not statistically significant.

**Conclusions:** Findings suggest that the weekly application of fluoride gel and urgent oral treatment, in addition to daily school-based toothbrushing with fluoride toothpaste, are realistic and effective strategies to lower the burden of dental caries in Filipino children. Implementation challenges may explain why no substantial caries-preventive benefits were demonstrated for school-based toothbrushing only. Intervention compliance should be considered in future programme implementation and evaluation research.

J Prev Med Hyg. 2022 Jul 31;63(2):E282-E287.

doi: 10.15167/2421-4248/jpmh2022.63.2.1772. eCollection 2022 Jun.

**[Antimicrobial efficacy of Xylitol, Probiotic and Chlorhexidine mouth rinses among children and elderly population at high risk for dental caries - A Randomized Controlled Trial](#)**

[N C Krupa](#)<sup>1</sup>, [H M Thippeswamy](#)<sup>1</sup>, [B R Chandrashekar](#)<sup>1</sup>

**Abstract**

**Introduction:** Chlorhexidine is considered the most potent chemotherapeutic agent against *Streptococcus mutans*. However, its side effects due to prolonged use, indicates need for alternatives. The study intended to assess and compare antimicrobial efficacies of probiotic, xylitol and chlorhexidine mouth rinses in children and elderly.

**Methods:** The study was a Double blind Randomized Controlled Trial conducted among residential school children aged 5-12 years and elderly greater than 60 years residing in old age homes. (ClinicalTrials.gov ID: [NCT04399161](#)). 30 participants each among children and elderly were chosen based on eligibility criterion (high risk for caries). They were further randomly divided into 3 groups with 10 participants in each group. Participants were asked to rinse with 15 ml of freshly prepared mouth rinses once daily for 2 minutes for 14 days. Antimicrobial efficacy was determined by assessing change in *Streptococcus mutans* levels in dental plaque.

**Results:** Significant reduction in *Streptococcus mutans* counts were observed in both children and elderly (Chlorhexidine: mean difference = 3.11 log<sub>10</sub>CFU/g, p = 0.022, Xylitol: mean difference = 0.93 log<sub>10</sub>CFU/g, p = 0.046, Probiotic: mean difference = 1.91 log<sub>10</sub>CFU/g, p = 0.023 in children); (Chlorhexidine: mean difference = 2.23 log<sub>10</sub>CFU/g, p = 0.004, Xylitol: mean difference = 1.39 log<sub>10</sub>CFU/g, p = 0.009, Probiotic: mean difference = 1.61 log<sub>10</sub>CFU/g, p = 0.018 in elderly). Intergroup comparison showed no significant difference.

**Conclusions:** Antimicrobial efficacy of xylitol and probiotic mouth rinses were comparable to that of chlorhexidine in both children and elderly. Probiotics could potentially be more efficacious than xylitol among children.

Community Dent Oral Epidemiol. 2022 Oct;50(5):453-460.

doi: 10.1111/cdoe.12702. Epub 2021 Oct 21.

### [Cost-effectiveness and efficacy of fluoride varnish for caries prevention in South African children: A cluster-randomized controlled community trial](#)

[Susanne Effenberger](#)<sup>1</sup>, [Linda Greenwall](#)<sup>2</sup>, [Marcus Cebula](#)<sup>1</sup>, [Neil Myburgh](#)<sup>3</sup>, [Karen Simpson](#)<sup>3</sup>, [Dirk Smit](#)<sup>3</sup>, [Michael J Wicht](#)<sup>4</sup>, [Falk Schwendicke](#)<sup>5</sup>

#### **Abstract**

**Objectives:** This cluster-randomized controlled community trial aimed to assess the efficacy and costs of fluoride varnish (FV) application for caries prevention in a high-risk population in South Africa.

**Methods:** 513 children aged 4-8 years from two schools in a township in South Africa were randomly allocated by class to the FV or Control (CO) groups. In addition to supervised toothbrushing with fluoridated toothpaste in both groups, FV was applied in 3-month intervals by trained local non-professional assistants. Intraoral examinations were conducted at baseline, 12, 21 and 24 months. Primary outcome was the increment of teeth with cavitated lesions (i.e. newly developed or progressed, formerly non-cavitated lesions), requiring restoration or extraction over the study period. Additionally, treatment and re-treatment costs were analyzed.

**Results:** 513 children ( $d_{1-4}$  mft  $5.9 \pm 4.3$  (mean  $\pm$  SD)) were randomly allocated to FV ( $n = 287$ ) or CO ( $n = 226$ ). 10.2% FV and CO teeth received or required a restoration; 3.9% FV and 4.1% CO teeth were extracted, without significant differences between groups. While FV generated high initial costs, follow-up costs were comparable in both groups, resulting in FV being significantly more expensive than CO ( $1667 \pm 1055$  ZAR vs.  $950 \pm 943$  ZAR,  $p < .001$ ).

**Conclusions:** Regular FV application, in addition to daily supervised toothbrushing, had no significant caries-preventive effect and was not cost-effective in a primary school setting within a peri-urban, high-risk community in South Africa. Alternative interventions on community or public health level should be considered to reduce the caries burden in high-risk communities.

J Clin Pediatr Dent. 2023 Mar;47(2):85-100.

doi: 10.22514/jocpd.2023.014. Epub 2023 Mar 3.

### [Effects of probiotics on preventing caries in preschool children: a systematic review and meta-analysis](#)

[Nan Meng](#)<sup>1</sup>, [Qi Liu](#)<sup>1</sup>, [Qing Dong](#)<sup>1</sup>, [Jianqi Gu](#)<sup>2</sup>, [Yuanbo Yang](#)<sup>3</sup>

#### **Abstract**

This paper systematically evaluate the effects of probiotics on preventing caries in preschool children. The present systematic review was conducted following the Transparent Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines and recorded in the International prospective register of systematic reviews (PROSPERO) database (registration no: CRD42022325286). Literature were screened from PubMed, Embase, Web of Sciences, China National Knowledge Infrastructure (CNKI), Wanfang and other databases from inception to April 2022 to identify randomized controlled trials on the clinical efficacies of probiotics in preventing dental caries in preschool children and extract relevant data. The meta-analysis was performed using the RevMan5.4 software and the Stata16. Cochrane handbook was used to assess the risk of bias. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiler 3.6) was used to determine the evidence quality. A total of 17 randomized controlled trials were eligible, of which two trials had certain levels of bias and 15 had a low risk of bias. Evidence quality assessment showed that



the included trials were of medium quality. The meta-analysis results showed that *Lactobacillus rhamnosus* was associated with a reduced incidence ( $p = 0.005$ ) and progression ( $p < 0.001$ ) of caries in preschool children. Probiotics could reduce the number of high-level *Streptococcus mutans* in saliva ( $p < 0.00001$ ) but could not reduce the number of *Streptococcus mutans* in dental plaque nor the amount of *Lactobacillus* in the saliva and dental plaque. Current evidence shows that probiotics could prevent caries in preschool children, but *Lactobacillus rhamnosus* was more effective in preventing caries than others. Although probiotics could reduce high levels of *Streptococcus mutans* in saliva, they could not reduce the amount of *Lactobacillus* in saliva and dental plaque.

## Pain

## Poisoning and toxins

(See envenomation)

## Refugee health and humanitarian settings

J Prev (2022). 2023 Jan 17.

doi: 10.1007/s10935-023-00721-7. Online ahead of print.

### [Children Immunization App \(CIMA\): A Non-randomized Controlled Trial Among Syrian Refugees in Zaatari Camp, Jordan](#)

[Soha El-Halabi](#)<sup>1</sup>, [Yousef S Khader](#)<sup>2</sup>, [Mohammad Abu Khdeir](#)<sup>3</sup>, [Claudia Hanson](#)<sup>1</sup>, [Tobias Alfvén](#)<sup>1</sup>, [Ziad El-Khatib](#)<sup>4,5</sup>

#### Abstract

Approximately 20 million children are not vaccinated, especially among refugees. There is a growing access to smartphones, among refugees, which can help in improving their vaccination. We assessed the impact of an app for the vaccination follow-up visit among refugees in Jordan. We developed an app and tested it through a non-randomized trial at the Zaatari refugees camp in Jordan. The study was conducted during March - December 2019 at three vaccination clinics inside the camp. The study included two study groups (intervention and control groups) for refugees living at the camp. The intervention group included parents who own an Android smartphone and have one newborn that require between one and four first vaccination doses and they accepted to participate in the study, during their regular visit to the vaccination clinics. The control group was for the usual care. We compared both study groups for returning back to one follow-up visit, using Kaplan-Meier survival analysis. We recruited 936 babies ( $n = 471$ ; 50.3% in the intervention group, both study groups were similar at baseline). The majority of mothers were literate (94.2%) with a median age of 24. The majority of the babies had a vaccination card ( $n = 878$ , 94%). One quarter (26%) of mother-babies pairs of the intervention group came back within one week (versus 22% for

control group); When it comes to lost-follow-up, 22% and 28% did not have a history of returning back (intervention and control groups respectively,  $p = 0.06$ ) (Relative risk reduction: 19%). The Kaplan-Meier Survival Analysis showed a statistically significant progressive reduction in the duration of coming back late for the follow-up vaccine visit. We tested a vaccination app for the first time, in a refugee population setting. The app can be used as a reminder for parents to come back on time for their children's vaccine follow-up visits.

Vaccine. 2023 May 5;41(19):3038-3046.

doi: 10.1016/j.vaccine.2023.02.016. Epub 2023 Mar 9.

**Use of an adapted participatory learning and action cycle to increase knowledge and uptake of child vaccination in internally displaced persons camps (IVACS): A cluster-randomised controlled trial**

[Andrew J Seal<sup>1</sup>](#), [Hodan Abdullahi Mohamed<sup>2</sup>](#), [Ronald Stokes-Walter<sup>3</sup>](#), [Sadik Mohamed<sup>4</sup>](#), [Amina Mohamed Abdille<sup>5</sup>](#), [Ellyn Yakowenko<sup>6</sup>](#), [Mohamed Sheikh Omar<sup>7</sup>](#), [Mohamed Jelle<sup>8</sup>](#)

**Abstract**

**Background:** Vaccination is a key public health intervention that can reduce excess mortality in humanitarian contexts. Vaccine hesitancy is thought to be a significant problem requiring demand side interventions. Participatory Learning and Action (PLA) approaches have proven effective in reducing perinatal mortality in low income settings and we aimed to apply an adapted approach in Somalia.

**Methods:** A randomised cluster trial was implemented in camps for internally displaced people near Mogadishu, from June to October 2021. An adapted PLA approach (hPLA) was used in partnership with indigenous 'Abaay-Abaay' women's social groups. Trained facilitators ran 6 meeting cycles that addressed topics of child health and vaccination, analysed challenges, and planned and implemented potential solutions. Solutions included a stakeholder exchange meeting involving Abaay-Abaay group members and services providers from humanitarian organisations. Data was collected at baseline and after completion of the 3 month intervention cycle.

**Results:** Overall, 64.6% of mothers were group members at baseline and this increased in both arms during the intervention ( $p = 0.016$ ). Maternal preference for getting young children vaccinated was >95% at baseline and did not change. The hPLA intervention improved the adjusted maternal/caregiver knowledge score by 7.9 points (maximum possible score 21) compared to the control (95% CI 6.93, 8.85;  $p < 0.0001$ ). Coverage of both measles vaccination (MCV1) (aOR 2.43 95% CI 1.96, 3.01;  $p < 0.001$ ) and completion of the pentavalent vaccination series (aOR 2.45 95% CI 1.27, 4.74;  $p = 0.008$ ) also improved. However, adherence to timely vaccination did not (aOR 1.12 95% CI 0.39, 3.26;  $p = 0.828$ ). Possession of a home-based, child health record card increased in the intervention arm from 18 to 35% (aOR 2.86 95% CI 1.35, 6.06;  $p = 0.006$ ).

**Conclusion:** A hPLA approach, run in partnership with indigenous social groups, can achieve important changes in public health knowledge and practice in a humanitarian context.

Further work to scale up the approach and address other vaccines and population groups is warranted.

J Child Psychol Psychiatry. 2022 Jul 15.

doi: 10.1111/jcpp.13668. Online ahead of print.

**[Supporting parenting among Syrian refugees in Lebanon: a randomized controlled trial of the caregiver support intervention](#)**

[Kenneth E Miller](#)<sup>1,2</sup>, [Alexandra Chen](#)<sup>3</sup>, [Gabriela V Koppenol-Gonzalez](#)<sup>2</sup>, [Ioannis Bakolis](#)<sup>4</sup>, [Maguy Arnous](#)<sup>5</sup>, [Fadila Tossyeh](#)<sup>5</sup>, [Ahmad El Hassan](#)<sup>5</sup>, [Ahmad Saleh](#)<sup>5</sup>, [Joy Saade](#)<sup>5</sup>, [Nayla Nahas](#)<sup>6</sup>, [Marianne Abboud](#)<sup>5</sup>, [Lya Jawad](#)<sup>5</sup>, [Mark J D Jordans](#)<sup>3,4,7</sup>

**Abstract**

**Background:** Parenting interventions in humanitarian settings have prioritized the acquisition of parenting knowledge and skills, while overlooking the adverse effects of stress and distress on parenting—a key mediator of refugee children's mental health. We evaluated the effectiveness of the Caregiver Support Intervention (CSI), which emphasizes caregiver wellbeing together with training in positive parenting.

**Methods:** We conducted a two-arm randomized controlled trial of the CSI with Syrian refugees in Lebanon, with an intent-to-treat design, from September 2019–December 2020. A total of 480 caregivers from 240 families were randomized to the CSI or a waitlist control group (1:1). Retention from baseline to endline was 93%. Data on parenting and caregiver psychological wellbeing were collected at baseline, endline, and three-month follow-up. Prospective trial registration: ISRCTN22321773.

**Results:** We did not find a significant change on overall parenting skills at endline (primary outcome endpoint) ( $d = .11$ ,  $p = .126$ ) or at follow-up (Cohen's  $d = .15$ ,  $p = .054$ ). We did find a significant effect on overall parenting skills among participants receiving the full intervention—the sub-sample not interrupted by (COVID-19) ( $d = 0.25$ ,  $p < .05$ ). The CSI showed beneficial effects in the full sample at endline and follow-up on harsh parenting ( $d = -.17$ ,  $p < .05$ ;  $d = .19$ ,  $p < .05$ ), parenting knowledge ( $d = .63$ ,  $p < .001$ ;  $d = .50$ ,  $p < .001$ ), and caregiver distress ( $d = -.33$ ,  $p < .001$ ;  $d = .23$ ,  $p < .01$ ). We found no effects on parental warmth and responsiveness, psychosocial wellbeing, stress, or stress management. Changes in caregiver wellbeing partially mediated the impact of the CSI on harsh parenting, accounting for 37% of the reduction in harsh parenting.

**Conclusions:** The CSI reduced harsh parenting and caregiver distress, and demonstrated the value of addressing caregiver wellbeing as a pathway to strengthening parenting in adversity. These effects were achieved despite a pandemic-related lockdown that impacted implementation, a severe economic crisis, and widespread social unrest. Replication under less extreme conditions may more accurately demonstrate the intervention's full potential.

PLoS Med. 2023 Feb 27;20(2):e1004180.

doi: 10.1371/journal.pmed.1004180. eCollection 2023 Feb.

**[Evaluation of conditional cash transfers and mHealth audio messaging in reduction of risk factors for childhood malnutrition in internally displaced persons camps in Somalia: A 2 × 2 factorial cluster-randomised controlled trial](#)**

[Carlos S Grijalva-Eternod](#)<sup>1,2</sup>, [Mohamed Jelle](#)<sup>1</sup>, [Hani Mohamed](#)<sup>3</sup>, [Katie Waller](#)<sup>4</sup>, [Bishar Osman Hussein](#)<sup>3</sup>, [Emmanuel Barasa](#)<sup>3</sup>, [Andrea Solomon](#)<sup>5</sup>, [Sajia Mehjabeen](#)<sup>5</sup>, [Andrew Copas](#)<sup>1</sup>, [Edward Fottrell](#)<sup>1</sup>, [Andrew J Seal](#)<sup>1</sup>

## Abstract

**Background:** Cash transfer programmes are increasingly used in humanitarian contexts to help address people's needs across multiple sectors. However, their impact on the key objectives of reducing malnutrition and excess mortality remains unclear. mHealth interventions show great promise in many areas of public health, but evidence for their impact on reducing the risk factors for malnutrition is uncertain. We therefore implemented a trial to determine the impacts of 2 interventions in a protracted humanitarian context, a cash transfer conditionality and mHealth audio messages.

**Methods and findings:** A 2 × 2 factorial cluster-randomised trial was implemented in camps for internally displaced people (IDP) near Mogadishu, Somalia, starting in January 2019. The main study outcomes were assessed at midline and endline and included coverage of measles vaccination and the pentavalent immunisation series, timely vaccination, caregiver's health knowledge, and child diet diversity. Twenty-three clusters (camps) were randomised to receive or not receive conditional cash transfers (CCTs) and an mHealth intervention, and 1,430 households were followed up over 9 months. All camps received cash transfers made at emergency humanitarian level (US\$70/household/month) for 3 months followed by a further 6 months at a safety net level (US\$35). To be eligible to receive cash, households in camps receiving CCT were required to take their children <5 years age to attend a single health screening at a local clinic and were issued with a home-based child health record card. Participants in camps receiving the mHealth intervention were asked (but not required) to listen to a series of audio messages about health and nutrition that were broadcast to their mobile phone twice a week for 9 months. Participants and investigators were not blinded. Adherence to both interventions was monitored monthly and found to be high (>85%). We conducted intention-to-treat analysis. During the humanitarian intervention phase, the CCT improved coverage of measles vaccination (MCV1) from 39.2% to 77.5% (aOR 11.7, 95% CI [5.2, 26.1];  $p < 0.001$ ) and completion of the pentavalent series from 44.2% to 77.5% (aOR 8.9, 95% CI [2.6, 29.8];  $p < 0.001$ ). By the end of the safety net phase, coverage remained elevated from baseline at 82.2% and 86.8%, respectively (aOR 28.2, 95% CI [13.9, 57.0];  $p < 0.001$  and aOR 33.8, 95% CI [11.0, 103.4];  $p < 0.001$ ). However, adherence to timely vaccination did not improve. There was no change in the incidence of mortality, acute malnutrition, diarrhoea, or measles infection over the 9 months of follow-up. Although there was no evidence that mHealth increased Mother's knowledge score (aOR 1.32, 95% CI [0.25, 7.11];  $p = 0.746$ ) household dietary diversity increased from a mean of 7.0 to 9.4 (aOR 3.75, 95% CI [2.04, 6.88];  $p < 0.001$ ). However, this was not reflected by a significant increase in child diet diversity score, which changed from 3.19 to 3.63 (aOR 2.1, 95% CI [1.0, 4.6];  $p = 0.05$ ). The intervention did not improve measles vaccination, pentavalent series completion, or timely vaccination, and there was no change in the incidence of acute malnutrition, diarrhoea, measles infection, exclusive breastfeeding, or child mortality. No significant interactions between the interventions were found. Study limitations included the limited time available to develop and test the mHealth audio messages and the necessity to conduct multiple statistical tests due to the complexity of the study design.

**Conclusions:** A carefully designed conditionality can help achieve important public health benefits in humanitarian cash transfer programmes by substantially increasing the uptake of child vaccination services and, potentially, other life-saving interventions. While mHealth audio messages increased household diet diversity, they failed to achieve any reductions in child morbidity, malnutrition, or mortality.

J Child Psychol Psychiatry. 2023 Jan 2.

doi: 10.1111/jcpp.13746. Online ahead of print.

**[Improving adolescent mental health and protection in humanitarian settings: longitudinal findings from a multi-arm randomized controlled trial of child-friendly spaces among South Sudanese refugees in Uganda](#)**

[Janna Metzler](#)<sup>1</sup>, [Terry Saw](#)<sup>1</sup>, [Denis Nono](#)<sup>2</sup>, [Agatha Kadondi](#)<sup>3</sup>, [Yuan Zhang](#)<sup>1</sup>, [Cheng-Shiun Leu](#)<sup>1</sup>, [Aimyleen Gabriel](#)<sup>4</sup>, [Kevin Savage](#)<sup>5</sup>, [Cassie Landers](#)<sup>1</sup>

**Abstract**

**Background:** The effects of conflict and displacement on adolescent mental health and protection are profound and can have lasting consequences. We aimed to investigate the effectiveness of two group-based psychosocial interventions on mental health and protection of South Sudanese refugee adolescents.

**Methods:** A randomized controlled trial was done in four villages within the Omugo extension of Rhino Camp refugee settlement in the West Nile region of Uganda. Male and female adolescents (aged 9-14 years) were randomly assigned to attend 12 weeks of either a Standard psychosocial intervention delivered in a child-friendly space (CFS) or a more structured sequential delivery of psychosocial sessions guided by a newly developed Toolkit for Child-Friendly Spaces in Humanitarian Settings. The primary outcomes were psychological distress and resilience 12 months after baseline assessment. The trial is registered with ClinicalTrials.gov, [NCT03897894](#).

**Results:** Between May 28, 2019, and February 20, 2020, 1,280 eligible adolescents were recruited. With 70.2% retention at follow-up, 214 assigned to the Standard, 211 assigned to the Toolkit, and 370 assigned to the waitlist control were included in the intention-to-treat and as-treated analysis. Both the Toolkit and Standard approaches were more effective in reducing psychological distress and perceived protection risks reported by adolescents compared to no intervention. Differential intervention impacts are indicated in subgroup analyses.

**Conclusions:** The trial found that both psychosocial interventions when implemented in a CFS are well suited as a first-line mental health and violence prevention intervention for adolescent populations exposed to conflict and forced displacement. Where feasible, CFS should be implemented as a primary response strategy soon after displacement to improve psychological health and reduce the risk environment for adolescents.

Confl Health. 2022 Jul 23;16(1):42.

doi: 10.1186/s13031-022-00475-9.

**[School violence, depression symptoms, and school climate: a cross-sectional study of Congolese and Burundian refugee children](#)**

[Camilla Fabbri](#)<sup>1</sup>, [Timothy Powell-Jackson](#)<sup>2</sup>, [Baptiste Leurent](#)<sup>2,3</sup>, [Katherine Rodrigues](#)<sup>4</sup>, [Elizabeth Shayo](#)<sup>5</sup>, [Vivien Barongo](#)<sup>5</sup>, [Karen M Devries](#)<sup>2</sup>

**Abstract**

Forcibly displaced children are at increased risk of violence and mental health disorders. In refugee contexts, schools are generally perceived as protective environments where children can build a sense of belonging and recover from trauma. Evidence shows that positive school

climates can support student skills development and socio-emotional wellbeing and protect them against a host of adverse outcomes. However, schools are also places where children may experience violence, from both teachers and peers. Prevalence estimates of violence against children in humanitarian settings are scarce and evidence on the relationship between school climate and student outcomes in these contexts is non-existent. The aim of the study is to estimate the prevalence of school-based violence against children and to explore the association between perceptions of school climate and students' experiences and use of violence and their depression symptoms. We relied on data from a cross-sectional survey of students and teachers in all primary and secondary schools in Nyarugusu Refugee Camp in Tanzania, conducted as part of a cluster randomised controlled trial, to compute prevalence estimates and used mixed logistic regression analysis to assess the association between school climate and students' outcomes. We found that students in Nyarugusu experienced high levels of violence from both peers and teachers in both primary and secondary schools in the camp, with little difference between boys and girls. Nearly one in ten students screened positive for symptoms of depression. We found that opportunities for students and teachers to be involved in decision-making were associated with higher odds of violent discipline and teachers' self-efficacy was a significant protective factor against student depression symptoms. However, generally, school-level perceptions of school climate were not associated with student outcomes after adjusting for potential confounders. Our findings suggest that interventions to prevent and respond to teacher and peer violence in schools and to support students' mental health are urgently needed. Our results challenge the assumption that education environments are inherently protective for children and call for further investigation of norms around violence among students and teachers to better understand the role of school climate in refugee settings.

Int J Hyg Environ Health. 2023 May;250:114163.

doi: 10.1016/j.ijheh.2023.114163. Epub 2023 Apr 1.

[Effect of a novel hygiene intervention on older children's handwashing in a humanitarian setting in Kahda district, Somalia: A cluster-randomised controlled equivalence trial](#)

[Julie Watson](#)<sup>1</sup>, [Maud Akissi Amon-Tanoh](#)<sup>2</sup>, [Claudio Deola](#)<sup>3</sup>, [Mohamed Abdi Haji](#)<sup>4</sup>, [Mohamed Rashid Sheikh](#)<sup>4</sup>, [Feysal Abdisalan Mohamud](#)<sup>4</sup>, [Salman Yasin Ali](#)<sup>4</sup>, [Amy MacDougall](#)<sup>5</sup>, [Oliver Cumming](#)<sup>2</sup>

**Abstract**

**Introduction:** Improving handwashing with soap (HWWS) among children in humanitarian emergencies has the potential to reduce the transmission of several important infectious diseases. However, there is limited evidence on which approaches are effective in increasing HWWS among children in humanitarian settings. One recent innovation - the "Surprise Soap" intervention - was shown to be successful in a small-scale efficacy trial in a humanitarian setting in Iraq. This intervention includes soap with embedded toys delivered through a short household session comprising a glitter game, instruction of how and when to wash hands, and HWWS practice. Whilst promising, this approach has not been evaluated at programmatic scale in a complex humanitarian setting.

**Methods:** We conducted a cluster-randomised controlled equivalence trial of the Surprise Soap intervention in IDP camps in Kahda district, Somalia. Proportionate stratified random sampling was employed to recruit 200 households, with at least one child aged 5-12, across



the camps. Eligible households were randomly allocated to receive the Surprise Soap intervention (n = 100) or an active comparator handwashing intervention in which plain soap was delivered in a short household session comprising standard health-based messaging and instruction of how and when to wash hands (n = 100). The primary outcome was the proportion of pre-specified occasions when HWWS was practiced by children aged 5-12 years, measured at baseline, 4-weeks, 12 weeks, and 16 weeks post intervention delivery.

**Results:** HWWS increased in both groups (by 48 percentage points in the intervention group and 51 percentage points in the control group, at the 4-week follow up), however, there was no evidence of a difference in HWWS between the groups at the 4-week (adjusted RR (aRR) = 1.0, 95% CI 0.9-1.1), 12-week (aRR = 1.1, 95% CI 0.9-1.3), or 16-week (aRR = 1.0, 95% CI 0.9-1.2) follow-up.

**Conclusions:** In this complex humanitarian setting, where soap availability and past exposure to handwashing promotion was low, it appears that well-designed, household-level targeted handwashing interventions that include soap provision can increase child HWWS and potentially reduce disease risk, but the Surprise Soap intervention offers no marginal benefit over a standard intervention that would justify the additional costs.

## Research

Trials. 2023 Jun 7;24(1):385.

doi: 10.1186/s13063-023-07320-1.

### [Whose knowledge counts? Involving communities in intervention and trial design using community conversations](#)

[Rochelle A Burgess](#) <sup>#1</sup>, [Funmilayo Shittu](#) <sup>#2,3</sup>, [Agnese Iuliano](#) <sup>3</sup>, [Ibrahim Haruna](#) <sup>4</sup>, [Paula Valentine](#) <sup>5</sup>, [Ayobami Adebayo Bakare](#) <sup>3,6</sup>, [Tim Colbourn](#) <sup>7</sup>, [Hamish R Graham](#) <sup>8</sup>, [Eric D McCollum](#) <sup>9</sup>, [Adegoke G Falade](#) <sup>2,10</sup>, [Carina King](#) <sup>7,3</sup>; [INSPIRING Project Consortium](#)

#### Abstract

**Background:** Current debates in Global Health call for expanding methodologies to allow typically silenced voices to contribute to processes of knowledge production and intervention design. Within trial research, this has typically involved small-scale qualitative work, with limited opportunities for citizens to contribute to the structure and nature of the trial. This paper reports on efforts to move past typical formative trial work, through adaptation of community conversations (CCs) methodology, an action-oriented approach that engages large numbers of community members in dialogue. We applied the CC method to explore community perspectives about pneumonia and managing the health of children under-5 in Northern Nigeria to inform our pragmatic cluster randomised controlled trial evaluating a complex intervention to reduce under-5 mortality in Nigeria.

**Methods:** We conducted 12 rounds of community conversations with a total of 320 participants, in six administrative wards in Kiyawa Local Government Area, Jigawa state, our intervention site. Participants were male and female caregivers of children under five. Conversations were structured around participatory learning and action activities, using drawings and discussion to reduce barriers to entry. During activities participants were

placed in subgroups: younger women (18-30 years of age), older women (31-49 years) and men (18 years above). Discussions were conducted over three 2-h sessions, facilitated by community researchers. Following an initial analysis to extract priority issues and perspectives on intervention structure, smaller focus group discussions were completed with participants in five new sites to ensure all 11 administrative wards in our study site contributed to the design.

**Results:** We identified enabling and limiting factors which could shape the future trial implementation, including complex power relationships within households and wider communities shaping women's health decision-making, and the gendered use of space. We also noted the positive engagement of participants during the CC process, with many participants valuing the opportunity to express themselves in ways they have not been able to in the past.

**Conclusions:** CCs provide a structured approach to deep meaningful engagement of everyday citizens in intervention and trial designs, but require appropriate resources, and commitment to qualitative research in trials.

Clin Trials. 2023 Jun 27;17407745231182417.

doi: 10.1177/17407745231182417. Online ahead of print.

[Data monitoring committees in pediatric randomized controlled trials registered in ClinicalTrials.gov](#)

[Tiago Machado](#)<sup>1,2</sup>, [Beatrice Mainoli](#)<sup>1,2,3</sup>, [Daniel Caldeira](#)<sup>1,2</sup>, [Joaquim J Ferreira](#)<sup>1,2,4</sup>, [Ricardo M Fernandes](#)<sup>1,2,5</sup>

### Abstract

**Background:** Data monitoring committees advise on clinical trial conduct through appraisal of emerging data to ensure participant safety and scientific integrity. While consideration of their use is recommended for trials performed with vulnerable populations, previous research has shown that data monitoring committees are reported infrequently in publications of pediatric randomized controlled trials. We aimed to assess the frequency of reported data monitoring committee adoption in ClinicalTrials.gov registry records and to examine the influence of key trial characteristics.

**Methods:** We conducted a cross-sectional data analysis of all randomized controlled trials performed exclusively in a pediatric population and registered in ClinicalTrials.gov between 2008 and 2021. We used the Access to Aggregate Content of ClinicalTrials.gov database to retrieve publicly available information on trial characteristics and data on safety results. Abstracted data included reported trial design and conduct parameters, population and intervention characteristics, reasons for prematurely halting, serious adverse events, and mortality outcomes. We performed descriptive analyses on the collected data and explored the influence of clinical, methodological, and operational trial characteristics on the reported adoption of data monitoring committees.

**Results:** We identified 13,928 pediatric randomized controlled trial records, of which 39.7% reported adopting a data monitoring committee, 49.0% reported not adopting a data monitoring committee, and 11.3% did not answer on this item. While the number of registered pediatric trials has been increasing since 2008, we found no clear time trend in the reported adoption of data monitoring committees. Data monitoring committees were more common in multicenter trials (50.6% vs 36.9% for single-center), multinational trials (60.2%

vs 38.7% for single-country), National Institutes of Health-funded (60.3% vs 40.1% for industry-funded or 37.5% for other funders), and placebo-controlled (47.6% vs 37.5% for other types of control groups). Data monitoring committees were also more common among trials enrolling younger participants, trials employing blinding techniques, and larger trials. Data monitoring committees were more common in trials with at least one serious adverse event (52.6% vs 38.4% for those without) as well as for trials with reported deaths (70.3% vs 38.9% for trials without reported deaths). In all, 4.9% were listed as halted prematurely, most often due to low accrual rates. Trials with a data monitoring committee were more often halted for reasons related to scientific data than trials without a data monitoring committee (15.7% vs 7.3%).

**Conclusion:** According to registry records, the use of data monitoring committees in pediatric randomized controlled trials was more frequent than previously reported in reviews of published trial reports. The use of data monitoring committees varied across key clinical and trial characteristics based on which their use is recommended. Data monitoring committees may still be underutilized in pediatric trials, and reporting of this item could be improved.

## Rheumatology

Rheumatology (Oxford). 2022 Aug 3;61(8):3370-3377.

doi: 10.1093/rheumatology/keab914.

### [Efficacy of pulse dexamethasone in non-systemic juvenile idiopathic arthritis: a double-blind randomized controlled trial](#)

[Umang Bhardwaj<sup>1</sup>](#), [Narendra K Bagri<sup>1</sup>](#), [Rakesh Lodha<sup>1</sup>](#), [Sushil K Kabra<sup>1</sup>](#), [Thirumurthy Velpandian<sup>2</sup>](#), [Ravindra M Pandey<sup>3</sup>](#)

#### **Abstract**

**Objective:** Early aggressive therapy using biologicals is increasingly being used in JIA for early disease remission. Pulse steroids are used in induction regimes for rheumatic disorders such as SLE and systemic JIA; however, no controlled studies have demonstrated their use in non-systemic JIA. The objective of the present study was to evaluate the efficacy and safety of pulse dexamethasone therapy in children with treatment-naïve non-systemic JIA as early aggressive therapy in resource-limited settings.

**Methods:** Sixty treatment-naïve children with non-systemic JIA with an active joint count of  $\geq 5$  and/or involvement of hip or cervical joints were randomized to receive either pulse dexamethasone (3 mg/kg/day, max 100 mg/day) or placebo (normal saline) for three consecutive days during each visit at 0, 6 ( $\pm 2$ ) and 12 ( $\pm 2$ ) weeks; along with standard therapy (MTX and NSAIDs). The use of oral bridge steroids was permissible for persistent severe disease as per predefined criteria. The primary outcome was ACR-Pedi 70 response at 16 ( $\pm 2$ ) weeks after enrolment in the two groups.

**Results:** The proportion of children achieving ACR-Pedi 70 in the two groups at last follow-up was 11/30 (36.7%) in pulse dexamethasone arm vs 11/28 (39.3%) in the placebo arm (P-value 0.837, relative risk 0.93, 95% CI 0.48, 1.80). We did not observe any significant difference in

the proportion of children requiring bridge steroids. Adverse events were comparable in the two groups.

**Conclusion:** The addition of pulse dexamethasone to standard treatment may not add any advantage in improving ACR-Pedi 70 scores at medium-term follow-up.

## Quality of care

Resusc Plus. 2022 Jun 29;11:100262.

doi: 10.1016/j.resplu.2022.100262. eCollection 2022 Sep.

### [Do paediatric early warning systems reduce mortality and critical deterioration events among children? A systematic review and meta-analysis](#)

[Shu-Ling Chong](#)<sup>1,2</sup>, [Mark Sen Liang Goh](#)<sup>3</sup>, [Gene Yong-Kwang Ong](#)<sup>1,2</sup>, [Jason Acworth](#)<sup>4,5</sup>, [Rehena Sultana](#)<sup>6</sup>, [Sarah Hui Wen Yao](#)<sup>1</sup>, [Kee Chong Ng](#)<sup>1,2</sup>, [International Liaison Committee on Resuscitation \(ILCOR\) and ILCOR Pediatric Life Support Task Force](#)

#### Abstract

**Aim:** We conducted a systematic review and meta-analysis to answer the question: Does the implementation of Paediatric Early Warning Systems (PEWS) in the hospital setting reduce mortality, cardiopulmonary arrests, unplanned codes and critical deterioration events among children, as compared to usual care without PEWS?

**Methods:** We conducted a comprehensive search using Medline, EMBASE, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature and Web of Science. We included studies published between January 2006 and April 2022 on children <18 years old performed in inpatient units and emergency departments, and compared patient populations with PEWS to those without PEWS. We excluded studies without a comparator, case control studies, systematic reviews, and studies published in non-English languages. We employed a random effects meta-analysis and synthesised the risk and rate ratios from individual studies. We used the Scottish Intercollegiate Guidelines Network (SIGN) to appraise the risk of bias.

**Results:** Among 911 articles screened, 15 were included for descriptive analysis. Fourteen of the 15 studies were pre- versus post-implementation studies and one was a multi-centre cluster randomised controlled trial (RCT). Among 10 studies (580,604 hospital admissions) analysed for mortality, we found an increased risk (pooled RR 1.18, 95% CI 1.01-1.38,  $p = 0.036$ ) in the group without PEWS compared to the group with PEWS. The sensitivity analysis performed without the RCT (436,065 hospital admissions) showed a non-significant relationship (pooled RR 1.17, 95% CI 0.98-1.40,  $p = 0.087$ ). Among four studies (168,544 hospital admissions) analysed for unplanned code events, there was an increased risk in the group without PEWS (pooled RR 1.73, 95%CI 1.01-2.96,  $p = 0.046$ ) There were no differences in the rate of cardiopulmonary arrests or critical deterioration events between groups. Our findings were limited by potential confounders and imprecision among included studies.

**Conclusions:** Healthcare systems that implemented PEWS were associated with reduced mortality and code rates. We recognise that these gains vary depending on resource availability and efferent response systems. PROSPERO registration: CRD42021269579.

## Safe sleeping practices

BMC Pediatr. 2023 Jan 19;23(1):31.

doi: 10.1186/s12887-022-03832-y.

### [The provision of the baby box was associated with safe sleep practices in a low-resource community: a randomized control trial in Ecuador](#)

[Hartley Feld](#)<sup>1</sup>, [Janeth Ceballos Osorio](#)<sup>2</sup>, [Marisol Bahamonde](#)<sup>3</sup>, [Thomas Young](#)<sup>2</sup>, [Pablo Boada](#)<sup>4</sup>, [Mary Kay Rayens](#)<sup>5</sup>

#### Abstract

**Background:** Sudden Unexpected Infant Deaths (SUID) can occur between 1 month and 1 year of age and are inequitably distributed with a greater burden in populations with numerous health disparities. Modifying the infant sleep environment to promote safe sleep is the most effective risk reduction strategy to reduce SUID. The provision of baby boxes with a mattress and infant supplies has been part of a larger anti-poverty social justice maternity package for decades in Finland. While infant mortality rates have generally improved after the maternity package was introduced, little is known about whether the provision of the baby box increased safe sleep practices. The purpose of the study was to evaluate whether the provision of a Finnish-style baby box reinforced safe infant sleep practice in the home in a low-resource community in Ecuador.

**Methods:** In this longitudinal randomized controlled trial all participants received the same safe sleep education in their third trimester of pregnancy (n = 100). This was followed by randomization into two groups; the control received a diaper bag and newborn gifts, and the intervention group received a baby box and the same gifts at each timepoint. Four infant sleep practices (room sharing, bed sharing/co-sleeping, position, and soft items in the sleep environment) were assessed at 1 month and 1 months post-delivery during a home visit where safe sleep education was also reinforced with both groups.

**Results:** Those in the baby box group were 2.5 times more likely to report safe sleep practices compared with mothers in the diaper bag group at 1 month (odds ratio [OR] = 2.45 and 95% confidence interval [CI]: 1.03-5.86;  $\chi^2 = 4.1$ , p = .043). The group difference was also present at 6-months post-birth: those in the baby box group were 2.9 times more likely to report safe sleep practices compared with those in the diaper bag group (OR = 2.86 and 95% CI: 1.16-7.05;  $\chi^2 = 5.2$ , p = .022).

**Conclusions:** While not all participants used the box regularly, the mothers who received the box were more likely to practice safe sleep at 1 month and 6 months. This suggests the baby box may have served as an important prompt towards safer infant sleep practice.

## Schistosomiasis

Lancet Infect Dis. 2023 Jul;23(7):867-876.

doi: 10.1016/S1473-3099(23)00048-8. Epub 2023 Mar 6.

### [Efficacy, safety, and palatability of arpraziquantel \(L-praziquantel\) orodispersible tablets in children aged 3 months to 6 years infected with Schistosoma in Côte d'Ivoire and Kenya: an open-label, partly randomised, phase 3 trial](#)

[Eliézer K N'Goran<sup>1</sup>](#), [Maurice R Odieré<sup>2</sup>](#), [Ronald Assandé Aka<sup>3</sup>](#), [Mamadou Ouattara<sup>1</sup>](#), [N A David Aka<sup>2</sup>](#), [Bernhards Ogutu<sup>4</sup>](#), [Fredrick Rawago<sup>2</sup>](#), [Wilhelmina M Bagchus<sup>5</sup>](#), [Matthias Bödding<sup>6</sup>](#), [Elly Kourany-Lefoll<sup>7</sup>](#), [Aliona Tappert<sup>6</sup>](#), [Xiaoyan Yin<sup>8</sup>](#), [Deon Bezuidenhout<sup>9</sup>](#), [Henk Badenhorst<sup>9</sup>](#), [Eric Huber<sup>10</sup>](#), [Benjamin Dälken<sup>11</sup>](#), [Okba Haj-Ali Saflo<sup>12</sup>](#)

## Abstract

**Background:** WHO has underlined the need for a child-friendly treatment for schistosomiasis, a prevalent parasitic disease in low-income and middle-income countries. After successful phase 1 and 2 trials, we aimed to evaluate the efficacy, safety, palatability, and pharmacokinetics of arpraziquantel (L-praziquantel) orodispersible tablets for preschool-aged children.

**Methods:** This open-label, partly randomised, phase 3 study was conducted at two hospitals in Côte d'Ivoire and Kenya. Children with a minimum bodyweight of 5 kg in those aged 3 months to 2 years and 8 kg in those aged 2-6 years were eligible. In cohort 1, participants aged 4-6 years infected with *Schistosoma mansoni* were randomly assigned (2:1) to receive a single dose of oral arpraziquantel 50 mg/kg (cohort 1a) or oral praziquantel 40 mg/kg (cohort 1b) using a computer-generated randomisation list. Cohorts 2 (aged 2-3 years) and 3 (aged 3 months to 2 years) infected with *S mansoni*, and the first 30 participants in cohort 4a (aged 3 months to 6 years) infected with *Schistosoma haematobium*, received a single dose of oral arpraziquantel 50 mg/kg. After follow-up assessments, arpraziquantel was increased to 60 mg/kg (cohort 4b). Laboratory personnel were masked to the treatment group, screening, and baseline values. *S mansoni* was detected using a point-of-care circulating cathodic antigen urine cassette test and confirmed using the Kato-Katz method. The primary efficacy endpoint was clinical cure rate at 17-21 days after treatment in cohorts 1a and 1b, measured in the modified intention-to-treat population and calculated using the Clopper-Pearson method. This study is registered with ClinicalTrials.gov, [NCT03845140](#).

**Findings:** Between Sept 2, 2019, and Aug 7, 2021, 2663 participants were prescreened and 326 were diagnosed with *S mansoni* or *S haematobium*. 288 were enrolled (n=100 in cohort 1a, n=50 in cohort 1b, n=30 in cohort 2, n=18 in cohort 3, n=30 in cohort 4a, and n=60 in cohort 4b), but eight participants received antimalarial drugs and were excluded from the efficacy analyses. The median age was 5.1 years (IQR 4.1-6.0) and 132 (47%) of 280 participants were female and 148 (53%) were male. Cure rates with arpraziquantel were similar to those with praziquantel (87.8% [95% CI 79.6-93.5] in cohort 1a vs 81.3% [67.4-91.1] in cohort 1b). No safety concerns were identified during the study. The most common drug-related treatment-emergent adverse events were abdominal pain (41 [14%] of 288 participants), diarrhoea (27 [9%]), vomiting (16 [6%]), and somnolence (21 [7%]).

**Interpretation:** Arpraziquantel, a first-line orodispersible tablet, showed high efficacy and favourable safety in preschool-aged children with schistosomiasis.

## School health and education

(See Adolescent health)



doi: 10.3390/nu15071768.

### [\*\*School Feeding to Improve Cognitive Performance in Disadvantaged Children: A 3-Arm Parallel Controlled Trial in Northwest Pakistan\*\*](#)

[Nicola M Lowe<sup>1</sup>](#), [Pamela Qualter<sup>2</sup>](#), [Jonathan K Sinclair<sup>1</sup>](#), [Swarnim Gupta<sup>1</sup>](#), [Mukhtiar Zaman<sup>3</sup>](#)

#### **Abstract**

Malnutrition is associated with reduced learning aptitude and growth during childhood. We examined the impact of providing two school lunch variants, a standard school meal (school feeding,  $n = 70$ ), or the standard meal with additional micronutrients (school feeding + micronutrient powder (MNP),  $n = 70$ ), in children attending two schools in northwest Pakistan. A third local government school, where no lunch was provided (no school feeding,  $n = 70$ ), served as the control. The primary outcome, cognitive function, was assessed using the Raven's Coloured Progressive Matrices (RCPM) test, alongside haemoglobin, at three-time points: T1 (baseline, before the initiation of the school lunch programme), T2 and T3 (5 and 12 months, respectively, after the introduction of the school lunch). Data were analysed using linear mixed-effects models to contrast between trial groups, the changes from T1 to T2 and T3. Adjusted for T1 and other co-variables, improvements in the RCPM scores were significantly greater in the school feeding group at T2 ( $b = 1.61$ , (95% CI = 0.71-2.52),  $t = 3.52$ ,  $p = 0.001$ ) and T3 ( $b = 1.28$ , (95% CI = 0.22-2.35),  $t = 2.38$ ,  $p = 0.019$ ) compared with no school feeding. In addition, at T2 ( $b = 1.63$ , (95% CI = -0.10-3.37),  $t = 1.86$ ,  $p = 0.065$ ), there were no significant differences between school feeding + MNP and no school feeding groups. However, improvements in the RCPM scores were significantly greater in the school feeding + MNP group at T3 ( $b = 2.35$ , (95% CI = 0.51-4.20),  $t = 2.53$ ,  $p = 0.013$ ) compared with no school feeding. The findings indicate an improvement in cognitive performance in children who received a school meal with and without MNP, over a 12-month period. Currently there is no operational school feeding programme at the national or provincial level in Pakistan. Our findings, therefore, highlight the need for school feeding programmes to improve learning opportunities for children from underprivileged communities.

Dialogues Health. 2023 Dec;2:100123.

doi: 10.1016/j.dialog.2023.100123. Epub 2023 Mar 8.

### [\*\*Effect of an educational intervention on diet and physical activity among school-aged adolescents in Delhi -The i-PROMISE \(PROMoting health literacy in Schools\) Plus Study\*\*](#)

[Tina Rawal<sup>1,2</sup>](#), [Jean W M Muris<sup>2</sup>](#), [Vijay Kumar Mishra<sup>1</sup>](#), [Monika Arora<sup>1</sup>](#), [Nikhil Tandon<sup>3</sup>](#), [Onno C P van Schayck<sup>2</sup>](#)

#### **Abstract**

**Purpose:** Emerging lifestyle changes due to rapid urbanization have led to an epidemiological transition and the rising prevalence of obesity is responsible for major non-communicable diseases (NCDs) which have further aggravated due to the COVID-19 pandemic. This study aims to assess the effectiveness of a comprehensive school-based intervention on diet and physical activity-related behavior of adolescents.

**Methods:** In 2019, a cluster-randomized controlled trial was conducted in randomly selected ( $n = 8$ ) private schools. A 2-year intervention program was implemented over consecutive academic years (2019-2020 and 2020-2021) with students who were in the 6th and 7th grades when the study began. Four schools were randomly assigned to the intervention ( $n = 794$ ) and four schools to the control group ( $n = 774$ ).

**Results:** The difference in changes in diet and physical-activity-related behaviors of the students between the intervention and control schools were not significant in the intention to treat analysis probably due to the large drop-out due to COVID-19 measures: 304 students were available for follow-up in the intervention group and 122 in the control group (391 cases were excluded to make data comparable with baseline survey). The intake of vegetables (once a day) [ $\beta = 0.35$ , OR = 1.42, 95% CI (1.03, 1.95)] in the per-protocol analysis has increased among adolescents in the intervention group as compared to the control group.

**Conclusion:** The findings of this study indicated a positive effect of the intervention on diet and physical-activity-related changes in the expected direction and highlights the importance of addressing such behavior to prevent obesity among adolescents and thus NCDs in the later stage of life.

Rev Bras Epidemiol. 2022 Jul 22;25:e220019.

doi: 10.1590/1980-549720220019. eCollection 2022.

**[Environment modification at school to promote physical activity among adolescents: a cluster randomized controlled trial](#)**

[Raycauan Silva Benthroldo<sup>1</sup>](#), [Vitor Barreto Paravidino<sup>1,2</sup>](#), [Diana Barbosa Cunha<sup>1</sup>](#), [Mauro Felipe Felix Mediano<sup>3</sup>](#), [Rosely Sichieri<sup>1</sup>](#), [Emanuele Souza Marques<sup>1</sup>](#)

**Abstract**

**Objective:** To assess the effect of modifications of the school environment on physical activity in Brazilian adolescent students.

**Methods:** Seven public schools in Duque de Caxias (Brazil) were randomized into control and intervention groups. The intervention group underwent modifications in the school environment (painting of hopscotch and school courts) and the provision of sports equipment (balls, basketball table, soccer goalpost, volleyball nets, and others) to stimulate physical activity. Additionally, footsteps towards the court and materials were painted, and a superhero character called Super Active was introduced. Total physical activity was measured using a validated questionnaire for adolescents. Generalized linear models were used to evaluate the effect of the intervention, adjusted by sex.

**Results:** The sample consisted of 975 adolescents, with a mean age of 11.52 years (standard deviation - SD 1.43), and 56.7% were boys. After the one-month intervention, both groups' total physical activity time increased. The estimated changes from baseline were not different between the intervention and control groups ( $\Delta=102.75$  and  $\Delta=99.76$ , respectively;  $p=0.52$ ).

**Conclusion:** The painting, supply of equipment and other strategies to encourage physical activity in the school environment did not promote a positive effect on improving physical activity among adolescents. Future research is necessary to evaluate the effect of the intervention in the long-term period, particularly in other population contexts in middle-income countries.

AIDS Care. 2023 May;35(5):643-650.

doi: 10.1080/09540121.2022.2119473. Epub 2022 Sep 5.

### **Multi-media teacher training and HIV-related stigma among primary and secondary school teachers in Western Kenya**

[Winstone Nyandiko<sup>1,2</sup>](#), [Ashley Chory<sup>1,3</sup>](#), [Aaron Baum<sup>3</sup>](#), [Josephine Aluoch<sup>1</sup>](#), [Celestine Ashimosi<sup>1</sup>](#), [Michael Scanlon<sup>1,4</sup>](#), [Roxanne Martin<sup>3</sup>](#), [Juddy Wachira<sup>1,5</sup>](#), [Whitney Beigon<sup>1</sup>](#), [Dennis Munyoro<sup>1</sup>](#), [Edith Apondi<sup>1,6</sup>](#), [Rachel Vreeman<sup>1,3</sup>](#)

#### **Abstract**

**ABSTRACT** HIV stigma is associated with delayed HIV disclosure and worse clinical outcomes for adolescents living with HIV (ALWH). Teachers critically influence school environments, but are understudied in terms of HIV stigma. We implemented a school-level, cluster-randomized trial to assess the impact of a one-day multi-media training on the knowledge, attitudes and beliefs (K/A/B) of school teachers in western Kenya. Teachers' K/A/B were evaluated at baseline and six months. Additionally, we assessed stigma with ALWH enrolled in the included schools to explore the impact of the training. Teachers (N = 311) and ALWH (N = 19) were enrolled from 10 primary and 10 secondary schools. The intervention and control groups did not significantly differ in overall stigma score (mean 1.83 vs. 1.84; adjusted difference, 0.18 [95% CI, -0.082 to 0.045]) at six months; however, we found a trend towards improvement in overall stigma score and a significant difference in the community discrimination sub-scale among secondary school teachers (mean 3.02 vs. 3.19; adjusted difference, -0.166 [95% CI, -0.310 to -0.022]). ALWH reported few experiences of discrimination, but emphasized keeping their HIV status secret (84%). The teacher-training reduced secondary school teacher perceptions of community-level stigma, but did not impact individual attitudes or beliefs..

Prev Sci. 2023 May 26;1-12.

doi: 10.1007/s11121-023-01550-0. Online ahead of print.

### **Reducing Violent Discipline by Teachers: a Matched Cluster-Randomized Controlled Trial in Tanzanian Public Primary Schools**

[Faustine Bwire Masath<sup>1,2</sup>](#), [Katharina Mattonet<sup>1</sup>](#), [Katharin Hermenau<sup>3</sup>](#), [Mabula Nkuba<sup>2</sup>](#), [Tobias Hecker<sup>4</sup>](#)

#### **Abstract**

Violent discipline in schools infringes on children's rights and is associated with harmful developmental consequences for students. This calls for effective intervention programs, particularly in countries with high prevalence of violent discipline in schools. This study tested the effectiveness of the preventative intervention Interaction Competencies with Children-for Teachers (ICC-T) in reducing violent discipline by teachers in a two-arm matched cluster-randomized controlled trial. The sample comprised teachers (n = 173, 53.7% female) and students (n = 914, 50.5% girls) from 12 public primary schools from six regions in Tanzania. Teacher physical and emotional violent discipline reported by teachers and students was assessed before and six to eight and a half months after the intervention. The schools were randomly allocated to either intervention (6; ICC-T) or control condition (6; no intervention). Teachers were not blinded. Students and research assistants conducting the follow-up assessment were blinded. A series of multivariate multilevel models revealed significant time\*intervention effects on physical violent discipline reported by teachers and students and teachers' favorable attitudes towards physical violent discipline, FDRs < .05. In addition, we found a spill-over effect on peer-to-peer violence and students' externalizing, ps

< .05. There were no significant time\*intervention effects either on emotional violent discipline, FDRs > .05, teachers' favorable attitudes towards emotional violent discipline or on student's internalizing problems and academic performance, ps > .05. Our results provide further evidence that ICC-T may positively change teachers' violent disciplining behavior and their attitudes towards violent discipline.

Complement Ther Clin Pract. 2022 Aug;48:101614.

doi: 10.1016/j.ctcp.2022.101614. Epub 2022 Jun 5.

[Effect of yoga on cognitive functions and anxiety among female school children with low academic performance: A randomized control trial](#)

[Niranjan Parajuli<sup>1</sup>, Balaram Pradhan<sup>2</sup>, Saeed Bapat<sup>2</sup>](#)

**Abstract**

**Background:** To achieve better academic performance, students should improve their cognitive faculties and overcome anxiety. Therefore, the present research was conducted to assess the effect of yoga on the cognitive functions of female adolescents with low academic performance.

**Methods:** The present study is a randomized control trial (RCT). Eighty-nine female students in the age range of 12-14 years were randomly assigned into two groups [yoga (n = 45); physical exercise (n = 44)] at a school setting. Both groups were assessed before and after on Raven's standard progressive matrices (RSPM), Corsi Block Tapping Test (CBTT), Six Letter Cancellation Test (SLCT), Digit Letter Substitution Test (DLST), Stroop Color and Word Test (SCWT), and State-Trait Anxiety Inventory for Children (STAIC).

**Results:** Findings of the present study showed significant ( $p < .05$ ) differences in scores of forward CBTT, SWCT, and SLCT in group  $\times$  time interaction. Both the groups showed significant ( $p < .05$ ) improvement in SLCT, backward scores of CBTT, and STAIC-T. All outcomes measured were significantly ( $p < .05$ ) improved in the yoga group except STAIC-S.

**Conclusion:** Yoga improves general intelligence, visuospatial working memory, and attention, as well as reduces the anxiety of students with low academic performance. Similarly, physical exercise was also found to be improving visuospatial working memory, sustained attention, and reduce trait anxiety. However, the finding of the present study indicated yoga to be more effective compared to physical exercise in regards to students' fluid intelligence and executive function. Improvement in general intelligence, visuospatial working memory, and attention is expected to positively influence students' academic performance.

## Sepsis and serious bacterial infection

J Glob Health. 2022 Nov 21;12:04084.

doi: 10.7189/jogh.12.04084.

[Oral amoxicillin plus gentamicin regimens may be superior to the procaine-penicillin plus gentamicin regimens for treatment of young infants with possible serious bacterial](#)

## **infection when referral is not feasible: Pooled analysis from three trials in Africa and Asia**

[Adrien Lokangaka Longombe<sup>1</sup>](#), [Adejumoke Idowu Ayede<sup>2</sup>](#), [Irene Marete<sup>3</sup>](#), [Fatima Mir<sup>4</sup>](#), [Clara Ladi Ejemi<sup>5</sup>](#), [Mohammad Shahidullah<sup>6</sup>](#), [Ebunoluwa A Adejuyigbe<sup>7</sup>](#), [Robinson D Wammamda<sup>8</sup>](#), [Antoinette Tshefu<sup>1</sup>](#), [Fabian Esamai<sup>3</sup>](#), [Anita K Zaidi<sup>4,9</sup>](#), [Abdullah H Baqui<sup>10</sup>](#), [Simon Cousens<sup>11</sup>](#)

### **Abstract**

**Background:** Hospital referral and admission in many- low and middle-income countries are not feasible for many young infants with sepsis/possible serious bacterial infection (PSBI). The effectiveness of simplified antibiotic regimens when referral to a hospital was not feasible has been shown before. We analysed the pooled data from the previous trials to compare the risk of poor clinical outcome for young infants with PSBI with the two regimens containing injectable procaine penicillin and gentamicin with the oral amoxicillin plus gentamicin regimen currently recommended by the World Health Organization (WHO) when referral is not feasible.

**Methods:** Infant records from three individually randomised trials conducted in Africa and Asia were collated in a standard format. All trials enrolled young infants aged 0-59 days with any sign of PSBI (fever, hypothermia, stopped feeding well, movement only when stimulated, or severe chest indrawing). Eligible young infants whose caretakers refused hospital admission and consented were enrolled and randomised to a trial reference arm (arm A: procaine benzylpenicillin and gentamicin) or two experimental arms (arm B: oral amoxicillin and gentamicin or arm C: procaine benzylpenicillin and gentamicin initially, followed by oral amoxicillin). We compared the rate of poor clinical outcomes by day 15 (deaths till day 15, treatment failure by day 8, and relapse between day 9 and 15) in reference arm A with experimental arms and present risk differences with 95% confidence interval (CI), adjusted for trial.

**Results:** A total of 7617 young infants, randomised to arm A, arm B, or arm C in the three trials, were included in this analysis. Most were 7-59 days old (71%) and predominately males (56%). Slightly over one-fifth of young infants had more than one sign of PSBI at the time of enrolment. Severe chest indrawing (45%), fever (43%), and feeding problems (25%) were the most common signs. Overall, those who received arm B had a lower risk of poor clinical outcome compared to arm A for both per-protocol (risk difference = -2.1%, 95% CI = -3.8%, -0.4%; P = 0.016) and intention-to-treat (risk difference = -1.8%, 95% CI = -3.5%, -0.2%; P = 0.031) analyses. Those who received arm C did not have an increased risk of poor clinical outcome compared to arm A for both per-protocol (risk difference = -1.1%, 95% CI = -2.8%, 0.6%) and intention-to-treat (risk difference = -0.8%, 95% CI = -2.5%, 0.9%) analyses. Overall, those who received arm B had a lower risk of poor clinical outcome compared to the combined arms A and C for both per-protocol (risk difference = -1.6%, 95% CI = -3.5%, -0.1%; P = 0.035) and intention-to-treat (risk difference = -1.4%, 95% CI = -2.8%, -0.1%; P = 0.049) analyses.

**Conclusions:** Analysis of pooled individual patient-level data from three large trials in Africa and Asia showed that the WHO-recommended simplified antibiotic regimen B (oral amoxicillin and injection gentamicin) was superior to regimen A (injection procaine penicillin and injection gentamicin) and combined arms A and C (injection procaine penicillin and injection gentamicin, followed by oral amoxicillin) in terms of poor clinical outcome for the outpatient treatment of young infants with PSBI when inpatient treatment was not feasible.

## Shock

Crit Care Explor. 2022 Dec 28;5(1):e0815.

doi: 10.1097/CCE.0000000000000815. eCollection 2023 Jan.

### [A Randomized Controlled Trial of Norepinephrine Plus Dobutamine Versus Epinephrine As First-Line Vasoactive Agents in Children With Fluid Refractory Cold Septic Shock](#)

[Kiran Kumar Banothu<sup>1</sup>](#), [Jhuma Sankar<sup>1</sup>](#), [U Vijaya Kumar<sup>1</sup>](#), [Priyanka Gupta<sup>1</sup>](#), [Mona Pathak<sup>2</sup>](#), [Kana Ram Jat<sup>1</sup>](#), [Sushil Kumar Kabra<sup>1</sup>](#), [Rakesh Lodha<sup>1</sup>](#)

#### Abstract

Our objective was to compare norepinephrine plus dobutamine versus epinephrine as the first-line agent in children with fluid refractory cold septic shock.

**Design:** Open-label randomized controlled study.

**Setting:** A single-center PICU from North India.

**Patients:** Children 2 months to less than 18 years old with fluid refractory cold septic shock.

**Interventions:** In the intervention group, norepinephrine and dobutamine were started and in the control group, epinephrine was started as the first-line vasoactive agent. The primary outcome was the proportion attaining shock resolution (attaining all the therapeutic endpoints) at 1 hour of therapy.

**Measurements and main results:** We enrolled 67 children: 34 in the norepinephrine plus dobutamine group (intervention) and 33 in the epinephrine group (control). There was no difference in shock resolution at 1 hour (17.6% vs 9%; risk ratio [RR], 2.0; 95% CI, 0.54-7.35;  $p = 0.25$ ), 6 hours (76.4% vs 54.5%; RR, 1.69; 95% CI, 0.92-3.13;  $p = 0.06$ ), and 24 hours between the intervention and control groups, respectively. Children in the norepinephrine plus dobutamine group attained shock resolution earlier (measured from starting of vasoactive agents to attaining all the therapeutic endpoints) (hazard ratio, 1.84 [1.1-3.08]). The difference in 28-day mortality was not significant (23.5% vs 39.3% in the intervention and control groups, respectively [RR, 0.59; 95% CI, 0.28-1.25]).

**Conclusions:** In children with fluid refractory cold septic shock, with use of norepinephrine plus dobutamine as first-line agents, the difference in the proportion of children attaining shock resolution at 1 hour between the groups was inconclusive. However, the time to shock resolution was earlier in the norepinephrine plus dobutamine group. Also, fewer children in the intervention group were refractory to treatment. Further studies powered to detect (or exclude) an important difference would be required to test this intervention.

## Skin and hair disease

J Glob Health. 2022 Jul 25;12:12002.

doi: 10.7189/jogh.12.12002.

### [Topical emollient application in term healthy newborns: A systematic review](#)

[Mayank Priyadarshi<sup>1</sup>](#), [Bharathi Balachander<sup>2</sup>](#), [Shuchita Gupta<sup>3</sup>](#), [Mari J Sankar<sup>4</sup>](#)

#### Abstract

**Background:** This systematic review of randomized trials assessed the effect of emollient application compared to no emollient application in term or near-term healthy newborns.



**Methods:** We searched MEDLINE via PubMed, Cochrane CENTRAL, Embase, and CINAHL (updated until November 2021), clinical trials databases, and reference lists of retrieved articles. Key outcomes were neonatal mortality, systemic infections, atopic dermatitis, skin condition, and adverse events. Two authors separately evaluated the risk of bias, extracted data, and synthesized effect estimates using relative risks (RR). The GRADE approach was used to assess the certainty of evidence.

**Results:** We screened 19 243 records and included 16 eligible trials involving 5643 participants. Five trials recruited 3352 healthy newborns (term = 728; gestation  $\geq$ 35 weeks = 2624); and 11 trials included 2291 term newborns who were 'at risk' for developing atopy but were otherwise healthy. We conducted a separate analysis for these two groups of newborns. Emollient application (creams or nut, seed, and vegetable oils) started in the neonatal period and continued for four weeks to two years across studies. Meta-analysis for term healthy newborns suggests that topical emollient application may have little to no effect on atopic dermatitis (RR = 1.29, 95% CI = 0.96-1.72; two trials, 1408 newborns; low certainty evidence). Effects on food allergy (RR = 0.84; 95% CI = 0.42-1.70; one trial, 233 newborns), allergic sensitization to food allergens (RR 1.31; 95% CI 1.03 to 1.68; one trial, 234 newborns) and inhalational allergens (RR = 0.97; 95% CI = 0.44, 2.14; 1 trial, 234 newborns), skin dryness (RR = 0.74, 95% CI = 0.55-1.00; two trials, 294 newborns), and skin problems (RR = 0.92, 95% CI = 0.81-1.05; two trials, 292 newborns) were uncertain. Meta-analysis for 'at-risk' newborns suggests that intervention probably lowers the risk of atopic dermatitis (RR = 0.74, 95% CI = 0.63-0.86; 11 studies, 1988 infants; moderate certainty evidence), but may have little or no effect on food allergy and allergic sensitization to food or inhalation allergens. The effect on skin dryness and skin rash was uncertain.

**Conclusions:** Topical emollient application may not prevent atopic dermatitis in term healthy newborns. There is little data for other skin and allergic outcomes.

Pediatr Dermatol. 2023 Jun 3.

doi: 10.1111/pde.15355. Online ahead of print.

**[Evaluation of a paraffin-based moisturizer compared to a ceramide-based moisturizer in children with atopic dermatitis: A double-blind, randomized controlled trial](#)**

**[Sachin Gupta](#)<sup>1</sup>, [M Ramam](#)<sup>1</sup>, [V K Sharma](#)<sup>2</sup>, [G Sethuraman](#)<sup>1</sup>, [R M Pandey](#)<sup>3</sup>, [Neetu Bhari](#)<sup>1</sup>**

**Abstract**

**Background:** Moisturizers are first-line therapy for treatment of atopic dermatitis (AD). Although there are multiple types of moisturizers available, head-to-head trials between different moisturizers are limited.

**Objective:** To evaluate if a paraffin-based moisturizer is as effective as ceramide-based moisturizer in children with AD.

**Materials and methods:** In this double-blind, randomized comparative trial of pediatric patients with mild to moderate AD, subjects applied either a paraffin-based or ceramide-based moisturizer twice daily. Clinical disease activity using SCOring Atopic Dermatitis (SCORAD), quality of life using Children/Infants Dermatology Life Quality Index (CDLQI/IDLQI), and transepidermal water loss (TEWL) were measured at baseline and at follow-up at 1, 3, and 6 months.

**Results:** Fifty-three patients were recruited (27 ceramide group and 26 paraffin group) with a mean age of 8.2 years and mean disease duration of 60 months. The mean change in SCORAD

at 3 months in the ceramide-based and paraffin-based moisturizer groups was 22.1 and 21.4, respectively ( $p = .37$ ). The change in CDLQI/IDLQI, TEWL over forearm and back, amount and days of topical corticosteroid required, median time to remission and disease-free days at 3 months were similar in both groups. As the 95% confidence interval (CI) of mean change in SCORAD at 3 months in both groups (0.78, 95% CI: -7.21 to 7.52) was not within the predefined margin of equivalence (-4 to +4), the conclusion of equivalence could not be proven.

**Conclusion:** Both the paraffin-based and ceramide-based moisturizers were comparable in improving the disease activity in children with mild to moderate AD.

Biol Trace Elem Res. 2023 Jul;201(7):3152-3161.

doi: 10.1007/s12011-022-03411-3. Epub 2022 Sep 8.

### [Docosahexaenoic Acid Effect on Prenatal Exposure to Arsenic and Atopic Dermatitis in Mexican Preschoolers](#)

[Ivan Figueroa-Garduño<sup>1</sup>](#), [Consuelo Escamilla-Núñez<sup>2</sup>](#), [Albino Barraza-Villarreal<sup>1</sup>](#), [Leticia Hernández-Cadena<sup>1</sup>](#), [Erika Noelia Onofre-Pardo<sup>3</sup>](#), [Isabelle Romieu<sup>1</sup>](#)

#### **Abstract**

Childhood atopic dermatitis (AD) is a chronic and recurrent health problem that involves multiple factors, particularly immunological and environmental. We evaluated the impact of docosahexaenoic acid (DHA) supplementation on prenatal arsenic exposure on the risk of atopic dermatitis in preschool children as part of the POSGRAD (Prenatal Omega-3 fatty acid Supplements, GRowth, And Development) clinical trial study in the city of Morelos, Mexico. Our study population included 300 healthy mother-child pairs. Of these, 146 were in the placebo group and 154 in the supplement group. Information on family history, health, and other variables was obtained through standardized questionnaires used during follow-up. Prenatal exposure to arsenic concentrations, which appear in maternal urine, was measured by inductively coupled plasma optical emission spectrometry. To assess the effect of prenatal arsenic exposure on AD risk, we ran a generalized estimating equation model for longitudinal data, adjusting for potential confounders, and testing for interaction by omega-3 fatty acid supplementation during pregnancy. The mean and SD (standard deviation) of arsenic concentration during pregnancy was 0.06 mg/L, SD (0.04 mg/L). We found a marginally significant association between prenatal arsenic exposure and AD (OR = 1.12, 95% CI: 0.99, 1.26); however, DHA supplementation during pregnancy modified the effect of arsenic on AD risk ( $p < 0.05$ ). The results of this study strengthen the evidence that arsenic exposure during pregnancy increases the risk of atopic dermatitis early in life. However, supplementation with omega-3 fatty acids during pregnancy could modify this association.

## **Snake bite and envenomation**

## **Surgical problems**

\*\*\* J Pediatr Surg. 2023 Feb;58(2):293-298.

doi: 10.1016/j.jpedsurg.2022.10.029. Epub 2022 Oct 21.

### [A randomised control trial using soap in the prevention of surgical site infection in Tanzania](#)

[Godfrey Sama Philipo<sup>1</sup>](#), [Zaitun Mohamed Bokhary<sup>2</sup>](#), [Neema Lala Bayyo<sup>3</sup>](#), [Soham Bandyopadhyay<sup>4</sup>](#), [Miriam Gerd Pueschel<sup>5</sup>](#), [Rajabu Athumani Bakari<sup>3</sup>](#), [Kokila Lakhoo<sup>6</sup>](#)

#### **Abstract**

**Background:** Surgical site infections (SSIs) are common and serious complications of surgery. Guidelines on preventing SSIs have been developed, but the role of preoperative bathing with plain soap among paediatric population is unclear. We aimed to assess the effectiveness of pre-operative bathing using plain soap in preventing SSIs among paediatric surgical patients.

**Materials and methods:** An open-label, randomised trial was conducted at Muhimbili National Hospital in Tanzania. Preoperatively, patients in the intervention group washed their body using plain soap, while those in the control group did not. The primary outcome was SSI postoperatively. Statistical tests included  $\chi^2$ , Wilcoxon rank sum, and univariate and multivariable logistic regression.

**Results:** Of the 252 patients recruited, 114 were randomised to the intervention arm. In the control arm, 40.6% (56/138) of participants developed SSIs compared to 11.4% (13/114) in the intervention arm ( $p < 0.01$ ). After adjusting for confounding factors in multivariable analysis, the intervention reduced the odds of an SSI by 80% (OR: 0.20 [95% CI: 0.10, 0.41];  $p < 0.01$ ). Preoperative antibiotics were deemed to be an effect modifier of the association between the intervention and SSI ( $p = 0.05$ ). The intervention significantly reduced the odds of an SSI by 88% among participants not given preoperative antibiotics (OR: 0.12 [95% CI: 0.05, 0.30];  $p < 0.01$ ).

**Conclusion:** This study has shown that preoperative bathing with soap significantly reduces SSIs in paediatric surgical patients. It is a simple, cost effective and sustainable intervention.

Lancet. 2022 Nov 19;400(10365):1767-1776.

doi: 10.1016/S0140-6736(22)01884-0. Epub 2022 Oct 31.

### [Routine sterile glove and instrument change at the time of abdominal wound closure to prevent surgical site infection \(ChEETAH\): a pragmatic, cluster-randomised trial in seven low-income and middle-income countries](#)

[NIHR Global Research Health Unit on Global Surgery](#)

#### **Abstract**

**Background:** Surgical site infection (SSI) remains the most common complication of surgery around the world. WHO does not make recommendations for changing gloves and instruments before wound closure owing to a lack of evidence. This study aimed to test whether a routine change of gloves and instruments before wound closure reduced abdominal SSI.

**Methods:** ChEETAH was a multicentre, cluster randomised trial in seven low-income and middle-income countries (Benin, Ghana, India, Mexico, Nigeria, Rwanda, South Africa). Any hospitals (clusters) doing abdominal surgery in participating countries were eligible. Clusters were randomly assigned to current practice (42) versus intervention (39; routine change of gloves and instruments before wound closure for the whole scrub team). Consecutive adults

and children undergoing emergency or elective abdominal surgery (excluding caesarean section) for a clean-contaminated, contaminated, or dirty operation within each cluster were identified and included. It was not possible to mask the site investigators, nor the outcome assessors, but patients were masked to the treatment allocation. The primary outcome was SSI within 30 days after surgery (participant-level), assessed by US Centers for Disease Control and Prevention criteria and on the basis of the intention-to-treat principle. The trial has 90% power to detect a minimum reduction in the primary outcome from 16% to 12%, requiring 12 800 participants from at least 64 clusters. The trial was registered with ClinicalTrials.gov, [NCT03700749](https://clinicaltrials.gov/ct2/show/study/NCT03700749).

**Findings:** Between June 24, 2020 and March 31, 2022, 81 clusters were randomly assigned, which included a total of 13 301 consecutive patients (7157 to current practice and 6144 to intervention group). Overall, 11 825 (88.9%) of 13 301 patients were adults, 6125 (46.0%) of 13 301 underwent elective surgery, and 8086 (60.8%) of 13 301 underwent surgery that was clean-contaminated or 5215 (39.2%) of 13 301 underwent surgery that was contaminated-dirty. Glove and instrument change took place in 58 (0.8%) of 7157 patients in the current practice group and 6044 (98.3%) of 6144 patients in the intervention group. The SSI rate was 1280 (18.9%) of 6768 in the current practice group versus 931 (16.0%) of 5789 in the intervention group (adjusted risk ratio: 0.87, 95% CI 0.79-0.95;  $p=0.0032$ ). There was no evidence to suggest heterogeneity of effect across any of the prespecified subgroup analyses. We did not anticipate or collect any specific data on serious adverse events.

**Interpretation:** This trial showed a robust benefit to routinely changing gloves and instruments before abdominal wound closure. We suggest that it should be widely implemented into surgical practice around the world.

Afr J Paediatr Surg. 2022 Jul-Sep;19(3):160-163.

doi: 10.4103/ajps.AJPS\_176\_20.

**[Comparison of clinical outcome and anal manometry following laparoscopic-assisted anorectoplasty and posterior sagittal anorectoplasty in patients with high and intermediate anorectal malformation: A randomised controlled trial](#)**

[Chhabi Ranu Gupta](#)<sup>1</sup>, [Tejal Bhoj](#)<sup>1</sup>, [Anup Mohta](#)<sup>1</sup>, [Mamta Sengar](#)<sup>1</sup>, [Niyaz A Khan](#)<sup>1</sup>, [Vivek Manchanda](#)<sup>1</sup>, [Parveen Kumar](#)<sup>1</sup>

**Abstract**

**Introduction:** High and intermediate types of anorectal malformations (ARMs) may be managed by either open posterior sagittal anorectoplasty (PSARP) or by laparoscopic-assisted anorectoplasty (LAARP). Most of the literature favours one approach over the other based on retrospective analysis. We performed this study with the aim to compare the short-term outcomes of both procedures.

**Materials and methods:** All paediatric patients with high and intermediate ARM were enrolled and randomised into two groups: open PSARP group and LAARP group. Outcome parameters such as faecal continence using Kelly's scoring system, anal manometric parameters and post-operative complications were compared between the groups.

**Results:** A total of 16 patients were included with equal distribution in the open PSARP and LAARP group. Patient's variables were comparable in both the groups. Five patients developed immediate post-operative complications, three in the LAARP and two in the open group. The mean Kelly's score was  $3.63 \pm 1.6$  versus  $2.57 \pm 1.9$  ( $P = 0.132$ ) for LAARP and

PSARP group, respectively. The mean resting pressure was  $34.71 \pm 6.26$  cm of H<sub>2</sub>O and  $35 \pm 6.16$  cm of H<sub>2</sub>O ( $P = 0.384$ ) in LAARP and open group, respectively. Rectoanal inhibitory reflex was demonstrated in 6/7 patients in LAARP group and 5/7 patients in open group.

**Conclusion:** Faecal continence in patients undergoing either of the procedure is comparable. However, wound-related complications are lesser in LAARP procedure.

Pediatr Surg Int. 2022 Sep;38(9):1291-1296.

doi: 10.1007/s00383-022-05155-6. Epub 2022 Jun 30.

**[Laparoscopic appendectomy for complicated appendicitis in children: does the post-operative peritoneal drain make any difference? A pilot prospective randomised controlled trial](#)**

[M J Human](#)<sup>1</sup>, [N Tshifularo](#)<sup>2</sup>, [M Mabitsela](#)<sup>2</sup>

**Abstract**

**Purpose:** This was a pilot randomised, prospective study, which aimed to determine and compare the post-operative complications of paediatric patients undergoing laparoscopic appendectomy (LA) for complicated appendicitis, with and without a peritoneal drain.

**Methods:** Patients younger than 13 years, undergoing LA for complicated appendicitis at the Dr George Mukhari Academic Hospital (DGMAH), over a 15-month period during 2019-2020 were enrolled. Randomisation was achieved by a blocked randomisation plan. Patients were randomised in a 1:1 ratio into the "drain" (D) and "no drain" (ND) groups.

**Results:** Thirty-four patients were included in this study; seventeen in each group. The complication rate was 26%. Intra-abdominal collection accounted for 89% of the complications. The complication rate in the "D" group was 18% and 35% in the "ND" group, with no statistically significant difference. Complication rates were higher (38%) in patients with generalised pus when compared to localised pus (7%), although not statistically significant. The mean theatre time, hospital stay, and duration of antibiotic use did not differ significantly between the groups.

**Conclusion:** From our study, the post-operative peritoneal drain did not make any statistically significant difference in patient outcome. The amount of intra-abdominal contamination is more likely to contribute in the development of complications.

Niger Postgrad Med J. 2022 Oct-Dec;29(4):310-316.

doi: 10.4103/npmj.npmj\_189\_22.

**[Evaluation of the effect of nutritive versus non-nutritive pacifiers as adjuncts to local anaesthesia in male neonatal circumcision using the plastibell technique - A prospective randomised controlled study](#)**

[Chibuike George Ihediwa](#)<sup>1</sup>, [Christopher O Bode](#)<sup>2</sup>, [Felix M Alakaloko](#)<sup>1</sup>, [Olumide A Elebute](#)<sup>2</sup>, [Justina O Seyi-Olajide](#)<sup>1</sup>, [Oluwaseun Abiola Ladipo-Ajayi](#)<sup>1</sup>, [Adesoji O Ademuyiwa](#)<sup>2</sup>

**Abstract**

**Background:** Male circumcision is the most common surgical procedure worldwide and is often carried out for religious, cultural, medical and public health reasons. It is commonly performed during the neonatal period. Many studies have now shown that pain is a common intra- and post-operative complication. To ensure proper analgesia during the procedure, many surgeons opt for the use of pacifiers as an adjunct to anaesthesia during neonatal circumcision. The aim of this study is to compare nutritive pacifiers (NPs) versus non-NPs

(NNPs) as adjuncts to local anaesthesia in male neonatal circumcision using the Plastibell technique.

**Methods:** A prospective randomised controlled study was carried out between October 2019 and March 2020. A total of 100 neonates were circumcised using the Plastibell technique and randomised into NP (Group A, n = 33), NNP (Group B, n = 33) and controls (Group C, n = 34), respectively. The differences in pain scores using the Neonatal Infant Pain Scale, total crying time and heart rate during circumcision were recorded and assessed.

**Results:** The age of participants ranged from 5 to 28 days and the weight ranged from 2.5 to 5.0 kg. The overall mean age, birth weight and current weight of the participants were  $15.5 \pm 6.1$  days,  $3.4 \pm 0.4$  kg and  $3.5 \pm 0.6$  kg, respectively. The control group had the highest average pain score of 5.5 (4.5-5.8) compared to the intervention groups with median pain score (NP: 3.3 [1.3-4.3] and (NNP: 4.3 [3.1-5.1], respectively). NPs had significantly lower pain scores ( $P = 0.023$ ) and reduced total crying time ( $P = 0.019$ ) at all stages of the circumcision compared to those given NNPs and controls.

## Trypanosomiasis

## Tuberculosis

(See also Vaccines: Tuberculosis vaccine)

## Treatment of tuberculosis

Clin Infect Dis. 2022 Oct 29;75(9):1594-1601.

doi: 10.1093/cid/ciac208.

### [Randomized Clinical Trial of High-Dose Rifampicin With or Without Levofloxacin Versus Standard of Care for Pediatric Tuberculous Meningitis: The TBM-KIDS Trial](#)

[Mandar S Paradkar](#)<sup>1,2</sup>, [Bella Devaleenal D](#)<sup>3</sup>, [Tisungane Mvalo](#)<sup>4,5</sup>, [Ana Arenivas](#)<sup>6</sup>, [Kiran T Thakur](#)<sup>7</sup>, [Lisa Wolf](#)<sup>8</sup>, [Smita Nimkar](#)<sup>1,2</sup>, [Sadaf Inamdar](#)<sup>1,2</sup>, [Prathiksha Giridharan](#)<sup>3</sup>, [Elilarasi Selladurai](#)<sup>9</sup>, [Aarti Kinikar](#)<sup>1,10</sup>, [Chhaya Valvi](#)<sup>1,10</sup>, [Saltanat Khwaja](#)<sup>1,2</sup>, [Daphne Gadama](#)<sup>4</sup>, [Sarath Balaji](#)<sup>3</sup>, [Krishna Yadav Kattagoni](#)<sup>3</sup>, [Mythily Venkatesan](#)<sup>3</sup>, [Radojka Savic](#)<sup>11</sup>, [Soumya Swaminathan](#)<sup>12</sup>, [Amita Gupta](#)<sup>8</sup>, [Nikhil Gupte](#)<sup>1,2,8</sup>, [Vidya Mave](#)<sup>1,2,8</sup>, [Kelly E Dooley](#)<sup>8</sup>, [TuBerculous Meningitis in Kids \(TBM-KIDS\) Study Team](#)

### Abstract

**Background:** Pediatric tuberculous meningitis (TBM) commonly causes death or disability. In adults, high-dose rifampicin may reduce mortality. The role of fluoroquinolones remains unclear. There have been no antimicrobial treatment trials for pediatric TBM.

**Methods:** TBM-KIDS was a phase 2 open-label randomized trial among children with TBM in India and Malawi. Participants received isoniazid and pyrazinamide plus: (i) high-dose rifampicin (30 mg/kg) and ethambutol (R30HZE, arm 1); (ii) high-dose rifampicin and



levofloxacin (R30HZL, arm 2); or (iii) standard-dose rifampicin and ethambutol (R15HZE, arm 3) for 8 weeks, followed by 10 months of standard treatment. Functional and neurocognitive outcomes were measured longitudinally using Modified Rankin Scale (MRS) and Mullen Scales of Early Learning (MSEL).

**Results:** Of 2487 children prescreened, 79 were screened and 37 enrolled. Median age was 72 months; 49%, 43%, and 8% had stage I, II, and III disease, respectively. Grade 3 or higher adverse events occurred in 58%, 55%, and 36% of children in arms 1, 2, and 3, with 1 death (arm 1) and 6 early treatment discontinuations (4 in arm 1, 1 each in arms 2 and 3). By week 8, all children recovered to MRS score of 0 or 1. Average MSEL scores were significantly better in arm 1 than arm 3 in fine motor, receptive language, and expressive language domains ( $P < .01$ ).

**Conclusions:** In a pediatric TBM trial, functional outcomes were excellent overall. The trend toward higher frequency of adverse events but better neurocognitive outcomes in children receiving high-dose rifampicin requires confirmation in a larger trial.

Lancet Infect Dis. 2022 Nov 14;S1473-3099(22)00668-5.

doi: 10.1016/S1473-3099(22)00668-5. Online ahead of print.

**[Effect of systematic tuberculosis detection on mortality in young children with severe pneumonia in countries with high incidence of tuberculosis: a stepped-wedge cluster-randomised trial](#)**

[Olivier Marcy](#)<sup>1</sup>, [Eric Wobudeya](#)<sup>2</sup>, [Hélène Font](#)<sup>3</sup>, [Aurélia Vessière](#)<sup>3</sup>, [Chishala Chabala](#)<sup>4</sup>, [Celso Khosa](#)<sup>5</sup>, [Jean-voisin Taguebue](#)<sup>6</sup>, [Raoul Moh](#)<sup>7</sup>, [Juliet Mwanga-Amumpaire](#)<sup>8</sup>, [Manon Lounnas](#)<sup>9</sup>, [Veronica Mulenga](#)<sup>4</sup>, [Sandra Mavale](#)<sup>10</sup>, [Josina Chilundo](#)<sup>10</sup>, [Dalila Rego](#)<sup>11</sup>, [Bwendo Nduna](#)<sup>12</sup>, [Perfect Shankalala](#)<sup>4</sup>, [Uzima Chirwa](#)<sup>13</sup>, [Agathe De Lauzanne](#)<sup>14</sup>, [Bunnet Dim](#)<sup>14</sup>, [Emeline Tiogouo Ngouana](#)<sup>15</sup>, [Madeleine Folquet Amorrissani](#)<sup>16</sup>, [Lassina Cisse](#)<sup>17</sup>, [Flore Amon Tanoh Dick](#)<sup>18</sup>, [Eric A Komona](#)<sup>7</sup>, [Sylvie Kwedi Nolna](#)<sup>19</sup>, [Gerald Businge](#)<sup>2</sup>, [Naome Natukunda](#)<sup>8</sup>, [Saniata Cumbe](#)<sup>5</sup>, [Prossy Mbekeka](#)<sup>20</sup>, [Ang Kim](#)<sup>21</sup>, [Chanritha Kheang](#)<sup>22</sup>, [Sokha Pol](#)<sup>23</sup>, [Elizabeth Maleche-Obimbo](#)<sup>24</sup>, [James A Seddon](#)<sup>25</sup>, [Tan Eang Mao](#)<sup>26</sup>, [Stephen M Graham](#)<sup>27</sup>, [Christophe Delacourt](#)<sup>28</sup>, [Laurence Borand](#)<sup>14</sup>, [Maryline Bonnet](#)<sup>19</sup>; [TB-Speed Pneumonia Study Group](#)

**Abstract**

**Background:** Tuberculosis diagnosis might be delayed or missed in children with severe pneumonia because this diagnosis is usually only considered in cases of prolonged symptoms or antibiotic failure. Systematic tuberculosis detection at hospital admission could increase case detection and reduce mortality.

**Methods:** We did a stepped-wedge cluster-randomised trial in 16 hospitals from six countries (Cambodia, Cameroon, Côte d'Ivoire, Mozambique, Uganda, and Zambia) with high incidence of tuberculosis. Children younger than 5 years with WHO-defined severe pneumonia received either the standard of care (control group) or standard of care plus Xpert MTB/RIF Ultra (Xpert Ultra; Cepheid, Sunnyvale, CA, USA) on nasopharyngeal aspirate and stool samples (intervention group). Clusters (hospitals) were progressively switched from control to intervention at 5-week intervals, using a computer-generated random sequence, stratified on incidence rate of tuberculosis at country level, and masked to teams until 5 weeks before switch. We assessed the effect of the intervention on primary (12-week all-cause mortality) and secondary (including tuberculosis diagnosis) outcomes, using generalised linear mixed models. The primary analysis was by intention to treat. We

described outcomes in children with severe acute malnutrition in a post hoc analysis. This study is registered with ClinicalTrials.gov ([NCT03831906](https://clinicaltrials.gov/ct2/show/study/NCT03831906)) and the Pan African Clinical Trial Registry (PACTR202101615120643).

**Findings:** From March 21, 2019, to March 30, 2021, we enrolled 1401 children in the control group and 1169 children in the intervention group. In the intervention group, 1140 (97.5%) children had nasopharyngeal aspirates and 942 (80.6%) had their stool collected; 24 (2.1%) had positive Xpert Ultra. At 12 weeks, 110 (7.9%) children in the control group and 91 (7.8%) children in the intervention group had died (adjusted odds ratio [OR] 0.986, 95% CI 0.597-1.630,  $p=0.957$ ), and 74 (5.3%) children in the control group and 88 (7.5%) children in the intervention group had tuberculosis diagnosed (adjusted OR 1.238, 95% CI 0.696-2.202,  $p=0.467$ ). In children with severe acute malnutrition, 57 (23.8%) of 240 children in the control group and 53 (17.8%) of 297 children in the intervention group died, and 36 (15.0%) of 240 children in the control group and 56 (18.9%) of 297 children in the intervention group were diagnosed with tuberculosis. The main adverse events associated with nasopharyngeal aspirates were samples with blood in 312 (27.3%) of 1147 children with nasopharyngeal aspirates attempted, dyspnoea or SpO<sub>2</sub> less than 95% in 134 (11.4%) of children, and transient respiratory distress or SpO<sub>2</sub> less than 90% in 59 (5.2%) children. There was no serious adverse event related to nasopharyngeal aspirates reported during the trial.

**Interpretation:** Systematic molecular tuberculosis detection at hospital admission did not reduce mortality in children with severe pneumonia. High treatment and microbiological confirmation rates support more systematic use of Xpert Ultra in this group, notably in children with severe acute malnutrition.

Expert Rev Anti Infect Ther. 2022 Jul;20(7):1049-1059.

doi: 10.1080/14787210.2022.2071702. Epub 2022 May 10.

### [\*\*Efficacy and safety of vitamin D in tuberculosis patients: a systematic review and meta-analysis\*\*](#)

[Jagdish Prasad Goyal<sup>1</sup>](#), [Surjit Singh<sup>2</sup>](#), [Ramakishan Bishnoi<sup>3</sup>](#), [Pankaj Bhardwaj<sup>4</sup>](#), [Rimple Jeet Kaur<sup>2</sup>](#), [Sameer Dhingra<sup>5</sup>](#), [Dharmveer Yadav<sup>6</sup>](#), [Siddhartha Dutta<sup>7</sup>](#), [Jaykaran Charan<sup>2</sup>](#)

#### **Abstract**

**Background:** Evidence from the basic research and epidemiological studies indicates a beneficial effect of vitamin D in the treatment of tuberculosis (TB). However, the evidence from randomized controlled trials (RCTs) is inconsistent.

**Objectives:** This systematic review and meta-analysis was performed to synthesize evidence regarding role of vitamin D versus placebo for the management of TB.

**Materials and methods:** We searched PubMed and Cochrane Clinical Trial Registry for RCTs comparing vitamin D versus placebo for the treatment of TB. RCTs enrolling adult patients with TB receiving vitamin D in addition to standard treatment were included. Data were pooled using random effects model. The study was conducted according to PRISMA guidelines and protocol was registered with PROSPERO (CRD42016052841).

**Results:** Of 605 identified references, 12 RCTs were included. The overall risk of bias in included studies was low or unclear. There was no significant difference between vitamin D and placebo group for any outcomes of efficacy (time to culture conversion, time to smear

conversion, rate of culture conversion, and rate of smear conversion) or safety (mortality, serious adverse events, and nonserious adverse events).

**Conclusion:** Vitamin D administered with standard treatment has no beneficial effect in the TB patients as compared to the placebo.

## Prevention of tuberculosis, treatment of latent tuberculosis

Int J Tuberc Lung Dis. 2022 Jul 1;26(7):612-622.

doi: 10.5588/ijtld.21.0558.

[Effectiveness of a community-based intervention to prevent childhood TB in Lesotho](#)  
[Y Hirsch-Moverman<sup>1</sup>](#), [A A Howard<sup>1</sup>](#), [K A Yuengling<sup>2</sup>](#), [L Lebelo<sup>3</sup>](#), [K Frederix<sup>3</sup>](#), [A C Hesselning<sup>4</sup>](#), [S Nachman<sup>5</sup>](#), [L B Maama<sup>6</sup>](#), [W M El-Sadr<sup>1</sup>](#), [J E Mantell<sup>7</sup>](#)

### Abstract

**BACKGROUND:** Child contact management (CCM) is a recognized strategy to prevent TB; however, implementation is suboptimal. PREVENT was a cluster-randomized trial that evaluated the effectiveness and acceptability of a community-based intervention (CBI) to improve CCM in Lesotho. **METHODS:** Ten health facilities (HFs) were randomized to CBI or standard-of-care (SOC). CBI included nurse training/mentorship, health education by village health workers (VHW), adherence support, and multidisciplinary team meetings. Information on TB cases registered from February 2016 to June 2018 and their child contacts was abstracted. Outcomes were TB preventive treatment (TPT) initiation, TPT completion, and CBI acceptability. Generalized linear mixed models were used to test for differences between study arms and qualitative interview thematic analysis for acceptability. **RESULTS:** Among 547 registered children (CBI:  $n = 399$ ; SOC:  $n = 148$ ) of 426 adult TB patients, 46% were <2 years, 48% female, and 3% HIV-exposed/positive, with no significant differences between study arms. A total of 501 children initiated TPT—98% at CBI and 88% at SOC HFs ( $P < 0.0001$ ). TPT completion was 82% in CBI vs. 59% in SOC sites ( $P = 0.048$ ). Caregivers and providers reported that CBI was acceptable. **CONCLUSION:** The CBI was acceptable and significantly improved TPT initiation and completion in Lesotho, offering the opportunity to mitigate the threat of TB among children.

PLoS One. 2022 Sep 8;17(9):e0269219.

doi: 10.1371/journal.pone.0269219. eCollection 2022.

[Effect of patient-delivered household contact tracing and prevention for tuberculosis: A household cluster-randomised trial in Malawi](#)

[Kruger Kaswaswa<sup>1,2</sup>](#), [Peter MacPherson<sup>3,4</sup>](#), [Moses Kumwenda<sup>3</sup>](#), [James Mpunga<sup>2</sup>](#), [Deus Thindwa<sup>3</sup>](#), [Marriott Nliwasa<sup>1,3,5</sup>](#), [Mphatso Mwapasa<sup>1</sup>](#), [Jon Odland<sup>6</sup>](#), [Tamiwe Tomoka<sup>1</sup>](#), [Geoffrey Chipungu<sup>1</sup>](#), [Mavuto Mukaka<sup>4,7</sup>](#), [Elizabeth L Corbett<sup>1,3,8</sup>](#)

### Abstract

**Background:** Household contact tracing provides TB screening and TB preventive therapy (TPT) to contacts at high risk of TB disease. However, it is resource intensive, inconvenient, and often poorly implemented. We investigated a novel model aiming to improve uptake. **Methods:** Between May and December 2014, we randomised patient with TB who consented to participate in the trial to either standard of care (SOC) or intervention (PACTS) arms.

Participants randomised to PACTS received one screening/triage tool (adapted from WHO integrated management of adolescent and adult illnesses [IMAI] guidelines) and sputum pots for each reported household contact. The tool guided participants through symptom screening; TPT (6-months of isoniazid) eligibility; and sputum collection for contacts. Patients randomised to SOC were managed in accordance with national guidelines, that is, they received verbal instruction on who to bring to clinics for investigation using national guidelines.

**Main outcome and measures:** The primary outcome was the proportion of adult contacts receiving treatment for TB within 3 months of randomisation. Secondary outcomes were the proportions of child contacts under age 5 years (U5Y) who were commenced on, and completed, TPT. Data were analyzed by logistic regression with random effects to adjust for household clustering.

**Results:** Two hundred and fourteen index TB participants were block-randomized from two sites (107 PACTS, reporting 418 contacts; and 107 SOC, reporting 420 contacts). Overall, 62.8% of index TB participants were HIV-positive and 52.1% were TB culture-positive. 250 otherwise eligible TB patients declined participation and 6 households (10 PACTS, 6 SOC) were lost to follow-up and were not included in the analysis. By three months, nine contacts (PACTS: 6, [1.4%]; SOC: 3, [0.7%]) had TB diagnosed, with no difference between groups (adjusted odds ratio [aOR]: 2.18, 95% CI: 0.60-7.95). Eligible PACTS contacts (37/96, 38.5%) were more likely to initiate TPT by 3-months compared to SOC contacts (27/101, 26.7%; aOR 2.27, 95% CI: 1.04-4.98). U5Y children in the PACTS arm (47/81 58.0%) were more likely to have initiated TPT before the 3-month visit compared to SOC children (36/89, 41.4%; aOR: 2.31, 95% CI: 1.05-5.06).

**Conclusions and relevance:** A household-centred patient-delivered symptom screen and IPT eligibility assessment significantly increased timely TPT uptake among U5Y children, but did not significantly increase TB diagnosis. This model needs to be optimized for acceptability, given low participation, and investigated in other low resource settings.

Clin Infect Dis. 2022 Sep 14;75(5):849-856.

doi: 10.1093/cid/ciab1047.

### [\*\*Household Contact Tracing With Intensified Tuberculosis and Human Immunodeficiency Virus Screening in South Africa: A Cluster-Randomized Trial\*\*](#)

[Neil A Martinson<sup>1,2</sup>](#), [Limakatso Lebina<sup>1</sup>](#), [Emily L Webb<sup>3</sup>](#), [Andrew Ratsela<sup>4</sup>](#), [Ebrahim Varavia<sup>1,5</sup>](#), [Anthony Kinghorn<sup>1</sup>](#), [Sanjay G Lala<sup>1,6</sup>](#), [Jonathan E Golub<sup>2</sup>](#), [Zama Bosch<sup>1</sup>](#), [Kegaugetswe P Motsomi<sup>1</sup>](#), [Peter MacPherson<sup>7,8,9</sup>](#)

#### **Abstract**

**Background:** Household contact tracing for tuberculosis (TB) may facilitate diagnosis and access to TB preventive treatment (TPT). We investigated whether household contact tracing and intensive TB/human immunodeficiency virus (HIV) screening would improve TB-free survival.

**Methods:** Household contacts of index TB patients in 2 South African provinces were randomized to home tracing and intensive HIV/TB screening or standard of care (SOC; clinic referral letters). The primary outcome was incident TB or death at 15 months. Secondary outcomes included tuberculin skin test (TST) positivity in children  $\leq 14$  years and undiagnosed HIV.

**Results:** From December 2016 through March 2019, 1032 index patients (4459 contacts) and 1030 (4129 contacts) were randomized to the intervention and SOC arms. Of intervention arm contacts, 3.2% (69 of 2166) had prevalent microbiologically confirmed TB. At 15 months, the cumulative incidence of TB or death did not differ between the intensive screening (93 of 3230, 2.9%) and SOC (80 of 2600, 3.1%) arms (hazard ratio, 0.90; 95% confidence interval [CI], .66-1.24). TST positivity was higher in the intensive screening arm (38 of 845, 4.5%) compared with the SOC arm (15 of 800, 1.9%; odds ratio, 2.25; 95% CI, 1.07-4.72). Undiagnosed HIV was similar between arms (41 of 3185, 1.3% vs 32 of 2543, 1.3%; odds ratio, 1.02; 95% CI, .64-1.64).  
**Conclusions:** Household contact tracing with intensive screening and referral did not reduce incident TB or death. Providing referral letters to household contacts of index patients is an alternative strategy to home visits.

Arch Public Health. 2023 May 5;81(1):82.

doi: 10.1186/s13690-023-01098-z.

**Efficacy and safety of different regimens in the treatment of patients with latent tuberculosis infection: a systematic review and network meta-analysis of randomized controlled trials**

[Dawit Getachew Assefa](#)<sup>1</sup>, [Ahmed Bedru](#)<sup>2</sup>, [Eden Dagnachew Zeleke](#)<sup>3</sup>, [Solomon Emiru Negash](#)<sup>4</sup>, [Dejene Tolossa Debela](#)<sup>5</sup>, [Wondowsen Molla](#)<sup>6</sup>, [Nebiyu Mengistu](#)<sup>7</sup>, [Tigist Tekle Woldesenbet](#)<sup>8</sup>, [Neway Fekede Bedane](#)<sup>9</sup>, [Violet Dismas Kajogoo](#)<sup>10</sup>, [Mary Gorret Atim](#)<sup>11</sup>, [Tsegahun Manyazewal](#)<sup>5</sup>

**Abstract**

**Background:** Treatment of latent tuberculosis infection (LTBI) is effective in preventing progression to TB disease. This study aimed to synthesize available evidence on the efficacy, adherence, and safety of LTBI treatment in order to assist policymakers to design appropriate national treatment policies and treatment protocols.

**Method:** The PRISMA-NMA was used to review and report this research. Randomized controlled trials which compared the efficacy and safety of LTBI treatments were included. A systematic literature search was done to identify relevant articles from online databases PubMed/ MEDLINE, Embase, and Cochrane Center for Clinical Trial database (CENTRAL). The network meta-analysis was done using R- studio Version 1.4.1103.

**Result:** In this review, 42 studies were included, which enrolled 46,022 people who had recent contact with patients with active tuberculosis, evidence radiological of previous tuberculosis, tuberculin test equal or greater than 5 mm, radiographs that indicated inactive fibrotic or calcified parenchymal and/or lymph node lesions, had conversion to positive results on a tuberculin skin test, participants living with HIV, chronic Silicosis, immigrants, prisoners, old people, and pregnant women who were at risk for latent TB were included. The incidence of TB among people living with HIV who have taken 3RH as TPT was lower, followed by 48%, followed by 6H (41%). However, 3HP has also the potential to reduce the incidence of TB by 36% among HIV negative patients who had TB contact history. Patients' adherence to TPT was higher among patients who have taken 4R (RR 1.38 95% CI 1.0,1.89) followed by 3RH (34%). The proportion of subjects who permanently discontinued a study drug because of an adverse event were three times higher in the 3RH treatment group. Furthermore, the risk of grade 3 and 4 liver toxicity was significantly higher in 9H followed by 1HP, and 6H.

**Conclusion:** From this review, it can be concluded 3RH and 6H has a significant impact on the reduction of TB incidence among PLWH and 3HP among HIV negative people who had TB



contact history. However, combinations of rifampicin either with isoniazid were significantly associated with adverse events which resulted in permanent discontinuation among adult patients. Furthermore, grade 3 and 4 liver toxicity was more common in patients who have taken 9H, 1HP, and 6H. This may support the current recommended TPT regimen of 3HP, 3RH, and 6H.

Int J Infect Dis. 2023 May 19;S1201-9712(23)00562-3.

doi: 10.1016/j.ijid.2023.05.010. Online ahead of print.

**[Vitamin D supplementation to prevent tuberculosis infection in South African schoolchildren: multicentre phase 3 double-blind randomised placebo-controlled trial \(ViDiKids\)](#)**

[Keren Middelkoop](#)<sup>1</sup>, [Justine Stewart](#)<sup>1</sup>, [Neil Walker](#)<sup>2</sup>, [Carmen Delport](#)<sup>3</sup>, [David A Jolliffe](#)<sup>4</sup>, [Anna K Coussens](#)<sup>5</sup>, [James Nuttall](#)<sup>6</sup>, [Jonathan C Y Tang](#)<sup>7</sup>, [William D Fraser](#)<sup>7</sup>, [Christopher J Griffiths](#)<sup>2</sup>, [Geeta Trilok Kumar](#)<sup>8</sup>, [Suzanne Filteau](#)<sup>9</sup>, [Richard L Hooper](#)<sup>2</sup>, [Robert J Wilkinson](#)<sup>10</sup>, [Linda-Gail Bekker](#)<sup>3</sup>, [Adrian R Martineau](#)<sup>11</sup>

**Abstract**

**Background:** Vitamin D metabolites induce innate antimycobacterial responses in vitro. Observational studies consistently report independent associations between vitamin D deficiency and increased susceptibility to Mycobacterium tuberculosis infection.

**Methods:** We conducted a randomised placebo-controlled trial to determine whether weekly oral supplementation with 10,000 IU vitamin D<sub>3</sub> for 3 years reduced risk of sensitisation to M. tuberculosis in Cape Town schoolchildren aged 6-11 years with negative QuantiFERON-TB Gold Plus (QFT-Plus) assay results at baseline. The primary outcome was a positive end-trial QFT-Plus result, analysed using a mixed effects logistic regression model with school of attendance included as a random effect.

**Results:** 1682 children attending 23 schools were randomised (829 to vitamin D, 853 to placebo). Mean end-study 25(OH)D concentrations in participants randomised to vitamin D vs. placebo were 104.3 vs. 64.7 nmol/L, respectively (95% CI for difference, 37.6 to 41.9 nmol/L). 76/667 (11.4%) participants allocated to vitamin D vs. 89/687 (13.0%) participants allocated to placebo tested QFT-Plus positive at 3-year follow-up (adjusted odds ratio 0.86, 95% CI 0.62 to 1.19, P=0.35).

**Conclusions:** Weekly oral supplementation with 10,000 IU vitamin D<sub>3</sub> for 3 years elevated serum 25(OH)D concentrations among Cape Town schoolchildren but did not reduce their risk of QFT-Plus conversion.

## Diagnosis of tuberculosis

Wien Med Wochenschr. 2022 Sep;172(11-12):261-267.

doi: 10.1007/s10354-021-00871-5. Epub 2021 Aug 12.

**[Effectiveness of inhaled hypertonic saline application for sputum induction to improve Mycobacterium tuberculosis identification in patients with pulmonary tuberculosis](#)**



[Dmytro Butov](#)<sup>1</sup>, [Yurii Feshchenko](#)<sup>2</sup>, [Valeriy Myasoedov](#)<sup>3</sup>, [Mykhailo Kuzhko](#)<sup>2</sup>, [Mykola Gumeniuk](#)<sup>2</sup>, [Galyna Gumeniuk](#)<sup>2</sup>, [Anton Tkachenko](#)<sup>3</sup>, [Nekrasova Nataliya](#)<sup>3</sup>, [Olena Borysova](#)<sup>3</sup>, [Tetiana Butova](#)<sup>3</sup>

## Abstract

**Background:** This study assessed the effectiveness and diagnostic significance of hypertonic saline sputum induction for improving Mycobacterium tuberculosis (MTB) detection.

**Methods:** A prospective, randomized, open, two-arm, comparative study on MTB identification effectiveness when using inhaled sodium chloride hypertonic solution was performed in patients diagnosed with pulmonary tuberculosis (TB). Patients were randomly assigned into two groups: group 1 (inhalation group) included patients who inhaled a 7% sodium chloride solution upon admission to the hospital, and group 2 (control group) coughed up their sputum as usual. For both groups, specimens were tested by bacterioscopic, bacteriological, and molecular genetic methods. Diagnostic chest radiography was performed for all participants.

**Results:** In this study, 644 patients (mean age 42.2 years; 151 women, 23.4%) were randomly divided into two groups. Low-quality sputum samples were observed in 7.4% of patients from the inhalation group and 28.8% in the control group ( $p < 0.001$ ). Acid-fast bacilli (AFB) smear was positive in 65.1% of patients from the inhalation group and 51.3% of controls ( $p = 0.002$ ). A similar statistically significant situation was observed when culture methods (93.9% inhalation group and 81.9% control group,  $p < 0.001$ ) and molecular genetic tests (92.2% inhalation group and 79.4% control group,  $p < 0.001$ ) were used. Thus, active pulmonary TB was not verified microbiologically in 6.1% of patients from the inhalation group and in 18.1% of controls ( $p < 0.001$ ).

**Conclusions:** Hypertonic saline sputum induction improves the quality of collected samples. This method may be appropriate to increase the rate of MTB detection in sputum using microscopic, bacteriological, and molecular genetic methods for diagnosing TB on the day of specimen collection. Hypertonic saline sputum induction is suitable for middle- and low-income countries with limited resources and causes no severe adverse effects in TB patients.

Cochrane Database Syst Rev. 2022 Sep 6;9(9):CD013359.

doi: 10.1002/14651858.CD013359.pub3.

## [Xpert MTB/RIF Ultra assay for tuberculosis disease and rifampicin resistance in children](#)

[Alexander W Kay](#)<sup>1</sup>, [Tara Ness](#)<sup>1</sup>, [Sabine E Verkuil](#)<sup>2</sup>, [Kerri Viney](#)<sup>2</sup>, [Annemieke Brands](#)<sup>2</sup>, [Tiziana Masini](#)<sup>2</sup>, [Lucia González Fernández](#)<sup>1</sup>, [Michael Eisenhut](#)<sup>3</sup>, [Anne K Detjen](#)<sup>4</sup>, [Anna M Mandalakas](#)<sup>1</sup>, [Karen R Steingart](#)<sup>5</sup>, [Yemisi Takwoingi](#)<sup>6</sup>

## Abstract

**Background:** Every year, an estimated one million children and young adolescents become ill with tuberculosis, and around 226,000 of those children die. Xpert MTB/RIF Ultra (Xpert Ultra) is a molecular World Health Organization (WHO)-recommended rapid diagnostic test that simultaneously detects Mycobacterium tuberculosis complex and rifampicin resistance. We previously published a Cochrane Review 'Xpert MTB/RIF and Xpert MTB/RIF Ultra assays for tuberculosis disease and rifampicin resistance in children'. The current review updates evidence on the diagnostic accuracy of Xpert Ultra in children presumed to have tuberculosis disease. Parts of this review update informed the 2022 WHO updated guidance on management of tuberculosis in children and adolescents.

**Objectives:** To assess the diagnostic accuracy of Xpert Ultra for detecting: pulmonary tuberculosis, tuberculous meningitis, lymph node tuberculosis, and rifampicin resistance, in children with presumed tuberculosis. Secondary objectives To investigate potential sources of heterogeneity in accuracy estimates. For detection of tuberculosis, we considered age, comorbidity (HIV, severe pneumonia, and severe malnutrition), and specimen type as potential sources. To summarize the frequency of Xpert Ultra trace results.

**Search methods:** We searched the Cochrane Infectious Diseases Group Specialized Register, MEDLINE, Embase, three other databases, and three trial registers without language restrictions to 9 March 2021.

**Selection criteria:** Cross-sectional and cohort studies and randomized trials that evaluated Xpert Ultra in HIV-positive and HIV-negative children under 15 years of age. We included ongoing studies that helped us address the review objectives. We included studies evaluating sputum, gastric, stool, or nasopharyngeal specimens (pulmonary tuberculosis), cerebrospinal fluid (tuberculous meningitis), and fine needle aspirate or surgical biopsy tissue (lymph node tuberculosis). For detecting tuberculosis, reference standards were microbiological (culture) or composite reference standard; for stool, we also included Xpert Ultra performed on a routine respiratory specimen. For detecting rifampicin resistance, reference standards were drug susceptibility testing or MTBDRplus.

**Data collection and analysis:** Two review authors independently extracted data and, using QUADAS-2, assessed methodological quality judging risk of bias separately for each target condition and reference standard. For each target condition, we used the bivariate model to estimate summary sensitivity and specificity with 95% confidence intervals (CIs). We stratified all analyses by type of reference standard. We summarized the frequency of Xpert Ultra trace results; trace represents detection of a very low quantity of Mycobacterium tuberculosis DNA. We assessed certainty of evidence using GRADE.

**Main results:** We identified 14 studies (11 new studies since the previous review). For detection of pulmonary tuberculosis, 335 data sets (25,937 participants) were available for analysis. We did not identify any studies that evaluated Xpert Ultra accuracy for tuberculous meningitis or lymph node tuberculosis. Three studies evaluated Xpert Ultra for detection of rifampicin resistance. Ten studies (71%) took place in countries with a high tuberculosis burden based on WHO classification. Overall, risk of bias was low. Detection of pulmonary tuberculosis Sputum, 5 studies Xpert Ultra summary sensitivity verified by culture was 75.3% (95% CI 64.3 to 83.8; 127 participants; high-certainty evidence), and specificity was 97.1% (95% CI 94.7 to 98.5; 1054 participants; high-certainty evidence). Gastric aspirate, 7 studies Xpert Ultra summary sensitivity verified by culture was 70.4% (95% CI 53.9 to 82.9; 120 participants; moderate-certainty evidence), and specificity was 94.1% (95% CI 84.8 to 97.8; 870 participants; moderate-certainty evidence). Stool, 6 studies Xpert Ultra summary sensitivity verified by culture was 56.1% (95% CI 39.1 to 71.7; 200 participants; moderate-certainty evidence), and specificity was 98.0% (95% CI 93.3 to 99.4; 1232 participants; high certainty-evidence). Nasopharyngeal aspirate, 4 studies Xpert Ultra summary sensitivity verified by culture was 43.7% (95% CI 26.7 to 62.2; 46 participants; very low-certainty evidence), and specificity was 97.5% (95% CI 93.6 to 99.0; 489 participants; high-certainty evidence). Xpert Ultra sensitivity was lower against a composite than a culture reference standard for all specimen types other than nasopharyngeal aspirate, while specificity was similar against both reference standards. Interpretation of results In theory, for a population of 1000 children: • where 100 have pulmonary tuberculosis in sputum (by culture): - 101 would be Xpert Ultra-positive, and of these, 26 (26%) would not have pulmonary tuberculosis

(false positive); and - 899 would be Xpert Ultra-negative, and of these, 25 (3%) would have tuberculosis (false negative). • where 100 have pulmonary tuberculosis in gastric aspirate (by culture): - 123 would be Xpert Ultra-positive, and of these, 53 (43%) would not have pulmonary tuberculosis (false positive); and - 877 would be Xpert Ultra-negative, and of these, 30 (3%) would have tuberculosis (false negative). • where 100 have pulmonary tuberculosis in stool (by culture): - 74 would be Xpert Ultra-positive, and of these, 18 (24%) would not have pulmonary tuberculosis (false positive); and - 926 would be Xpert Ultra-negative, and of these, 44 (5%) would have tuberculosis (false negative). • where 100 have pulmonary tuberculosis in nasopharyngeal aspirate (by culture): - 66 would be Xpert Ultra-positive, and of these, 22 (33%) would not have pulmonary tuberculosis (false positive); and - 934 would be Xpert Ultra-negative, and of these, 56 (6%) would have tuberculosis (false negative). Detection of rifampicin resistance Xpert Ultra sensitivity was 100% (3 studies, 3 participants; very low-certainty evidence), and specificity range was 97% to 100% (3 studies, 128 participants; low-certainty evidence). Trace results Xpert Ultra trace results, regarded as positive in children by WHO standards, were common. Xpert Ultra specificity remained high in children, despite the frequency of trace results.

**Authors' conclusions:** We found Xpert Ultra sensitivity to vary by specimen type, with sputum having the highest sensitivity, followed by gastric aspirate and stool. Nasopharyngeal aspirate had the lowest sensitivity. Xpert Ultra specificity was high against both microbiological and composite reference standards. However, the evidence base is still limited, and findings may be imprecise and vary by study setting. Although we found Xpert Ultra accurate for detection of rifampicin resistance, results were based on a very small number of studies that included only three children with rifampicin resistance. Therefore, findings should be interpreted with caution. Our findings provide support for the use of Xpert Ultra as an initial rapid molecular diagnostic in children being evaluated for tuberculosis.

## Typhus

Int J Infect Dis. 2022 Sep;122:461-468.

doi: 10.1016/j.ijid.2022.06.024. Epub 2022 Jun 18.

### [The efficacy and tolerability of antibiotics in scrub typhus: an updated network meta-analysis of randomized controlled trials](#)

[Bing-Syuan Zeng<sup>1</sup>](#), [Bing-Yan Zeng<sup>2</sup>](#), [Chao-Ming Hung<sup>3</sup>](#), [Hung-Chang Kuo<sup>4</sup>](#), [Yen-Wen Chen<sup>5</sup>](#), [Mein-Woei Suen<sup>6</sup>](#), [Yow-Ling Shiue<sup>7</sup>](#), [Ping-Tao Tseng<sup>8</sup>](#), [Chang-Hua Chen<sup>9</sup>](#)

#### **Abstract**

**Objectives:** Inadequate treatment of scrub typhus results in severe complications such as septic shock and is also associated with a high median mortality rate of 6%. However, there has been no conclusive evidence about the superiority of different antibiotics in managing scrub typhus in terms of efficacy and tolerability.

**Methods:** We conducted a network meta-analysis (NMA) using the frequentist method. The included participants were pediatric and adult patients infected with scrub typhus. The primary outcome was the cure rate in the patients included. The subgroup analysis was done according to pediatric or adult patients.

**Results:** Overall, 14 randomized controlled trials (RCTs) with 1264 participants were included in this study. The NMA revealed that all the investigated antibiotics were associated with cure rates similar to those of doxycycline. The chloramphenicol and minocycline were ranked to be associated with the highest cure rate in the pediatric subgroup and adult subgroup, respectively. Second-generation quinolones, including ofloxacin, ciprofloxacin, and chloramphenicol, were associated with significantly lower adverse event rates than doxycycline.

**Conclusion:** The current updated NMA provides evidence for the efficacy of chloramphenicol and minocycline in scrub typhus management. However, future large-scale RCTs with longer follow-up times are warranted.

**Keywords:** Antibiotics;

## Typhoid

Cochrane Database Syst Rev. 2022 Nov 24;11(11):CD010452.

doi: 10.1002/14651858.CD010452.pub2.

[Treatment of enteric fever \(typhoid and paratyphoid fever\) with cephalosporins](#)

[Rebecca Kuehn](#)<sup>1</sup>, [Nicole Stoesser](#)<sup>2</sup>, [David Eyre](#)<sup>3</sup>, [Thomas C Darton](#)<sup>4</sup>, [Buddha](#)

[Basnyat](#)<sup>2,5</sup>, [Christopher Martin Parry](#)<sup>1,2</sup>

### Abstract

**Background:** Typhoid and paratyphoid (enteric fever) are febrile bacterial illnesses common in many low- and middle-income countries. The World Health Organization (WHO) currently recommends treatment with azithromycin, ciprofloxacin, or ceftriaxone due to widespread resistance to older, first-line antimicrobials. Resistance patterns vary in different locations and are changing over time. Fluoroquinolone resistance in South Asia often precludes the use of ciprofloxacin. Extensively drug-resistant strains of enteric fever have emerged in Pakistan. In some areas of the world, susceptibility to old first-line antimicrobials, such as chloramphenicol, has re-appeared. A Cochrane Review of the use of fluoroquinolones and azithromycin in the treatment of enteric fever has previously been undertaken, but the use of cephalosporins has not been systematically investigated and the optimal choice of drug and duration of treatment are uncertain.

**Objectives:** To evaluate the effectiveness of cephalosporins for treating enteric fever in children and adults compared to other antimicrobials.

**Search methods:** We searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL, MEDLINE, Embase, LILACS, the WHO ICTRP and ClinicalTrials.gov up to 24 November 2021. We also searched reference lists of included trials, contacted researchers working in the field, and contacted relevant organizations.

**Selection criteria:** We included randomized controlled trials (RCTs) in adults and children with enteric fever that compared a cephalosporin to another antimicrobial, a different cephalosporin, or a different treatment duration of the intervention cephalosporin. Enteric fever was diagnosed on the basis of blood culture, bone marrow culture, or molecular tests.

**Data collection and analysis:** We used standard Cochrane methods. Our primary outcomes were clinical failure, microbiological failure and relapse. Our secondary outcomes were time

to defervescence, duration of hospital admission, convalescent faecal carriage, and adverse effects. We used the GRADE approach to assess certainty of evidence for each outcome.

**Main results:** We included 27 RCTs with 2231 total participants published between 1986 and 2016 across Africa, Asia, Europe, the Middle East and the Caribbean, with comparisons between cephalosporins and other antimicrobials used for the treatment of enteric fever in children and adults. The main comparisons are between antimicrobials in most common clinical use, namely cephalosporins compared to a fluoroquinolone and cephalosporins compared to azithromycin. Cephalosporin (cefixime) versus fluoroquinolones Clinical failure, microbiological failure and relapse may be increased in patients treated with cefixime compared to fluoroquinolones in three small trials published over 14 years ago: clinical failure (risk ratio (RR) 13.39, 95% confidence interval (CI) 3.24 to 55.39; 2 trials, 240 participants; low-certainty evidence); microbiological failure (RR 4.07, 95% CI 0.46 to 36.41; 2 trials, 240 participants; low-certainty evidence); relapse (RR 4.45, 95% CI 1.11 to 17.84; 2 trials, 220 participants; low-certainty evidence). Time to defervescence in participants treated with cefixime may be longer compared to participants treated with fluoroquinolones (mean difference (MD) 1.74 days, 95% CI 0.50 to 2.98, 3 trials, 425 participants; low-certainty evidence). Cephalosporin (ceftriaxone) versus azithromycin Ceftriaxone may result in a decrease in clinical failure compared to azithromycin, and it is unclear whether ceftriaxone has an effect on microbiological failure compared to azithromycin in two small trials published over 18 years ago and in one more recent trial, all conducted in participants under 18 years of age: clinical failure (RR 0.42, 95% CI 0.11 to 1.57; 3 trials, 196 participants; low-certainty evidence); microbiological failure (RR 1.95, 95% CI 0.36 to 10.64, 3 trials, 196 participants; very low-certainty evidence). It is unclear whether ceftriaxone increases or decreases relapse compared to azithromycin (RR 10.05, 95% CI 1.93 to 52.38; 3 trials, 185 participants; very low-certainty evidence). Time to defervescence in participants treated with ceftriaxone may be shorter compared to participants treated with azithromycin (mean difference of -0.52 days, 95% CI -0.91 to -0.12; 3 trials, 196 participants; low-certainty evidence). Cephalosporin (ceftriaxone) versus fluoroquinolones It is unclear whether ceftriaxone has an effect on clinical failure, microbiological failure, relapse, and time to defervescence compared to fluoroquinolones in three trials published over 28 years ago and two more recent trials: clinical failure (RR 3.77, 95% CI 0.72 to 19.81; 4 trials, 359 participants; very low-certainty evidence); microbiological failure (RR 1.65, 95% CI 0.40 to 6.83; 3 trials, 316 participants; very low-certainty evidence); relapse (RR 0.95, 95% CI 0.31 to 2.92; 3 trials, 297 participants; very low-certainty evidence) and time to defervescence (MD 2.73 days, 95% CI -0.37 to 5.84; 3 trials, 285 participants; very low-certainty evidence). It is unclear whether ceftriaxone decreases convalescent faecal carriage compared to the fluoroquinolone gatifloxacin (RR 0.18, 95% CI 0.01 to 3.72; 1 trial, 73 participants; very low-certainty evidence) and length of hospital stay may be longer in participants treated with ceftriaxone compared to participants treated with the fluoroquinolone ofloxacin (mean of 12 days (range 7 to 23 days) in the ceftriaxone group compared to a mean of 9 days (range 6 to 13 days) in the ofloxacin group; 1 trial, 47 participants; low-certainty evidence).

**Authors' conclusions:** Based on very low- to low-certainty evidence, ceftriaxone is an effective treatment for adults and children with enteric fever, with few adverse effects. Trials suggest that there may be no difference in the performance of ceftriaxone compared with azithromycin, fluoroquinolones, or chloramphenicol. Cefixime can also be used for treatment of enteric fever but may not perform as well as fluoroquinolones. We are unable to draw firm general conclusions on comparative contemporary effectiveness given that most

trials were small and conducted over 20 years previously. Clinicians need to take into account current, local resistance patterns in addition to route of administration when choosing an antimicrobial.

## Ultrasound

## Urinary tract infection

## Urology

## Vaccines and immunization

(see also deworming)

## Vaccine coverage and administration

EClinicalMedicine. 2022 Jun 25;50:101500.

doi: 10.1016/j.eclinm.2022.101500. eCollection 2022 Aug.

[Small mobile conditional cash transfers \(mCCTs\) of different amounts, schedules and design to improve routine childhood immunization coverage and timeliness of children aged 0-23 months in Pakistan: An open label multi-arm randomized controlled trial](#)

[Subhash Chandir<sup>1</sup>](#), [Danya Arif Siddiqi<sup>1</sup>](#), [Sara Abdullah<sup>2</sup>](#), [Esther Duflo<sup>3</sup>](#), [Aamir Javed Khan<sup>1</sup>](#), [Rachel Glennerster<sup>3</sup>](#)

### Abstract

**Background:** Cost-effective demand-side interventions are needed to increase childhood immunization. Multiple studies find tying income support programs ( $\geq$ USD 50 per year) to immunization raises coverage. Research on maximizing impact from small mobile-based conditional cash transfers (mCCTs) ( $\leq$ USD 15 per fully immunized child) delivered in lower-income settings remains sparse.

**Methods:** Participants in Karachi, Pakistan, were individually randomized into a seven arm, factorial open label study with five mCCT arms, one reminder (SMS) only arm, and one control arm. The mCCT arms varied by amount (high  $\sim$ USD 15 per fully immunized child versus low  $\sim$ USD 5 per fully immunized child), schedule (flat versus rising payments over the schedule), design (certain versus lottery payments), and payment method (airtime or mobile money). Children were enrolled at BCG, pentavalent-1 (penta-1) or pentavalent-2 (penta-2) vaccination and followed until at least 18 months of age. A serosurvey in 15% sub-sample validated reported study coverage. The full immunization coverage (FIC) at 12 months (primary outcome) was analyzed using logit regression. ClinicalTrials.gov ([NCT03355989](#)), 3ie registry (58f6ee7725fc1), and AEA RCT Registry (AEARCTR-0001953).



**Findings:** Between November 6, 2017, and October 10, 2018, a total of 11,197 caregiver-child pairs were enrolled, with 1598-1600 caregiver-child pairs per arm. FIC at 12 months was statistically significantly higher for any mCCT versus SMS (OR:1.18, 95% CI: 1.05-1.33;  $p = 0.005$ ). Within the mCCT arms, FIC was statistically significantly higher for high versus low amount (OR: 1.16, 95% CI: 1.04-1.29;  $p = 0.007$ ), certain versus lottery payment (OR: 1.30, 95% CI: 1.17-1.45;  $p < 0.001$ ) and airtime versus mobile money (OR: 1.17, 95% CI:1.01-1.36;  $p = 0.043$ ). There was no statistically significant difference between a flat and increasing schedule (OR: 1.03, 95% CI: 0.93-1.15;  $p = 0.550$ ). SMS had a marginally statistically significant impact on FIC versus control (OR: 1.16, 95% CI: 1.00-1.35;  $p = 0.046$ ). Findings were similar for up-to-date coverage of penta-3, measles-1 and measles-2 at 18 months.

**Interpretation:** Small mCCTs (USD 0.8-2.4 per immunization visit) can increase FIC at 12 months and up-to-date coverage at 18 months at USD 23 per additional fully immunized child, in resource-constrained settings like Pakistan. Design details (certainty, schedule and delivery method of mCCTs) matter as much as the size of payments.

Front Public Health. 2022 Sep 8;10:898636.

doi: 10.3389/fpubh.2022.898636. eCollection 2022.

**[Improving timeliness and completion of infant vaccination among infants in Nigerian urban slums through older women's participation](#)**

[Folusho Mubowale Balogun](#)<sup>1,2</sup>, [Eniola Adetola Bamgboye](#)<sup>3</sup>, [Abimbola Ellen Akindolire](#)<sup>2,4</sup>

**Abstract**

Nigerian urban slums have a high population of infants with suboptimal vaccination despite previous interventions. Older women traditionally play supervisory roles in infant care in Nigeria but their influence is untapped in infant vaccination. This study sought to determine if training of older women ( $\geq 35$  years) in urban slum communities in Ibadan, South west Nigeria, and involving them in infant vaccination will improve infant vaccination timeliness and completion. This was a randomized experimental community study and pregnant women in their third trimester, residing in seven urban slum communities were randomized using their antenatal clinics (ANCs) into intervention (six ANCs) and control groups (six ANCs). The older women who will supervise the care of the infants of pregnant women in the intervention group had seven sessions of training on the importance of infant vaccination timeliness and completion. The vaccinations of the infants from both groups were compared from birth till 9 months. Data were analyzed using descriptive statistics and Chi square test at  $\alpha = 0.05$ . There were 96 older women, 198 pregnant women (105 in intervention group and 93 controls) and 202 infants (109 in intervention group and 93 controls). Infants in the intervention group (67.9%) significantly had both timely and complete vaccinations compared with those in the control group (36.6%). Vaccines given at birth were the least timely in both groups. More infants whose older women caregiver were married had timely and complete vaccinations. Also, a higher proportion of male infants, low birth weight babies and infants with older women caregiver with at most two children had timely and completed vaccinations but these were not statistically significant. Training of older women caregivers improved infant vaccination timeliness and completion in these urban slum communities. This model may improve infant vaccination in other similar urban slum settings.

## Vaccine-related adverse effects

### BCG and other TB vaccines

Lancet Infect Dis. 2022 Oct;22(10):1472-1483.

doi: 10.1016/S1473-3099(22)00222-5. Epub 2022 Jun 27.

#### [Safety and immunogenicity of VPM1002 versus BCG in South African newborn babies: a randomised, phase 2 non-inferiority double-blind controlled trial](#)

[Mark F Cotton](#)<sup>1</sup>, [Shabir A Madhi](#)<sup>2</sup>, [Angelique K Luabeya](#)<sup>3</sup>, [Michele Tameris](#)<sup>3</sup>, [Anneke C Hesselning](#)<sup>4</sup>, [Justin Shenje](#)<sup>3</sup>, [Elisma Schoeman](#)<sup>3</sup>, [Mark Hatherill](#)<sup>5</sup>, [Sajjad Desai](#)<sup>6</sup>, [Dhananjay Kapse](#)<sup>6</sup>, [Sina Brückner](#)<sup>7</sup>, [Anthonet Koen](#)<sup>2</sup>, [Lisa Jose](#)<sup>2</sup>, [Andrew Moultrie](#)<sup>2</sup>, [Sutika Bhikha](#)<sup>2</sup>, [Gerhard Walzl](#)<sup>8</sup>, [Andrea Gutschmidt](#)<sup>8</sup>, [Leigh A Kotze](#)<sup>8</sup>, [Devon L Allies](#)<sup>8</sup>, [Andre G Loxton](#)<sup>8</sup>, [Umesh Shaligram](#)<sup>6</sup>, [Maria Abraham](#)<sup>9</sup>, [Hilary Johnstone](#)<sup>10</sup>, [Leander Grode](#)<sup>7</sup>, [S H E Kaufmann](#)<sup>11</sup>, [Prasad S Kulkarni](#)<sup>12</sup>

#### Abstract

**Background:** Tuberculosis is a major public health problem worldwide. Immunisation with Mycobacterium bovis BCG vaccine is partially effective in infants, reducing the incidence of miliary and tuberculosis meningitis, but is less effective against pulmonary tuberculosis. We aimed to compare safety and immunogenicity of VPM1002-a recombinant BCG vaccine developed to address this gap-with BCG in HIV exposed and HIV unexposed newborn babies.

**Methods:** This double-blind, randomised, active controlled phase 2 study was conducted at four health centres in South Africa. Eligible neonates were aged 12 days or younger with a birthweight of 2.5-4.2 kg, and could be HIV exposed (seropositive mothers) or unexposed (seronegative mothers). Newborn babies were excluded if they had acute or chronic illness, fever, hypothermia, sepsis, cancer, or congenital malformation, or if they received blood products or immunosuppressive therapy. Participants were excluded if their mothers (aged ≥18 years) had active tuberculosis disease, diabetes, a history of immunodeficiency except for HIV, hepatitis B or syphilis seropositivity, received blood products in the preceding 6 months, any acute infectious disease, or any suspected substance abuse. Participants were randomly assigned to VPM1002 or BCG vaccination in a 3:1 ratio, stratified by HIV status using the random number generator function in SAS, using a block size of eight participants. The primary outcome was non-inferiority (margin 15%) of VPM1002 to BCG vaccine in terms of incidence of grade 3-4 adverse drug reactions or ipsilateral or generalised lymphadenopathy of 10 mm or greater in diameter by 12 months. The primary outcome was assessed in all vaccinated participants (safety population) at regular follow-up visits until 12 months after vaccination. Secondary immunogenicity outcomes were interferon-γ levels and percentages of multifunctional CD4<sup>+</sup> and CD8<sup>+</sup> T cells among all lymphocytes across the 12 month study period. The study was registered with ClinicalTrials.gov, [NCT02391415](#).

**Findings:** Between June 4, 2015 and Oct 16, 2017, 416 eligible newborn babies were randomly assigned and received study vaccine. Seven (2%) of 312 participants in the VPM1002 group had a grade 3-4 vaccine-related adverse reaction or lymphadenopathy of 10 mm or greater in diameter compared with 34 (33%) of 104 participants in the BCG group (risk difference -30.45% [95% CI -39.61% to -21.28%];  $p < 0.0001$ ); VPM1002 was thus non-inferior to BCG for the primary outcome. Incidence of severe injection site reactions was lower with VPM1002 than BCG: scarring occurred in 65 (21%) participants

in the VPM1002 group versus 77 (74%) participants in the BCG group ( $p < 0.0001$ ); ulceration occurred in one (<1%) versus 15 (14%;  $p < 0.0001$ ); and abscess formation occurred in five (2%) versus 23 (22%;  $p < 0.0001$ ). Restimulated IFN $\gamma$  concentrations were lower in the VPM1002 group than the BCG group at week 6, week 12, month 6, and month 12. The percentage of multifunctional CD4<sup>+</sup> T cells was higher in the VPM1002 group than the BCG group at day 14 but lower at week 6, week 12, month 6, and month 12. The percentage of multifunctional CD8<sup>+</sup> T cells was lower in the VPM1002 group than the BCG group at week 6, week 12, and month 6, but did not differ at other timepoints. **Interpretation:** VPM1002 was less reactogenic than BCG and was not associated with any serious safety concern. Both vaccines were immunogenic, although responses were higher with the BCG vaccine. VPM1002 is currently being studied for efficacy and safety in a multicentric phase 3 clinical trial in babies in sub-Saharan Africa.

## Cholera vaccine

Clin Infect Dis. 2023 Jan 13;76(2):263-270.

doi: 10.1093/cid/ciac782.

### [Co-administration of Oral Cholera Vaccine With Oral Polio Vaccine Among Bangladeshi Young Children: A Randomized Controlled Open Label Trial to Assess Interference](#)

[Md Taufiqul Islam](#)<sup>1,2</sup>, [Kashmira Date](#)<sup>3</sup>, [Ashraful Islam Khan](#)<sup>1</sup>, [Taufiqur Rahman Bhuiyan](#)<sup>1</sup>, [Zahid Hasan Khan](#)<sup>1</sup>, [Shamim Ahmed](#)<sup>1</sup>, [Motaheer Hossain](#)<sup>1</sup>, [Fatema Khaton](#)<sup>1</sup>, [K Zaman](#)<sup>1</sup>, [Nigel A J McMillan](#)<sup>2</sup>, [Abhijeet Anand](#)<sup>3</sup>, [Qian An](#)<sup>3</sup>, [Chenhua Zhang](#)<sup>3</sup>, [William C Weldon](#)<sup>4</sup>, [Alexander Yu](#)<sup>5</sup>, [Stephen Luby](#)<sup>5</sup>, [Firdausi Qadri](#)<sup>1</sup>

#### Abstract

**Background:** Cholera remains a public health threat for low- and middle-income countries, particularly in Asia and Africa. Shanchol™, an inactivated oral cholera vaccine (OCV) is currently in use globally. OCV and oral poliovirus vaccines (OPV) could be administered concomitantly, but the immunogenicity and safety of coadministration among children aged 1-3 years is unknown.

**Methods:** We undertook an open-label, randomized, controlled, inequality trial in Dhaka city, Bangladesh. Healthy children aged 1-3 years were randomly assigned to 1 of 3 groups: bivalent OPV (bOPV)-alone, OCV-alone, or combined bOPV + OCV and received vaccines on the day of enrollment and 28 days later. Blood samples were collected on the day of enrollment, day 28, and day 56. Serum poliovirus neutralizing antibodies and vibriocidal antibodies against *Vibrio cholerae* O1 were assessed using microneutralization assays.

**Results:** A total of 579 children aged 1-3 years were recruited, 193 children per group. More than 90% of the children completed visits at day 56. Few adverse events following immunization were recorded and were equivalent among study arms. On day 28, 60% (90% confidence interval: 53%-67%) and 54% (46%-61%) of participants with co-administration of bOPV + OCV responded to polioviruses type 1 and 3, respectively, compared to 55% (47%-62%) and 46% (38%-53%) in the bOPV-only group. Additionally, >50% of participants showed a  $\geq 4$ -fold increase in vibriocidal antibody titer responses on day 28, comparable to the responses observed in OCV-only arm.

**Conclusions:** Co-administration of bOPV and OCV is safe and effective in children aged 1-3 years and can be cost-beneficial.

## Covid-19 vaccine

Vaccine. 2022 Nov 22;40(49):7130-7140.

doi: 10.1016/j.vaccine.2022.10.045. Epub 2022 Oct 31.

### [Safety, tolerability and immunogenicity of Biological E's CORBEVAX™ vaccine in children and adolescents: A prospective, randomised, double-blind, placebo controlled, phase-2/3 study](#)

[Subhash Thuluva<sup>1</sup>](#), [Vikram Paradkar<sup>2</sup>](#), [SubbaReddy Gunneri<sup>2</sup>](#), [Vijay Yerroju<sup>2</sup>](#), [Rammohan Reddy Mogulla<sup>2</sup>](#), [Pothakamuri Venkata Suneetha<sup>2</sup>](#), [Kishore Turaga<sup>2</sup>](#), [Mahesh Kyasani<sup>2</sup>](#), [Senthil Kumar Manoharan<sup>2</sup>](#), [Srikanth Adabala<sup>2</sup>](#), [Aditya Sri Javvadi<sup>2</sup>](#), [Guruprasad Medigeshi<sup>3</sup>](#), [Janmejaya Singh<sup>3</sup>](#), [Heena Shaman<sup>3</sup>](#), [Akshay Binayke<sup>3</sup>](#), [Aymaan Zaheer<sup>3</sup>](#), [Amit Awasthi<sup>3</sup>](#), [Manish Narang<sup>4</sup>](#), [Pradeep Nanjappa<sup>5</sup>](#), [Niranjana Mahantshetti<sup>6</sup>](#), [Bishan Swarup Garg<sup>7</sup>](#), [Anil Kumar Pandey<sup>8</sup>](#)

#### **Abstract**

**Background:** After establishing safety and immunogenicity of Biological-E's CORBEVAX™ vaccine in adult population (18-80 years) in Phase 1-3 studies, vaccine is further tested in children and adolescents in this study.

**Methods:** This is a phase-2/3 prospective, randomised, double-blind, placebo-controlled study evaluating safety, reactogenicity, tolerability and immunogenicity of CORBEVAX™ vaccine in children and adolescents of either gender between <18 to ≥12 years of age in Phase-2 and <18 to ≥5 years of age in Phase-Phase-2/Phase-3 with placebo as a control. This study has two age sub-groups; subgroup-1 with subjects <18 to ≥12 years of age and subgroup-2 with subjects <12 to ≥5 years of age. In both sub groups, eligible subjects (SARS-CoV-2 RT-PCR negative and seronegative at baseline) were randomized to receive either CORBEVAX™ vaccine or Placebo in 3:1 ratio.

**Findings:** The safety profile of CORBEVAX™ vaccine in both pediatric cohorts was comparable to the placebo-control group. Majority of reported adverse events (AEs) were mild in nature. No severe or serious-AEs, medically attended AEs (MAAEs) or AEs of special interest (AESI) were reported during the study period and all reported AEs resolved without any sequelae. In both pediatric age groups, CORBEVAX™ vaccinated subjects showed significant improvement in humoral immune-responses in terms of anti-RBD-IgG concentrations, anti-RBD-IgG1 titers, neutralizing-antibody (nAb)-titers against Ancestral-Wuhan and Delta-strains. Significantly high interferon-gamma immune- response (cellular) was elicited by CORBEVAX™ vaccinated subjects with minimal effect on IL-4 cytokine secretion.

**Interpretations:** The safety profile of CORBEVAX™ vaccine in <18 to ≥5 years' children and adolescents was found to be safe and tolerable. Significant increase in anti-RBD-IgG and nAb-titers and IFN-gamma immune-responses were observed post-vaccination in both pediatric age sub-groups. The nAb titers observed in both the pediatric age cohorts were non-inferior to the adult cohort (BECT069 study) in terms of ratio of the GMT's of both the

cohorts. This study shows that CORBEVAX™ vaccine is highly immunogenic and can be safely administered to pediatric population as young as 5 years old.

Int J Infect Dis. 2023 Feb 23;S1201-9712(23)00066-8.

doi: 10.1016/j.ijid.2023.02.017. Online ahead of print.

**[The immunogenicity of an extended dosing interval of BNT162b2 against SARS-CoV-2 Omicron variant among healthy school-aged children, a randomized controlled trial](#)**

[Napaporn Chantasrisawad<sup>1</sup>](#), [Chonnamet Techasaensiri<sup>2</sup>](#), [Pope Kosalaraksa<sup>3</sup>](#), [Wanatpreeya Phongsamart<sup>4</sup>](#), [Auchara Tangsathapornpong<sup>5</sup>](#), [Peera Jaru-Ampornpan<sup>6</sup>](#), [Jiratchaya Sophonphan<sup>7</sup>](#), [Piyarat Suntarattiwong<sup>8</sup>](#), [Thanyawee Puthanakit<sup>9</sup>](#); [KIDSVAX study team](#)

**Abstract**

**Objectives:** To evaluate the immunogenicity of an extended interval regimen of BNT162b2 among healthy school-age children.

**Methods:** A randomized-control trial conducted among healthy Thai children aged 5-11 years. Participants received 2 doses of BNT162b2 with an 8-week (extended dosing) versus 3-week interval. Immunogenicity was determined by neutralization test (NT) against the Omicron variant; surrogate virus NT (sVNT; BA.1, % inhibition) and pseudovirus NT (pVNT; BA.2, ID<sub>50</sub>). The third dose was offered to participants who had sVNT <68% inhibition. The immunogenicity outcome was evaluated at 14 days after the second and third dose.

**Results:** During February to April 2022, 382 children with a median age (IQR) of 8.4 years (6.6-10.0) were enrolled. At 14 days after 2-doses of BNT162b2, geometric means (GMs) of sVNT in 8-week versus 3-week interval groups were 49.6 (95%CI 44.8-54.9), versus 16.5 (95%CI 13.0-20.9), with a geometric means ratio of 3.0 (95%CI 2.4-3.8). Among 102 participants who received the third dose at a median of 15 weeks from the second dose, the GMs of sVNT increased to 73.3 (95%CI 69.0-77.8) and pVNT was 326 (95%CI 256-415).

**Conclusion:** Extended 8-week interval regimen of BNT162b2 induced higher neutralizing antibodies than a standard 3-week interval regimen. The third dose induced high neutralizing antibodies against the Omicron variant.

## Dengue vaccine

## Ebola vaccine

N Engl J Med. 2022 Dec 29;387(26):2411-2424.

doi: 10.1056/NEJMoa2200072. Epub 2022 Dec 14.

**[Randomized Trial of Vaccines for Zaire Ebola Virus Disease](#)**

[PREVAC Study Team](#); [Mark Kieh<sup>1</sup>](#), [Laura Richert<sup>1</sup>](#), [Abdoul H Beavogui<sup>1</sup>](#), [Birgit Grund<sup>1</sup>](#), [Bailah Leigh<sup>1</sup>](#), [Eric D'Ortenzio<sup>1</sup>](#), [Seydou Doumbia<sup>1</sup>](#), [Edouard Lhomme<sup>1</sup>](#), [Samba Sow<sup>1</sup>](#), [Renaud Vatrinet<sup>1</sup>](#), [Céline Roy<sup>1</sup>](#), [Stephen B Kennedy<sup>1</sup>](#), [Sylvain Faye<sup>1</sup>](#), [Shelley Lees<sup>1</sup>](#), [Niouma P](#)

[Millimouno<sup>1</sup>](#), [Alseny M Camara<sup>1</sup>](#), [Mohamed Samaj<sup>1</sup>](#), [Gibrilla F Deen<sup>1</sup>](#), [Moussa Doumbia<sup>1</sup>](#), [Hélène Espérou<sup>1</sup>](#), [Jerome Pierson<sup>1</sup>](#), [Deborah Watson-Jones<sup>1</sup>](#), [Alpha Diallo<sup>1</sup>](#), [Deborah Wentworth<sup>1</sup>](#), [Chelsea McLean<sup>1</sup>](#), [Jakub Simon<sup>1</sup>](#), [Aurélie Wiedemann<sup>1</sup>](#), [Bonnie Dighero-Kemp<sup>1</sup>](#), [Lisa Hensley<sup>1</sup>](#), [H Clifford Lane<sup>1</sup>](#), [Yves Levy<sup>1</sup>](#), [Peter Piot<sup>1</sup>](#), [Brian Greenwood<sup>1</sup>](#), [Geneviève Chêne<sup>1</sup>](#), [James Neaton<sup>1</sup>](#), [Yazdan Yazdanpanah<sup>1</sup>](#)

## Abstract

**Background:** Questions remain concerning the rapidity of immune responses and the durability and safety of vaccines used to prevent Zaire Ebola virus disease.

**Methods:** We conducted two randomized, placebo-controlled trials - one involving adults and one involving children - to evaluate the safety and immune responses of three vaccine regimens against Zaire Ebola virus disease: Ad26.ZEBOV followed by MVA-BN-Filo 56 days later (the Ad26-MVA group), rVSVΔG-ZEBOV-GP followed by placebo 56 days later (the rVSV group), and rVSVΔG-ZEBOV-GP followed by rVSVΔG-ZEBOV-GP 56 days later (the rVSV-booster group). The primary end point was antibody response at 12 months, defined as having both a 12-month antibody concentration of at least 200 enzyme-linked immunosorbent assay units (EU) per milliliter and an increase from baseline in the antibody concentration by at least a factor of 4.

**Results:** A total of 1400 adults and 1401 children underwent randomization. Among both adults and children, the incidence of injection-site reactions and symptoms (e.g., feverishness and headache) was higher in the week after receipt of the primary and second or booster vaccinations than after receipt of placebo but not at later time points. These events were largely low-grade. At month 12, a total of 41% of adults (titer, 401 EU per milliliter) and 78% of children (titer, 828 EU per milliliter) had a response in the Ad26-MVA group; 76% (titer, 992 EU per milliliter) and 87% (titer, 1415 EU per milliliter), respectively, had a response in the rVSV group; 81% (titer, 1037 EU per milliliter) and 93% (titer, 1745 EU per milliliter), respectively, had a response in the rVSV-booster group; and 3% (titer, 93 EU per milliliter) and 4% (titer, 67 EU per milliliter), respectively, had a response in the placebo group ( $P < 0.001$  for all comparisons of vaccine with placebo). In both adults and children, antibody responses with vaccine differed from those with placebo beginning on day 14.

**Conclusions:** No safety concerns were identified in this trial. With all three vaccine regimens, immune responses were seen from day 14 through month 12.

## Enterovirus 71 vaccine

Hum Vaccin Immunother. 2022 Nov 30;18(5):2063630.

doi: 10.1080/21645515.2022.2063630. Epub 2022 Jun 17.

### [Clinical evaluation of the lot-to-lot consistency of an enterovirus 71 vaccine in a commercial-scale phase IV clinical trial](#)

[Jinhua Chen<sup>1</sup>](#), [Pengfei Jin<sup>2</sup>](#), [Xiaoqi Chen<sup>1</sup>](#), [Qunying Mao<sup>3</sup>](#), [Fanyue Meng<sup>2</sup>](#), [Xinguo Li<sup>1</sup>](#), [Wei Chen<sup>1</sup>](#), [Meizhi Du<sup>4</sup>](#), [Fan Gao<sup>3</sup>](#), [Pei Liu<sup>5</sup>](#), [Xiujuan Li<sup>4</sup>](#), [Changfu Guo<sup>1</sup>](#), [Tingbo Xie<sup>1</sup>](#), [Weiwei Lu<sup>6</sup>](#), [Qingliang Li<sup>1</sup>](#), [Li Li<sup>1</sup>](#), [Xing Yan<sup>1</sup>](#), [Xiang Guo<sup>1</sup>](#), [Hongqiao Du<sup>1</sup>](#), [Xiuling Li<sup>7</sup>](#), [Kai Duan<sup>1</sup>](#), [Fengcai Zhu<sup>2</sup>](#)

## Abstract



**Objective:** To evaluate the immunogenicity, safety and lot-to-lot consistency of an inactivated enterovirus 71 (EV71) vaccine cultured in bioreactors with different specifications after full immunization.

**Methods:** A randomized, double-blind trial was performed in 3,000 children aged 6 ~ 35 months with six vaccine batches, which were prepared in 40 L and 150 L bioreactors for three consecutive batches respectively. Children were immunized on day 0 and 28, serum samples were collected on day 0 and 56, and neutralizing antibody titers were determined by the microcytopathic method. Immediate reactions were recorded within 30 min, local and systemic symptoms were recorded within 0 ~ 28 days, and serious adverse events were recorded within 6 months.

**Results:** After immunization with two doses of the inactivated EV71 vaccine, the neutralizing antibody GMT was  $825.52 \pm 4.09$ , and the positive conversion rate was 96.18%, with no significant difference. The 95% CI of the serum neutralizing antibody GMT ratio between the two groups after immunization with the three vaccine batches produced in the 150 L and 40 L bioreactors ranged from .67 ~ 1.5. The overall incidence of adverse reactions, mainly grade 1 reactions, for all 6 batches from 0 to 28 days after vaccination was 49.62%, with no significant difference ( $p = .8736$ ). The incidence of systemic adverse reactions, primarily fever and diarrhea, was 45.14%; the incidence of local adverse reactions, primarily erythema and tenderness, was 9.43%.

**Conclusion:** The EV71 vaccine was highly immunogenic and safe in children aged 6-35 months, and 6 consecutive batches produced by the two bioreactors with different specifications were consistent.

## Hepatitis A vaccine

## Hepatitis B vaccine

Explore (NY). 2023 Mar-Apr;19(2):238-242.

doi: 10.1016/j.explore.2022.09.001. Epub 2022 Sep 8.

### [The effect of Helfer skin tap technique on hepatitis B vaccine intramuscular injection pain in neonates: A randomized controlled trial](#)

[Şefika Dilek Güven](#)<sup>1</sup>, [Nazan Çakırer Çalbayram](#)<sup>2</sup>

#### **Abstract**

**Context:** The aim of neonatal pain management is to reduce pain and help the baby cope with pain.

**Objective:** This study aimed to determine the effect of Helfer skin tap technique (HSTT) on hepatitis B vaccine intramuscular (IM) injection pain in neonates.

**Design:** Randomized controlled study SETTING: This study was conducted with neonatal infants born vaginally in the delivery room of a state hospital in Turkey.

**Participants:** This study was conducted total 60 neonates including 30 in the HSTT group and 30 in the Routine Technique (RT) group.

**Interventions:** Participants were randomized into the HSTT group and the Routine Technique (RT) group.

**Main outcome measures:** Data were collected using a questionnaire form and the Neonatal Infant Pain Scale (NIPS).

**Results:** While the means of the total pain scores in the HSTT group were found to be  $1.73 \pm 2.04$  during injection and  $1.73 \pm 0.98$  after injection, in the RT group, the mean scores were  $5.56 \pm 0.92$  during injection and  $4.90 \pm 1.25$  after injection. The difference between the groups arising in the comparison of means of the total pain scores obtained during and after injection in HSTT and RT groups was determined to be statistically significant ( $p < 0.05$ ).

**Conclusion:** In conclusion, HSTT was proven to be effective in reducing hepatitis B vaccine intramuscular (IM) injection pain in neonates. This study demonstrates that HSTT is associated with reduced pain in newborns during hepatitis B vaccine IM injections.

## HIV vaccine

## HPV vaccine

Lancet Glob Health. 2022 Oct;10(10):e1473-e1484.

doi: 10.1016/S2214-109X(22)00309-6.

### [Immunogenicity and safety of one-dose human papillomavirus vaccine compared with two or three doses in Tanzanian girls \(DoRIS\): an open-label, randomised, non-inferiority trial](#)

[Deborah Watson-Jones<sup>1</sup>](#), [John Changalucha<sup>2</sup>](#), [Hilary Whitworth<sup>3</sup>](#), [Ligia Pinto<sup>4</sup>](#), [Paul Mutani<sup>2</sup>](#), [Jackton Indangasi<sup>3</sup>](#), [Troy Kemp<sup>4</sup>](#), [Ramadhan Hashim<sup>2</sup>](#), [Beatrice Kamala<sup>2</sup>](#), [Rebecca Wiggins<sup>5</sup>](#), [Twaib Songoro<sup>2</sup>](#), [Nicholas Connor<sup>6</sup>](#), [Gladys Mbwani<sup>2</sup>](#), [Miquel A Pavon<sup>7</sup>](#), [Brett Lowe<sup>6</sup>](#), [Devis Mmbando<sup>2</sup>](#), [Saidi Kapiga<sup>8</sup>](#), [Philippe Mayaud<sup>6</sup>](#), [Silvia de SanJosé<sup>9</sup>](#), [Joakim Dillner<sup>10</sup>](#), [Richard J Hayes<sup>11</sup>](#), [Charles J Lacey<sup>5</sup>](#), [Kathy Baisley<sup>11</sup>](#)

#### **Abstract**

**Background:** An estimated 15% of girls aged 9-14 years worldwide have been vaccinated against human papillomavirus (HPV) with the recommended two-dose or three-dose schedules. A one-dose HPV vaccine schedule would be simpler and cheaper to deliver. We report immunogenicity and safety results of different doses of two different HPV vaccines in Tanzanian girls.

**Methods:** In this open-label, randomised, phase 3, non-inferiority trial, we enrolled healthy schoolgirls aged 9-14 years from Government schools in Mwanza, Tanzania. Eligible participants were randomly assigned to receive one, two, or three doses of either the 2-valent vaccine (Cervarix, GSK Biologicals, Rixensart) or the 9-valent vaccine (Gardasil-9, Sanofi Pasteur MSD, Lyon). The primary outcome was HPV 16 specific or HPV 18 specific seropositivity following one dose compared with two or three doses of the same HPV vaccine 24 months after vaccination. Safety was assessed as solicited adverse events up to 30 days after each dose and unsolicited adverse events up to 24 months after vaccination or to last study visit. The primary outcome was done in the per-protocol population, and safety was analysed in the total vaccinated population. This study was registered in ClinicalTrials.gov, [NCT02834637](#).

**Findings:** Between Feb 23, 2017, and Jan 6, 2018, we screened 1002 girls for eligibility. 72 girls were excluded. 930 girls were enrolled and randomly assigned to receive one dose of Cervarix (155 participants), two doses of Cervarix (155 participants), three doses of Cervarix

(155 participants), one dose of Gardasil-9 (155 participants), two doses of Gardasil-9 (155 participants), or three doses of Gardasil-9 (155 participants). 922 participants received all scheduled doses within the defined window (three withdrew, one was lost to follow-up, and one died before completion; two received their 6-month doses early, and one received the wrong valent vaccine in error; all 930 participants were included in the total vaccinated cohort). Retention at 24 months was 918 (99%) of 930 participants. In the according-to-protocol cohort, at 24 months, 99% of participants who received one dose of either HPV vaccine were seropositive for HPV 16 IgG antibodies, compared with 100% of participants who received two doses, and 100% of participants who received three doses. This met the prespecified non-inferiority criteria. Anti-HPV 18 seropositivity at 24 months did not meet non-inferiority criteria for one dose compared to two doses or three doses for either vaccine, although more than 98% of girls in all groups had HPV 18 antibodies. 53 serious adverse events (SAEs) were experienced by 42 (4.5%) of 930 girls, the most common of which was hospital admission for malaria. One girl died of malaria. Number of events was similar between groups and no SAEs were considered related to vaccination.

**Interpretation:** A single dose of the 2-valent or 9-valent HPV vaccine in girls aged 9-14 years induced robust immune responses up to 24 months, suggesting that this reduced dose regimen could be suitable for prevention of HPV infection among girls in the target age group for vaccination.

Lancet Glob Health. 2022 Oct;10(10):e1485-e1493.

doi: 10.1016/S2214-109X(22)00306-0.

**[Comparing one dose of HPV vaccine in girls aged 9-14 years in Tanzania \(DoRIS\) with one dose of HPV vaccine in historical cohorts: an immunobridging analysis of a randomised controlled trial](#)**

[Kathy Baisley](#)<sup>1</sup>, [Troy J Kemp](#)<sup>2</sup>, [Aimée R Kreimer](#)<sup>3</sup>, [Partha Basu](#)<sup>4</sup>, [John Chungalucha](#)<sup>5</sup>, [Allan Hildesheim](#)<sup>3</sup>, [Carolina Porras](#)<sup>6</sup>, [Hilary Whitworth](#)<sup>7</sup>, [Rolando Herrero](#)<sup>8</sup>, [Charles J Lacey](#)<sup>9</sup>, [John T Schiller](#)<sup>3</sup>, [Eric Lucas](#)<sup>4</sup>, [Paul Mutani](#)<sup>5</sup>, [Joakim Dillner](#)<sup>10</sup>, [Jackton Indangasi](#)<sup>7</sup>, [Richard Muwonge](#)<sup>4</sup>, [Richard J Hayes](#)<sup>11</sup>, [Ligia A Pinto](#)<sup>2</sup>, [Deborah Watson-Jones](#)<sup>7</sup>

**Abstract**

**Background:** Human papillomavirus (HPV) vaccines are given as a two-dose schedule in children aged 9-14 years, or as three doses in older individuals. We compared antibody responses after one dose of HPV vaccine in the Dose Reduction Immunobridging and Safety Study (DoRIS), a randomised trial of different HPV vaccine schedules in Tanzania, to those from two observational HPV vaccine trials that found high efficacy of one dose up to 11 years against HPV16 and HPV18 (Costa Rica Vaccine Trial [CVT] and Institutional Agency for Research on Cancer [IARC] India trial).

**Methods:** In this immunobridging analysis of an open-label randomised controlled trial, girls were recruited from 54 government schools in Mwanza, Tanzania, into the DoRIS trial. Girls were eligible if they were aged 9-14 years, healthy, and HIV negative. Participants were randomly assigned (1:1:1:1:1), using permuted block sizes of 12, 18, and 24, to one, two, or three doses of the 2-valent vaccine (Cervarix, GSK Biologicals, Rixensart, Belgium) or the 9-valent vaccine (Gardasil 9, Sanofi Pasteur MSD, Lyon, France). For this immunobridging analysis, the primary objective was to compare geometric mean concentrations (GMCs) at 24 months after one dose in the per-protocol population compared with in historical cohorts:

the one-dose 2-valent vaccine group in DoRIS was compared with recipients of the 2-valent vaccine Cervarix from CVT and the one-dose 9-valent vaccine group in DoRIS was compared with recipients of the 4-valent vaccine Gardasil (Merck Sharp & Dohme, Whitehouse Station, NJ, USA) from the IARC India trial. Samples were tested together with virus-like particle ELISA for HPV16 and HPV18 IgG antibodies. Non-inferiority of GMC ratios (DoRIS trial vs historical cohort) was predefined as when the lower bound of the 95% CI was greater than 0.50. This study is registered with ClinicalTrials.gov, [NCT02834637](https://clinicaltrials.gov/ct2/show/study/NCT02834637).

**Findings:** Between Feb 23, 2017, and Jan 6, 2018, we screened 1002 girls for eligibility, of whom 930 were enrolled into DoRIS and 155 each were assigned to one dose, two doses, or three doses of 2-valent vaccine, or one dose, two doses, or three doses of 9-valent vaccine. 154 (99%) participants in the one-dose 2-valent vaccine group (median age 10 years [IQR 9-12]) and 152 (98%) in the one-dose 9-valent vaccine group (median age 10 years [IQR 9-12]) were vaccinated and attended the 24 month visit, and so were included in the analysis. 115 one-dose recipients from the CVT (median age 21 years [19-23]) and 139 one-dose recipients from the IARC India trial (median age 14 years [13-16]) were included in the analysis. At 24 months after vaccination, GMCs for HPV16 IgG antibodies were 22.9 international units (IU) per mL (95% CI 19.9-26.4; n=148) for the DoRIS 2-valent vaccine group versus 17.7 IU/mL (13.9-22.5; n=97) for the CVT (GMC ratio 1.30 [95% CI 1.00-1.68]) and 13.7 IU/mL (11.9-15.8; n=145) for the DoRIS 9-valent vaccine group versus 6.7 IU/mL (5.5-8.2; n=131) for the IARC India trial (GMC ratio 2.05 [1.61-2.61]). GMCs for HPV18 IgG antibodies were 9.9 IU/mL (95% CI 8.5-11.5; n=141) for the DoRIS 2-valent vaccine group versus 8.0 IU/mL (6.4-10.0; n=97) for the CVT trial (GMC ratio 1.23 [95% CI 0.95-1.60]) and 5.7 IU/mL (4.9-6.8; n=136) for the DoRIS 9-valent vaccine group versus 2.2 IU/mL (1.9-2.7; n=129) for the IARC India trial (GMC ratio 2.12 [1.59-2.83]). Non-inferiority of antibody GMCs was met for each vaccine for both HPV16 and HPV18.

**Interpretation:** One dose of HPV vaccine in young girls might provide sufficient protection against persistent HPV infection. A one-dose schedule would reduce costs, simplify vaccine delivery, and expand access to the vaccine.

Hum Vaccin Immunother. 2022 Nov 30;18(5):2061248.

doi: 10.1080/21645515.2022.2061248. Epub 2022 Apr 13.

### [Long-Term immunopersistence and safety of the \*Escherichia coli\*-produced HPV-16/18 bivalent vaccine in Chinese adolescent girls](#)

[Xingmei Yao<sup>1</sup>](#), [Wengang He<sup>1</sup>](#), [Xianghong Wu<sup>2</sup>](#), [Jianxiang Gu<sup>2</sup>](#), [Jing Zhang<sup>2</sup>](#), [Bizhen Lin<sup>3</sup>](#), [Zhaofeng Bi<sup>1</sup>](#), [Yingying Su<sup>1</sup>](#), [Shoujie Huang<sup>1</sup>](#), [Yuemei Hu<sup>4</sup>](#), [Ting Wu<sup>1</sup>](#), [Jun Zhang<sup>1</sup>](#), [Ningshao Xia<sup>1,5</sup>](#)

#### **Abstract**

The study assessed long-term immunopersistence and safety of the *Escherichia coli* (*E. coli*)-produced HPV-16/18 bivalent vaccine. In total, 979 participants in the initial immunogenicity noninferiority study, including girls aged 9-14 years who were randomized in a 1:1 ratio to receive 2 doses at months 0 and 6 (n = 301) or 3 doses at months 0, 1 and 6 (n = 304); girls aged 15-17 years (n = 149) and women aged 18-26 years (n = 225) who received 3 doses of the vaccine, were invited to participate in follow-up to 30 months post vaccination ([NCT03206255](#)). Serum samples were collected at months 18 and 30, and anti-HPV-16/18 IgG antibodies were measured by enzyme-linked immunosorbent assay. Serious adverse events

(SAEs) occurred from month 7 through month 30 were recorded. At month 30, in the per-protocol set, all participants remained seropositive, except for one girl in the 9-14 years (2 doses) group who seroconverted to negative for HPV-18. HPV-16 and HPV-18 antibody levels were higher in girls aged 9-17 years who received 3 doses (125.3 and 60.2 IU/ml) than in women aged 18-26 years who received 3 doses (72.6 and 28.3 IU/ml), and those in girls aged 9-14 years who received 2 doses (73.2 and 24.9 IU/ml) were comparable to those in women aged 18-26 years who received 3 doses. No SAEs were reported to be causally related to vaccination. The *E. coli*-produced bivalent HPV-16/18 vaccine is safe and induces persistent protective antibodies for up to 30 months after vaccination in girls aged 9-17 years receiving 2 or 3 doses.

## Influenza vaccine

Vaccine. 2022 Jul 30;40(32):4339-4347.

doi: 10.1016/j.vaccine.2022.06.028. Epub 2022 Jun 16.

### [Clinical endpoints to inform vaccine policy: A systematic review of outcome measures from pediatric influenza vaccine efficacy trials](#)

[Jordan B Braunfeld](#)<sup>1</sup>, [Heather N Carson](#)<sup>2</sup>, [Sarah R Williams](#)<sup>3</sup>, [Lauren M Schwartz](#)<sup>4</sup>, [Kathleen M Neuzil](#)<sup>5</sup>, [Justin R Ortiz](#)<sup>6</sup>

#### Abstract

**Introduction:** We conducted a systematic review of pediatric influenza vaccine efficacy trials to assess clinical outcome measures and whether the trials defined important public health endpoints.

**Material and methods:** We systematically identified phase 3 or 4 influenza vaccine randomized controlled trials among children  $\leq 18$  years of age with laboratory-confirmed influenza outcomes since 1980. We recorded countries, age groups, vaccine formulations, specimen collection criteria, laboratory diagnostics, primary and secondary outcome measures, and funders, and we determined income category for study countries. We used descriptive statistics to summarize study characteristics. We analyzed the studies overall and a subset of studies conducted in at least one low- and middle-income country (LMIC).

**Results:** From 6455 potentially relevant articles, we identified 41 eligible studies. Twenty-one studies (51%) were conducted in at least one LMIC, while the remaining studies (49%) were conducted in high-income countries only. Thirty-one studies (76%) included children younger than six years. We found 40 different primary outcome measures among the 41 eligible studies. Thirty-three studies (80%) reported standardized symptoms or findings which defined a primary outcome or triggered specimen collection. One study defined a primary outcome which captured more severe illness; however, cases were mostly due to high body temperature without other severity criteria. Of the 21 studies from at least one LMIC, 15 (71%) were published since 2010 and 17 (81%) enrolled children younger than six years. Eighteen (86%) studies from at least one LMIC reported standardized symptoms or findings which defined a primary outcome or triggered specimen collection.

**Conclusions:** Among pediatric influenza vaccine efficacy trials, primary outcome measures and clinical specimen collection criteria were highly variable and, with one exception, focused on capturing any influenza illness. As most LMICs do not have influenza vaccination

programs, our study highlights a potential data limitation affecting policy and implementation decisions in these settings.

Vaccine. 2023 Jan 27;41(5):1009-1017.

doi: 10.1016/j.vaccine.2022.12.058. Epub 2023 Jan 4.

[Revisiting live attenuated influenza vaccine efficacy among children in developing countries](#)

[Sumedha Bagga](#)<sup>1</sup>, [Anand Krishnan](#)<sup>2</sup>, [Lalit Dar](#)<sup>3</sup>

**Abstract**

Seasonal influenza epidemics cause significant pediatric mortality and morbidity worldwide. Live attenuated influenza vaccines (LAIVs) can be administered intranasally, induce a broad and robust immune response, demonstrate higher yields during manufacturing as compared to inactivated influenza vaccines (IIVs), and thereby represent an attractive possibility for young children in developing countries. We summarize recent pediatric studies evaluating LAIV efficacy in developing countries where a large proportion of the influenza-virus-associated respiratory disease burden occurs. Recently, two randomized controlled trials (RCTs) assessing Russian-backbone trivalent LAIV in children reported contradictory results; vaccine efficacy varied between Bangladesh (41 %) and Senegal (0.0 %) against all influenza viral strains. Prior to 2013, Ann Arbor-based LAIV demonstrated superior efficacy as compared to IIV. However, due to low effectiveness of the Ann Arbor-based LAIV against influenza A(H1N1)pdm09-like viruses, the CDC Advisory Committee on Immunization Practices (ACIP) recommended against the use of LAIV during the 2016-17 and 2017-18 influenza seasons. Reduced replicative fitness of the A(H1N1)pdm09 LAIV strains is thought to have led to the low effectiveness of the Ann-Arbor-based LAIV. Once the A(H1N1)pdm09 component was updated, the ACIP reintroduced the Ann-Arbor-based LAIV as a vaccine choice for the 2018-19 influenza season. In 2021, results from a 2-year RCT evaluating the Russian-backbone trivalent LAIV in rural north India reported that LAIV demonstrated significantly lower efficacy compared to IIV, but in Year 2, the vaccine efficacy for LAIV and IIV was comparable. A profounder understanding of the mechanisms underlying varied efficacy of LAIV in developing countries is warranted. Assessing replicative fitness, in addition to antigenicity, when selecting annual A(H1N1)pdm09 components in the Russian-backbone trivalent LAIVs is essential and may ultimately, enable widespread utility in resource-poor settings.

## Japanese encephalitis virus vaccine

## Malaria vaccine

Front Immunol. 2022 Aug 31;13:978591.

doi: 10.3389/fimmu.2022.978591. eCollection 2022.

[Safety and immunogenicity of BK-SE36 in a blinded, randomized, controlled, age de-escalating phase Ib clinical trial in Burkinabe children](#)



[Edith Christiane Bougouma](#)<sup>1,2</sup>, [Nirianne Marie Q Palacpac](#)<sup>3</sup>, [Alfred B Tiono](#)<sup>1,2</sup>, [Issa Nebie](#)<sup>1,2</sup>, [Alphonse Ouédraogo](#)<sup>1,2</sup>, [Sophie Houard](#)<sup>4</sup>, [Masanori Yagi](#)<sup>5</sup>, [Sam Aboubacar Coulibaly](#)<sup>2</sup>, [Amidou Diarra](#)<sup>1,2</sup>, [Takahiro Tougan](#)<sup>5</sup>, [Amidou Z Ouedraogo](#)<sup>1,2</sup>, [Issiaka Soulama](#)<sup>2</sup>, [Nobuko Arisue](#)<sup>5</sup>, [Jean Baptiste Yaro](#)<sup>2</sup>, [Flavia D'Alessio](#)<sup>4</sup>, [Odile Leroy](#)<sup>4</sup>, [Simon Cousens](#)<sup>6</sup>, [Toshihiro Horii](#)<sup>3</sup>, [Sodiomon B Sirima](#)<sup>1,2</sup>

## Abstract

**Background:** A blood-stage vaccine targeting the erythrocytic-stages of the malaria parasite *Plasmodium falciparum* could play a role to protect against clinical disease. Antibodies against the *P. falciparum* serine repeat antigen 5 (SE47 and SE36 domains) correlate well with the absence of clinical symptoms in sero-epidemiological studies. A previous phase Ib trial of the recombinant SE36 antigen formulated with aluminum hydroxyl gel (BK-SE36) was promising. This is the first time the vaccine candidate was evaluated in young children below 5 years using two vaccination routes.

**Methods:** Safety and immunogenicity of BK-SE36 was assessed in a double-blind, randomized, controlled, age de-escalating phase Ib trial. Fifty-four Burkinabe children in each age cohort, 25-60 or 12-24 months, were randomized in a 1:1:1 ratio to receive three doses of BK-SE36 either by intramuscular (BK IM) or subcutaneous (BK SC) route on Day 0, Week 4, and 26; or the control vaccine, Synflorix<sup>®</sup> *via* IM route on Day 0, Week 26 (and physiological saline on Week 4). Safety data and samples for immunogenicity analyses were collected at various time-points.

**Results:** Of 108 subjects, 104 subjects (96.3%) (Cohort 1: 94.4%; Cohort 2: 98.1%) received all three scheduled vaccine doses. Local reactions, mostly mild or of moderate severity, occurred in 99 subjects (91.7%). The proportion of subjects that received three doses without experiencing Grade 3 adverse events was similar across BK-SE36 vaccines and control arms (Cohort 1: 100%, 89%, and 89%; and Cohort 2: 83%, 82%, and 83% for BK IM, BK SC, and control, respectively). BK-SE36 vaccine was immunogenic, inducing more than 2-fold change in antibody titers from pre-vaccination, with no difference between the two vaccination routes. Titers waned before the third dose but in both cohorts titers were boosted 6 months after the first vaccination. The younger cohort had 2-fold and 4-fold higher geometric mean titers compared to the 25- to 60-month-old cohort after 2 and 3 doses of BK-SE36, respectively.

**Conclusion:** BK-SE36 was well tolerated and immunogenic using either intramuscular or subcutaneous routes, with higher immune response in the younger cohort.

Lancet Infect Dis. 2022 Dec;22(12):1728-1736.

doi: 10.1016/S1473-3099(22)00442-X. Epub 2022 Sep 7.

## **Efficacy and immunogenicity of R21/Matrix-M vaccine against clinical malaria after 2 years' follow-up in children in Burkina Faso: a phase 1/2b randomised controlled trial**

[Mehreen S Dattoo](#)<sup>1</sup>, [Hamtandi Magloire Natama](#)<sup>2</sup>, [Athanasé Somé](#)<sup>2</sup>, [Duncan Bellamy](#)<sup>3</sup>, [Ousmane Traoré](#)<sup>2</sup>, [Toussaint Rouamba](#)<sup>2</sup>, [Marc Christian Tahita](#)<sup>2</sup>, [N Félix André Ido](#)<sup>2</sup>, [Prisca Yameogo](#)<sup>2</sup>, [Daniel Valia](#)<sup>2</sup>, [Aida Millogo](#)<sup>2</sup>, [Florence Ouedraogo](#)<sup>2</sup>, [Rachidatou Soma](#)<sup>2</sup>, [Seydou Sawadogo](#)<sup>2</sup>, [Faizatou Sorgho](#)<sup>2</sup>, [Karim Derra](#)<sup>2</sup>, [Eli Rouamba](#)<sup>2</sup>, [Fernando Ramos-Lopez](#)<sup>1</sup>, [Matthew Cairns](#)<sup>4</sup>, [Samuel Provstgaard-Morys](#)<sup>3</sup>, [Jeremy Aboagye](#)<sup>3</sup>, [Alison Lawrie](#)<sup>1</sup>, [Rachel Roberts](#)<sup>1</sup>, [Innocent Valéa](#)<sup>2</sup>, [Hermann Sorgho](#)<sup>2</sup>, [Nicola Williams](#)<sup>5</sup>, [Gregory Glenn](#)<sup>6</sup>, [Louis Fries](#)<sup>6</sup>, [Jenny Reimer](#)<sup>7</sup>, [Katie J Ewer](#)<sup>3</sup>, [Umesh Shaligram](#)<sup>8</sup>, [Adrian V S Hill](#)<sup>9</sup>, [Halidou Tinto](#)<sup>10</sup>

## Abstract

**Background:** Malaria is a leading cause of morbidity and mortality worldwide. We previously reported the efficacy of the R21/Matrix-M malaria vaccine, which reached the WHO-specified goal of 75% or greater efficacy over 12 months in the target population of African children. Here, we report the safety, immunogenicity, and efficacy results at 12 months following administration of a booster vaccination.

**Methods:** This double-blind phase 1/2b randomised controlled trial was done in children aged 5-17 months in Nanoro, Burkina Faso. Eligible children were enrolled and randomly assigned (1:1:1) to receive three vaccinations of either 5 µg R21/25 µg Matrix-M, 5 µg R21/50 µg Matrix-M, or a control vaccine (the Rabivax-S rabies vaccine) before the malaria season, with a booster dose 12 months later. Children were eligible for inclusion if written informed consent could be provided by a parent or guardian. Exclusion criteria included any existing clinically significant comorbidity or receipt of other investigational products. A random allocation list was generated by an independent statistician by use of block randomisation with variable block sizes. A research assistant from the University of Oxford, independent of the trial team, prepared sealed envelopes using this list, which was then provided to the study pharmacists to assign participants. All vaccines were prepared by the study pharmacists by use of the same type of syringe, and the contents were covered with an opaque label. Vaccine safety, efficacy, and a potential correlate of efficacy with immunogenicity, measured as anti-NANP antibody titres, were evaluated over 1 year following the first booster vaccination. The population in which the efficacy analyses were done comprised all participants who received the primary series of vaccinations and a booster vaccination. Participants were excluded from the efficacy analysis if they withdrew from the trial within the first 2 weeks of receiving the booster vaccine. This trial is registered with ClinicalTrials.gov ([NCT03896724](https://clinicaltrials.gov/ct2/show/study/NCT03896724)), and is continuing for a further 2 years to assess both the potential value of additional booster vaccine doses and longer-term safety.

**Findings:** Between June 2, and July 2, 2020, 409 children returned to receive a booster vaccine. Each child received the same vaccination for the booster as they received in the primary series of vaccinations; 132 participants received 5 µg R21 adjuvanted with 25 µg Matrix-M, 137 received 5 µg R21 adjuvanted with 50 µg Matrix-M, and 140 received the control vaccine. R21/Matrix-M had a favourable safety profile and was well tolerated. Vaccine efficacy remained high in the high adjuvant dose (50 µg) group, similar to previous findings at 1 year after the primary series of vaccinations. Following the booster vaccination, 67 (51%) of 132 children who received R21/Matrix-M with low-dose adjuvant, 54 (39%) of 137 children who received R21/Matrix-M with high-dose adjuvant, and 121 (86%) of 140 children who received the rabies vaccine developed clinical malaria by 12 months. Vaccine efficacy was 71% (95% CI 60 to 78) in the low-dose adjuvant group and 80% (72 to 85) in the high-dose adjuvant group. In the high-dose adjuvant group, vaccine efficacy against multiple episodes of malaria was 78% (95% CI 71 to 83), and 2285 (95% CI 1911 to 2568) cases of malaria were averted per 1000 child-years at risk among vaccinated children in the second year of follow-up. Among these participants, at 28 days following their last R21/Matrix-M vaccination, titres of malaria-specific anti-NANP antibodies correlated positively with protection against malaria in both the first year of follow-up (Spearman's  $\rho$  -0.32 [95% CI -0.45 to -0.19];  $p=0.0001$ ) and second year of follow-up (-0.20 [-0.34 to -0.06];  $p=0.02$ ).

**Interpretation:** A booster dose of R21/Matrix-M at 1 year following the primary three-dose regimen maintained high efficacy against first and multiple episodes of clinical malaria. Furthermore, the booster vaccine induced antibody concentrations that correlated with

vaccine efficacy. The trial is ongoing to assess long-term follow-up of these participants and the value of further booster vaccinations.

## Maternal immunization in pregnancy

Emerg Microbes Infect. 2023 Dec;12(1):2204146.

doi: 10.1080/22221751.2023.2204146.

### [Effect of immunization during pregnancy and pre-existing immunity on diphtheria-tetanus-acellular pertussis vaccine responses in infants](#)

[Aapo Knuutila<sup>1</sup>](#), [Alex-Mikael Barkoff<sup>1</sup>](#), [Lauri Ivaska<sup>2,3</sup>](#), [Eлина Tenhu<sup>1</sup>](#), [Johanna Teräsjärvi<sup>1</sup>](#), [Pieter van Gageldonk<sup>4</sup>](#), [Annemarie Buisman<sup>4</sup>](#), [Jussi Mertsola<sup>2,3</sup>](#), [Qiushui He<sup>1,3</sup>](#); [PERISCOPE consortium<sup>1</sup>](#)

#### **Abstract**

Immunization during pregnancy (IP) against pertussis is recommended in many countries to protect infants. Although maternal antibodies can influence the infants' antibody responses to primary vaccinations, their effect on the development of functional antibodies and B cells remain poorly studied. We investigated the maternal immune response to IP and the effect of IP and pre-existing antibodies on infants' primary vaccine responses in an open-label, non-randomized trial. Forty-seven mothers received tetanus-diphtheria-acellular pertussis (Tdap) vaccine during pregnancy, and 22 mothers were included as controls. Sixty-nine infants received primary doses of DTaP at three and five months of age. Geometric mean concentrations of antibodies to pertussis toxin, filamentous haemagglutinin, pertactin, diphtheria, and tetanus toxins, pertussis toxin neutralizing antibodies (PTNAs), and plasma and memory B-cell frequencies were studied at delivery, and at three, five and six months. Levels of antibodies, PTNAs, and frequencies of memory B-cells were significantly increased at delivery and up to six months after in mothers with IP compared to those without IP (all  $p < 0.05$ , except for PT-specific memory B-cells). In vaccinated pregnant women, high pre-existing antibody levels were positively correlated with higher antibody responses after IP. IP blunted the infants' antibody and plasma B-cell responses to all vaccine antigens, except for tetanus toxin. This blunting effect was the strongest in infants with high concentrations of maternal antibodies. In conclusion, IP resulted in significantly higher concentrations of antibodies in infants up to three months of age (all  $p < 0.05$ ); but was associated with blunting of various infants' vaccine responses.

## Measles vaccine

\*\*\* EClinicalMedicine. 2022 May 27;49:101467.

doi: 10.1016/j.eclinm.2022.101467. eCollection 2022 Jul.

### [Effect of early two-dose measles vaccination on childhood mortality and modification by maternal measles antibody in Guinea-Bissau, West Africa: A single-centre open-label randomised controlled trial](#)

[Sebastian Nielsen](#)<sup>1,2</sup>, [Ane B Fisker](#)<sup>1,2</sup>, [Isaquel da Silva](#)<sup>1</sup>, [Stine Byberg](#)<sup>1</sup>, [Sofie Biering-Sørensen](#)<sup>1</sup>, [Carlitos Balé](#)<sup>1</sup>, [Amarildo Barbosa](#)<sup>1</sup>, [Morten Bjerregaard-Andersen](#)<sup>1</sup>, [Nadja Skadkær Hansen](#)<sup>1</sup>, [Vu An Do](#)<sup>1</sup>, [Ole Bæk](#)<sup>1</sup>, [Stine Møller Rasmussen](#)<sup>1</sup>, [Lone Damkjær](#)<sup>1</sup>, [Sophus Hvidt](#)<sup>1</sup>, [Olga Baltzersen](#)<sup>1</sup>, [Amabelia Rodrigues](#)<sup>1</sup>, [Cesario Martins](#)<sup>1</sup>, [Kristoffer J Jensen](#)<sup>1,2</sup>, [Hilton C Whittle](#)<sup>3</sup>, [Gaby Smits](#)<sup>4</sup>, [Fiona van der Klis](#)<sup>4</sup>, [Peter Aaby](#)<sup>1,2</sup>, [Christine S Benn](#)<sup>1,2</sup>

## Abstract

**Background:** Early 2-dose measles vaccine (MV) at 4 and 9 months of age vs. the WHO strategy of MV at 9 months of age reduced all-cause child mortality in a previous trial. We aimed to test two hypotheses: 1) a 2-dose strategy reduces child mortality between 4 and 60 months of age by 30%; 2) receiving early MV at 4 months in the presence versus absence of maternal measles antibodies (MatAb) reduces child mortality by 35%.

**Methods:** Single-centre open-label community-based randomised controlled trial in Guinea-Bissau, with 2:1 block-randomisation by sex to a 2-dose (4 + 9 months) vs. 1-dose (9 months) MV strategy. Healthy children were eligible 4 weeks after the 3rd diphtheria-tetanus-pertussis-containing vaccine. Before randomisation a blood sample was collected to determine MatAb level. The primary outcome was all-cause mortality. Hazard ratios (HR) were derived from Cox regression in the per protocol population. We tested for interactions with national campaigns with oral polio vaccine (C-OPV). Trial registration: [NCT01486355](#).

**Findings:** Between August 2011-April 17th 2015, 6,636 children were enrolled, 6,598 [ $n_{2\text{-dose}}=4,397$ ;  $n_{1\text{-dose}}=2,201$ ] were included in the analysis of the primary outcome, The HR(2-dose/1-dose) between 4 and 60 months was 1.38 (95%CI: 0.92-2.06) [deaths:  $n_{2\text{-dose}}=90$ ;  $n_{1\text{-dose}}=33$ ]. Before the 9-month MV and the HR(1-dose/no dose) was 0.94 (0.45-1.96) [deaths:  $n_{2\text{-dose}}=21$ ;  $n_{1\text{-dose}}=11$ ]. The HR(2-dose/1-dose) was 0.81 (0.29-2.22) for children, who received no C-OPV [deaths/children:  $n_{2\text{-dose}}=10/2,801$ ;  $n_{1\text{-dose}}=6/1,365$ ], and 4.73 (1.44-15.6) for children, who received C-OPV before and after enrolment (p for interaction=0.027) [deaths/children:  $n_{2\text{-dose}}=27/1,602$ ;  $n_{1\text{-dose}}=3/837$ ]. In the 2-dose group receiving early MV at 4 months, mortality was 50% (20-68%) lower for those vaccinated in the presence of MatAb vs. the absence of MatAb [deaths/children:  $n_{\text{MatAb}}=51/3,132$ ;  $n_{\text{noMatAb}}=31/1,028$ ].

**Interpretation:** The main result contrasts with previous findings but may, though based on a small number of events, be explained by frequent OPV campaigns that reduced the mortality rate, but apparently interacted negatively with early MV. The beneficial non-specific effects of MV in the presence of MatAb should be investigated further.

Clin Infect Dis. 2022 Oct 12;75(8):1370-1378.

doi: 10.1093/cid/ciac155.

## [The Effect of a Second Dose of Measles Vaccine at 18 Months of Age on Nonaccidental Deaths and Hospital Admissions in Guinea-Bissau: Interim Analysis of a Randomized Controlled Trial](#)

[Mike L T Berendsen](#)<sup>1,2,3</sup>, [Isaquel Silva](#)<sup>2</sup>, [Carlitos Balé](#)<sup>2</sup>, [Sebastian Nielsen](#)<sup>1,2</sup>, [Sophus Hvidt](#)<sup>2</sup>, [Cesario L Martins](#)<sup>2</sup>, [Christine S Benn](#)<sup>1,4</sup>, [Peter Aaby](#)<sup>2</sup>

## Abstract

**Background:** The world is set on the eradication of measles. Continuation of the measles vaccine (MV) after eradication could still reduce morbidity because the MV has so-called

beneficial nonspecific effects. We evaluated the effect of a "booster" dose of the MV on overall severe morbidity.

**Methods:** We conducted a randomized controlled trial among children aged 17.5 to 48 months in Guinea-Bissau, where the MV is recommended only at 9 months of age. At the time of this interim analysis, 3164 children had been allocated 1:1 to a second dose of measles vaccine (MV2) at 18 months of age or to no vaccine. Severe morbidity (a composite outcome of nonaccidental deaths and hospital admissions) rate ratios (SMRRs) were calculated by Cox regression analysis censored for national oral polio vaccine (OPV) campaigns.

**Results:** There were no measles cases during the trial period. There were 43 nonaccidental deaths or hospital admissions during follow-up. Severe morbidity was 2.6 per 100 person-years in the MV2 group and 3.6 per 100 person-years among controls; hence, the estimated effect of MV2 on severe morbidity was 28% (SMRR, 0.72; 95% confidence interval [CI], .38-1.38). At 12 months of follow-up, the number needed to treat to prevent 1 severe morbidity event was 137 children. After OPV campaigns, the estimated effect of MV2 was reduced to 9% (SMRR, 0.91; 95% CI, .46-1.81).

**Conclusions:** MV2 may reduce nonmeasles severe morbidity by 28% (-38% to 62%), although this did not achieve statistical significance in this study. If significant in higher powered studies, this has major implications for child health, even after measles eradication.

## Measles, mumps, rubella (MMR) vaccine

BMC Infect Dis. 2023 Mar 17;23(1):165.

doi: 10.1186/s12879-023-08114-1.

### [Immune response to co-administration of measles, mumps, and rubella \(MMR\), and yellow fever vaccines: a randomized non-inferiority trial among one-year-old children in Argentina](#)

[Carla Vizzotti](#)<sup>#1</sup>, [Jennifer B Harris](#)<sup>#2</sup>, [Analía Aquino](#)<sup>1</sup>, [Carolina Rancaño](#)<sup>1</sup>, [Cristian Biscayart](#)<sup>1</sup>, [Romina Bonaventura](#)<sup>3</sup>, [Andrea Pontoriero](#)<sup>3</sup>, [Elsa Baumeister](#)<sup>3</sup>, [Maria Cecilia Freire](#)<sup>3</sup>, [Mirta Magariños](#)<sup>4</sup>, [Blanca Duarte](#)<sup>5</sup>, [Gavin Grant](#)<sup>6</sup>, [Susan Reef](#)<sup>6</sup>, [Janeen Laven](#)<sup>7</sup>, [Kathleen A Wannemuehler](#)<sup>6,8</sup>, [Alba Maria Roperó Alvarez](#)<sup>9</sup>, [J Erin Staples](#)<sup>7</sup>

#### **Abstract**

**Background:** In yellow fever (YF) endemic areas, measles, mumps, and rubella (MMR), and YF vaccines are often co-administered in childhood vaccination schedules. Because these are live vaccines, we assessed potential immune interference that could result from co-administration.

**Methods:** We conducted an open-label, randomized non-inferiority trial among healthy 1-year-olds in Misiones Province, Argentina. Children were randomized to one of three groups (1:1:1): Co-administration of MMR and YF vaccines (MMR<sub>1</sub>YF<sub>1</sub>), MMR followed by YF vaccine four weeks later (MMR<sub>1</sub>YF<sub>2</sub>), or YF followed by MMR vaccine four weeks later (YF<sub>1</sub>MMR<sub>2</sub>). Blood samples obtained pre-vaccination and 28 days post-vaccination were tested for immunoglobulin G antibodies against measles, mumps, and rubella, and for YF virus-specific neutralizing antibodies. Non-inferiority in seroconversion was assessed using a -5% non-inferiority margin. Antibody concentrations were compared with Kruskal-Wallis tests.



**Results:** Of 851 randomized children, 738 were correctly vaccinated, had  $\geq 1$  follow-up sample, and were included in the intention-to-treat population. Non-inferior seroconversion was observed for all antigens (measles seroconversion: 97.9% in the MMR<sub>1</sub>YF<sub>1</sub> group versus 96.3% in the MMR<sub>1</sub>YF<sub>2</sub> group, a difference of 1.6% [90% CI -1.5, 4.7]; rubella: 97.9% MMR<sub>1</sub>YF<sub>1</sub> versus 94.7% MMR<sub>1</sub>YF<sub>2</sub>, a difference of 3.3% [-0.1, 6.7]; mumps: 96.7% MMR<sub>1</sub>YF<sub>1</sub> versus 97.9% MMR<sub>1</sub>YF<sub>2</sub>, a difference of -1.3% [-4.1, 1.5]; and YF: 96.3% MMR<sub>1</sub>YF<sub>1</sub> versus 97.5% YF<sub>1</sub>MMR<sub>2</sub>, a difference of -1.2% [-4.2, 1.7]). Rubella antibody concentrations and YF titers were significantly lower following co-administration; measles and mumps concentrations were not impacted.

**Conclusion:** Effective seroconversion was achieved and was not impacted by the co-administration, although antibody levels for two antigens were lower. The impact of lower antibody levels needs to be weighed against missed opportunities for vaccination to determine optimal timing for MMR and YF vaccine administration.

## Meningococcal vaccine

Hum Vaccin Immunother. 2022 Dec 31;18(1):1981085.

doi: 10.1080/21645515.2021.1981085. Epub 2021 Oct 6.

### [Immunological non-inferiority of a new fully liquid presentation of the MenACWY-CRM vaccine to the licensed vaccine: results from a randomized, controlled, observer-blind study in adolescents and young adults](#)

[Javier Díez-Domingo<sup>1</sup>](#), [Juan Carlos Tinoco<sup>2</sup>](#), [Airi Poder<sup>3</sup>](#), [Ener Cagri Dinleyici<sup>4</sup>](#), [Haylene Nell<sup>5</sup>](#), [Ignacio Salamanca de la Cueva<sup>6</sup>](#), [Tolga Ince<sup>7</sup>](#), [Edson Duarte Moreira Jr<sup>8</sup>](#), [Khatija Ahmed<sup>9</sup>](#), [Kleber Luz<sup>10</sup>](#), [Yulia Kovshirina<sup>11</sup>](#), [Carlos Eduardo Medina Pech<sup>12</sup>](#), [Tauseefullah Akhund<sup>13</sup>](#), [Valerio Romolini<sup>14</sup>](#), [Marco Costantini<sup>14</sup>](#), [Thembile Mzolo<sup>15</sup>](#), [Barry Kunnel<sup>16</sup>](#), [Isabelle Lechevin<sup>17</sup>](#), [Marianna Aggravi<sup>18</sup>](#), [Paola Tiberi<sup>19</sup>](#), [K Narendran<sup>20</sup>](#), [Juan-Antonio García-Martínez<sup>21</sup>](#), [Venere Basile<sup>22</sup>](#), [Elena Fragapane<sup>13</sup>](#), [Maria Lattanzi<sup>13</sup>](#), [Michele Pellegrini<sup>13</sup>](#)

#### **Abstract**

A fully liquid MenACWY-CRM vaccine presentation has been developed, modifying the meningococcal serogroup A (MenA) component from lyophilized to liquid. The safety and immunogenicity of the liquid presentation at the end of the intended shelf-life (aged for 24 or 30 months) were compared to the licensed lyophilized/liquid presentation. This multicenter, randomized (1:1), observer-blind, phase 2b study ([NCT03433482](#)) enrolled adolescents and young adults (age 10-40 years). In part 1, 844 participants received one dose of liquid presentation stored for approximately 24 months or licensed presentation. In part 2, 846 participants received one dose of liquid presentation stored for approximately 30 months or licensed presentation. After storage, the MenA free saccharide (FS) level was approximately 25% and O-acetylation was approximately 45%. The primary objective was to demonstrate non-inferiority of the liquid presentation to licensed presentation, as measured by human serum bactericidal assay (hSBA) geometric mean titers (GMTs) against MenA, 1-month post-vaccination. Immune responses against each vaccine serogroup were similar between groups. Between-group ratios of hSBA GMTs for MenA were 1.21 (part 1) and 1.11 (part 2), with two-sided 95% confidence interval lower limits (0.94 and 0.87, respectively) greater than the prespecified non-inferiority margin (0.5), thus meeting the primary study objective. No safety concerns were identified. Despite reduced O-acetylation of MenA and increased FS



content, serogroup-specific immune responses induced by the fully liquid presentation were similar to those induced by the licensed MenACWY-CRM vaccine, with non-inferior anti-MenA responses. The safety profiles of the vaccine presentations were similar.

Vaccine. 2023 Jan 27;41(5):1153-1160.

doi: 10.1016/j.vaccine.2022.11.048. Epub 2023 Jan 6.

**[A phase 3, randomized, controlled, open-label study to evaluate the persistence up to 5 years of 1 or 2 doses of meningococcal conjugate vaccine MenACWY-TT given with or without 13-valent pneumococcal conjugate vaccine in 12-14-month-old children](#)**

[Clare L Cutland<sup>1</sup>](#), [Paula Peyrani<sup>2</sup>](#), [Chris Webber<sup>3</sup>](#), [Ryan Newton<sup>4</sup>](#), [Mark Cutler<sup>5</sup>](#), [John L Perez<sup>6</sup>](#)

**Abstract**

**Background:** Immunogenicity and safety up to 5 years after administration of 1 or 2 doses of quadrivalent meningococcal serogroup A, C, W, and Y tetanus toxoid conjugate vaccine (MenACWY-TT) given alone or with 13-valent pneumococcal conjugate vaccine (PCV13) in children was investigated.

**Methods:** This phase 3 study randomized healthy 12-24-month-olds to MenACWY-TT at Month 0 (ACWY1d), MenACWY-TT at Months 0 and 2 (ACWY2d), MenACWY-TT and PCV13 at Month 0 (Co-Ad), or PCV13 at Month 0 and MenACWY-TT at Month 2 (PCV13/ACWY). Immune responses 1, 3, and 5 years after primary vaccination were evaluated with serum bactericidal activity using rabbit complement (rSBA) titers  $\geq 1:8$  and geometric mean titers (GMTs). Evaluation of serious adverse events up to 5 years after primary vaccination are reported.

**Results:** Of the 802 children randomized in the study, 619 completed the study through Year 5. Immune responses after vaccination declined over time but were higher 5 years after vaccination compared with levels before vaccination. At Year 5, the percentages of children with rSBA titers  $\geq 1:8$  across all serogroups were 20.5 %-58.6 %, 28.4 %-65.8 %, 23.9 %-52.8 %, and 19.4 %-55.8 % in the ACWY1d, ACWY2d, Co-Ad, and PCV13/ACWY groups, respectively. Comparable antibody persistence at Year 5 was observed for participants receiving 1 or 2 doses of MenACWY-TT, although GMTs were elevated in those who received 2 versus 1 dose. The percentage of children with protective antibody titers at Year 5 was similar in participants who received PCV13 and MenACWY-TT compared with that observed for participants who only received 1 or 2 MenACWY-TT doses. No new safety concerns were identified during the study period.

**Conclusion:** Antibody responses persisted in the majority of children up to 5 years after primary vaccination with MenACWY-TT administered in a 1- or 2-dose regimen with or without PCV13, with no new safety concerns identified.

N Engl J Med. 2023 May 25;388(21):1942-1955.

doi: 10.1056/NEJMoa2214924.

**[Meningococcal ACWYX Conjugate Vaccine in 2-to-29-Year-Olds in Mali and Gambia](#)**

[Fadima C Haidara<sup>1</sup>](#), [Ama Umesi<sup>1</sup>](#), [Samba O Sow<sup>1</sup>](#), [Magnus Ochoge<sup>1</sup>](#), [Fatoumata Diallo<sup>1</sup>](#), [Abdulazeez Imam<sup>1</sup>](#), [Youssef Traore<sup>1</sup>](#), [Lucy Affleck<sup>1</sup>](#), [Moussa F Doumbia<sup>1</sup>](#), [Bubacarr Daffeh<sup>1</sup>](#), [Mamoudou Kodio<sup>1</sup>](#), [Oghenebrume Wariri<sup>1</sup>](#), [Awa Traoré<sup>1</sup>](#), [Edrissa Jallow<sup>1</sup>](#), [Beate Kampmann<sup>1</sup>](#), [Dhananjay Kapse<sup>1</sup>](#), [Prasad S Kulkarni<sup>1</sup>](#), [Asha Mallya<sup>1</sup>](#), [Sunil Goel<sup>1</sup>](#), [Pankaj Sharma<sup>1</sup>](#), [Annamraju D Sarma<sup>1</sup>](#), [Nikhil Avalaskar<sup>1</sup>](#), [F Marc LaForce<sup>1</sup>](#), [Mark R Alderson<sup>1</sup>](#), [Abdi](#)

[Naficy<sup>1</sup>](#), [Steve Lamola<sup>1</sup>](#), [Yuxiao Tang<sup>1</sup>](#), [Lionel Martellet<sup>1</sup>](#), [Nancy Hosken<sup>1</sup>](#), [Evangelos Simeonidis<sup>1</sup>](#), [Jo Anne Welsch<sup>1</sup>](#), [Milagritos D Tapia<sup>1</sup>](#), [Ed Clarke<sup>1</sup>](#)

## Abstract

**Background:** An effective, affordable, multivalent meningococcal conjugate vaccine is needed to prevent epidemic meningitis in the African meningitis belt. Data on the safety and immunogenicity of NmCV-5, a pentavalent vaccine targeting the A, C, W, Y, and X serogroups, have been limited.

**Methods:** We conducted a phase 3, noninferiority trial involving healthy 2-to-29-year-olds in Mali and Gambia. Participants were randomly assigned in a 2:1 ratio to receive a single intramuscular dose of NmCV-5 or the quadrivalent vaccine MenACWY-D. Immunogenicity was assessed at day 28. The noninferiority of NmCV-5 to MenACWY-D was assessed on the basis of the difference in the percentage of participants with a seroresponse (defined as prespecified changes in titer; margin, lower limit of the 96% confidence interval [CI] above -10 percentage points) or geometric mean titer (GMT) ratios (margin, lower limit of the 98.98% CI >0.5). Serogroup X responses in the NmCV-5 group were compared with the lowest response among the MenACWY-D serogroups. Safety was also assessed.

**Results:** A total of 1800 participants received NmCV-5 or MenACWY-D. In the NmCV-5 group, the percentage of participants with a seroresponse ranged from 70.5% (95% CI, 67.8 to 73.2) for serogroup A to 98.5% (95% CI, 97.6 to 99.2) for serogroup W; the percentage with a serogroup X response was 97.2% (95% CI, 96.0 to 98.1). The overall difference between the two vaccines in seroresponse for the four shared serogroups ranged from 1.2 percentage points (96% CI, -0.3 to 3.1) for serogroup W to 20.5 percentage points (96% CI, 15.4 to 25.6) for serogroup A. The overall GMT ratios for the four shared serogroups ranged from 1.7 (98.98% CI, 1.5 to 1.9) for serogroup A to 2.8 (98.98% CI, 2.3 to 3.5) for serogroup C. The serogroup X component of the NmCV-5 vaccine generated seroresponses and GMTs that met the prespecified noninferiority criteria. The incidence of systemic adverse events was similar in the two groups (11.1% in the NmCV-5 group and 9.2% in the MenACWY-D group).

**Conclusions:** For all four serotypes in common with the MenACWY-D vaccine, the NmCV-5 vaccine elicited immune responses that were noninferior to those elicited by the MenACWY-D vaccine. NmCV-5 also elicited immune responses to serogroup X. No safety concerns were evident.

## Norovirus vaccine

Hum Vaccin Immunother. 2023 Dec 31;19(1):2204787.

doi: 10.1080/21645515.2023.2204787. Epub 2023 May 4.

[Immunogenicity and tolerability of a bivalent virus-like particle norovirus vaccine candidate in children from 6 months up to 4 years of age: A phase 2 randomized, double-blind trial](#)

[Pio López<sup>1</sup>](#), [Eduardo López-Medina<sup>1</sup>](#), [Xavier Sáez-Llorens<sup>2,3,4</sup>](#), [Rodrigo deAntonio<sup>2</sup>](#), [Taisei Masuda<sup>5</sup>](#), [Paul M Mendelman<sup>6</sup>](#), [James Sherwood<sup>5,7</sup>](#), [Frank Baehner<sup>5</sup>](#), [Astrid Borkowski<sup>5,7</sup>](#)

## Abstract

We conducted a dose-finding phase 2 study of the HilleVax bivalent virus-like particle (VLP) vaccine candidate (HIL-214) in two cohorts of children, 6-≤12 months and 1-≤4 years of age (N

= 120 per cohort), in Panama and Colombia (ClinicalTrials.gov, identifier [NCT02153112](https://clinicaltrials.gov/ct2/show/study/NCT02153112)). On Day 1, children randomized to one of the four equal groups received intramuscular injections of four different HIL-214 formulations containing 15/15, 15/50, 50/50, or 50/150 µg of GI.1/GII.4c genotype VLPs and 0.5 mg Al(OH)<sub>3</sub>. On Day 29, half the children in each group received a second vaccination (N = 60), while the other half received saline placebo injections to maintain the blind. VLP-specific ELISA Pan-Ig and histo-blood group binding antigen-blocking antibodies (HBGA) were measured on Days 1, 29, 57 and 210. On Day 29, after one dose, there were large Pan-Ig and HBGA responses in both age cohorts with some indication of dose-dependence, and higher geometric mean titers (GMT) in the older children. A further increase in titers was observed 28 days after a second dose in the 6-≤12-month-old groups, but less so in the 1-≤4-year-old groups; GMTs at Day 57 were broadly similar across doses and in both age groups. GMTs of Pan-Ig and HBGA persisted above baseline up to Day 210. All formulations were well tolerated with mostly mild-to-moderate transient solicited adverse events reported by parents/guardians, and no vaccine-related serious adverse events occurred. Further development of HIL-214 is warranted to protect the most susceptible young children against norovirus.

## Prentavalent vaccine (DTP-HepB-Hib)

## Pneumococcal vaccine

Lancet Child Adolesc Health. 2023 Mar 16;S2352-4642(23)00025-1.

doi: 10.1016/S2352-4642(23)00025-1. Online ahead of print.

[\*\*Single priming and booster dose of ten-valent and 13-valent pneumococcal conjugate vaccines and Streptococcus pneumoniae colonisation in children in South Africa: a single-centre, open-label, randomised trial\*\*](#)

[Courtney P Olwage](#)<sup>1</sup>, [Alane Izu](#)<sup>1</sup>, [Eleonora A M L Mutsaerts](#)<sup>2</sup>, [Lisa Jose](#)<sup>1</sup>, [Anthonet Koen](#)<sup>1</sup>, [Sarah L Downs](#)<sup>1</sup>, [Lara Van Der Merwe](#)<sup>1</sup>, [Matt Laubscher](#)<sup>1</sup>, [Amit J Nana](#)<sup>1</sup>, [Andrew Moultrie](#)<sup>1</sup>, [Clare L Cutland](#)<sup>3</sup>, [Jeffrey R Dorfman](#)<sup>4</sup>, [Shabir A Madhi](#)<sup>5</sup>

### Abstract

**Background:** Pneumococcal conjugate vaccine (PCV) immunisation has reduced vaccine-serotype colonisation and invasive pneumococcal disease in South Africa, providing the opportunity to consider transitioning from a two-dose (2 + 1) to one-dose (1 + 1) primary series and a booster dose.

**Methods:** In this single-centre, open-label, randomised trial done in South Africa, infants aged 35-49 days without HIV infection, without childhood immunisations except for BCG and polio, and with gestation age at delivery of at least 37 weeks of age, a birthweight of at least 2500 g, and weight of at least 3500 g at the time of enrolment were randomly assigned (1:1:1:1:1:1), through block randomisation (block size of 30), to receive a single priming dose of ten-valent PCV (PCV10) or 13-valent PCV (PCV13) at either 6 weeks (6-week 1 + 1 group) or 14 weeks (14-week 1 + 1 group), compared with two priming doses at 6 weeks and 14 weeks

(2 + 1 group), followed by a booster dose at 9 months of age in all groups. The primary objective of the trial has been published previously. We report the secondary objective of the effect of alternative doses of PCV10 and PCV13 on serotype-specific *Streptococcus pneumoniae* colonisation at 9 months, 15 months, and 18 months of age and a further exploratory analysis in which we assessed non-inferiority of serotype-specific serum IgG geometric mean concentrations 1 month after the booster (10 months of age) and the percentage of participants with serotype-specific IgG titre above the putative thresholds associated with a risk reduction of serotype-specific colonisation between the 1 + 1 and 2 + 1 groups for both vaccines. Non-inferiority was established if the lower limit of the 95% CI for the difference between the proportion of participants (1 + 1 group vs 2 + 1 group) above the putative thresholds was greater than or equal to -10%. All analyses were done in the modified intention-to-treat population, which included all participants who received PCV10 or PCV13 according to assigned randomisation group and for whom laboratory results were available. The trial is registered with ClinicalTrials.gov, [NCT02943902](https://www.clinicaltrials.gov/ct2/show/study/NCT02943902).

**Findings:** 1564 nasopharyngeal swabs were available for molecular serotyping from 600 infants who were enrolled (100 were randomly assigned to each of the six study groups) between Jan 9 and Sept 20, 2017. There was no significant difference in the prevalence of overall or non-vaccine serotype colonisation between all PCV13 or PCV10 groups. PCV13 serotype colonisation was lower at 15 months of age in the 14-week 1 + 1 group than in the 2 + 1 group (seven [8%] of 85 vs 17 [20%] of 87; odds ratio 0.61 [95% CI 0.38-0.97],  $p=0.037$ ), but no difference was seen at 9 months (nine [11%] of 86 vs ten [11%] of 89; 0.92 [0.60-1.55],  $p=0.87$ ) or 18 months (nine [11%] of 85 vs 11 [14%] of 87; 0.78 [0.45-1.22],  $p=0.61$ ). Compared with the PCV13 2 + 1 group, both PCV13 1 + 1 groups did not meet the non-inferiority criteria for serotype-specific anti-capsular antibody concentrations above the putative thresholds purportedly associated with risk reduction for colonisation; however, the PCV10 14-week 1 + 1 group was non-inferior to the PCV10 2 + 1 group.

**Interpretation:** The serotype-specific colonisation data reported in this study together with the primary immunogenicity endpoints of the control trial support transitioning to a reduced 1 + 1 schedule in South Africa. Ongoing monitoring of colonisation should, however, be undertaken immediately before and after transitioning to a PCV 1 + 1 schedule to serve as an early indicator of whether PCV 1 + 1 could lead to an increase in vaccine-serotype disease.

Vaccine. 2023 Apr 10;S0264-410X(23)00388-2.

doi: 10.1016/j.vaccine.2023.04.008. Online ahead of print.

**[Effect of reduced two-dose \(1+1\) schedule of 10 and 13-valent pneumococcal conjugate vaccines \(Synflorix™ and Prevenar13™\) on nasopharyngeal carriage and serotype-specific immune response in the first two years of life: Results from an open-labelled randomized controlled trial in Indian children](#)**

[Anand Kawade<sup>1</sup>](#), [Girish Dayma<sup>2</sup>](#), [Aditi Apte<sup>2</sup>](#), [Nilima Telang<sup>3</sup>](#), [Meenakshi Satpute<sup>3</sup>](#), [Emma Pearce<sup>4</sup>](#), [Lucy Roalfe<sup>4</sup>](#), [Rakesh Patil<sup>2</sup>](#), [Yanyun Wang<sup>4</sup>](#), [Navideh Noori<sup>5</sup>](#), [Arun Gondhali<sup>2</sup>](#), [Sanjay Juvekar<sup>2</sup>](#), [Assaf P Oron<sup>6</sup>](#), [Sonali Sanghavi<sup>3</sup>](#), [David Goldblatt<sup>4</sup>](#), [Ron Dagan<sup>7</sup>](#), [Ashish Bavdekar<sup>8</sup>](#)

**Abstract**

**Introduction:** This study aimed to assess the effect of a reduced dose regime (1 + 1) of PCV10 and PCV13 along with 3-dose regimes on pneumococcal vaccine-type (VT) carriage and immunogenicity in the first two years of life in PCV-naïve Indian children.

**Methods:** A total of 805 healthy infants aged 6-8 weeks were randomised to 7 groups (n = 115). Six groups received Synflorix™(PCV10) or Prevenar13™(PCV13) in the following schedules: 3 + 0 (three primary at 6, 10, and 14 weeks); 2 + 1 (two primary 6 and 14 weeks with booster at 9 months); 1 + 1 (one primary at 14 weeks with booster at 9 months). The 7th group was a PCV-naïve control group. Nasopharyngeal swabs were collected at 6, 18 weeks, 9, 10, 15, and 18 months of age. Venous blood samples were collected at 18 weeks, 9, 10, and 18 months of age for assessment of sero-specific IgG antibodies. Additionally, functional activity using a serotype specific opsonophagocytic assay (OPA) was assessed at 10 and 18 months of age in a subset (20%) of participants.

**Results:** All schedules of PCV13 showed significant 13VT carriage reduction in the second year of life as compared to control. At 15 months of age, PCV13 (1 + 1) showed 45 % reduction in 13VT-carriage compared to the control [OR = 0.55 (95% CI; 0.31-0.97), p=0.038]. None of the PCV10 schedules showed significant reduction in 10VT carriage in the second year. Although not powered for these outcomes, at 18 months of age, 1 + 1 and 2 + 1 schedules of both vaccines demonstrated higher sero-responders for all serotypes, higher geometric mean concentrations (GMC) for all serotypes except 23F [with both vaccines], higher percent OPA responders and OPA geometric mean titres (GMT) compared to the 3 + 0 schedules for all serotypes.

**Conclusion:** The reduced dose schedule (1 + 1) of PCV13 results in significant VT-carriage reduction in the second year of life. Immune protection provided by 1 + 1 schedules of PCV10 and PCV13 in the second year of life is comparable to WHO-recommended 3-dose schedules.

Lancet Infect Dis. 2023 May;23(5):609-620.

doi: 10.1016/S1473-3099(22)00734-4. Epub 2023 Jan 10.

**[Immunogenicity and safety of a 10-valent pneumococcal conjugate vaccine administered as a 2 + 1 schedule to healthy infants in The Gambia: a single-centre, double-blind, active-controlled, randomised, phase 3 trial](#)**

[Ikechukwu Adigweme](#)<sup>1</sup>, [Ahmed Futa](#)<sup>1</sup>, [Ebrima Saidu-Jah](#)<sup>1</sup>, [Bassey Edem](#)<sup>1</sup>, [Edem Akpalu](#)<sup>1</sup>, [Tida Dibbasey](#)<sup>1</sup>, [Vistasp Sethna](#)<sup>2</sup>, [Rajeev Dhere](#)<sup>2</sup>, [Beate Kampmann](#)<sup>3</sup>, [Christopher Bengt](#)<sup>4</sup>, [Jake Sirr](#)<sup>4</sup>, [Nancy Hosken](#)<sup>5</sup>, [David Goldblatt](#)<sup>4</sup>, [Kalpana Antony](#)<sup>5</sup>, [Mark R Alderson](#)<sup>5</sup>, [Steve Lamola](#)<sup>5</sup>, [Ed Clarke](#)<sup>6</sup>

**Abstract**

**Background:** Three pneumococcal conjugate vaccines (PCVs) are currently licensed and WHO prequalified for supply by UN agencies. Here, we aimed to investigate the safety and immunogenicity of SIPL-PCV compared with PHiD-CV and PCV13, when administered to infants according to a 2 + 1 schedule.

**Methods:** This single-centre, double-blind, active-controlled, randomised, phase 3 trial was done in Medical Research Council Unit The Gambia at the London School of Hygiene & Tropical Medicine clinical trial facilities within two government health centres in the western region of The Gambia. Healthy, PCV-naïve infants aged 6-8 weeks were enrolled if they weighed at least 3.5 kg and had no clinically significant health complaints, as determined by history and clinical examination. Eligible infants were randomly assigned (1:1:1) to receive either SIPL-PCV, PHiD-CV, or PCV13 using permuted blocks of variable size. Parents and the trial staff assessing all study outcomes were masked to vaccine group. The first PCV vaccine was given with other routine Expanded Programme on Immunization vaccines when infants were aged 6-8 weeks (visit 1). At visit 2, routine vaccines alone (without a PCV) were administered. At visit 3, the second dose of the PCV was administered alongside other



routine vaccines. At visit 4, a blood sample was collected. Visits 1-4 took place at intervals of 4 weeks. The booster PCV was administered at age 9-18 months (visit 5), with final follow-up 4 weeks after the booster (visit 6). The primary immunogenicity outcome compared the serotype-specific IgG geometric mean concentrations (GMCs) generated by SIPL-PCV with those generated by PHiD-CV and PCV13, 4 weeks after the booster. We used descriptive 95% CIs without adjustment for multiplicity. Immunogenicity analyses were done in the per protocol population (defined as all children who received all the assigned study vaccines, who had an immunogenicity measurement available, and who had no protocol deviations that might interfere with the immunogenicity assessment). This trial was registered with the Pan African Clinical Trials Registry, PACTR201907754270299, and ClinicalTrials.gov, [NCT03896477](https://clinicaltrials.gov/ct2/show/study/NCT03896477).

**Findings:** Between July 18 and Nov 14, 2019, 745 infants were assessed for study eligibility. Of these, 85 infants (11%) were ineligible and 660 (89%) were enrolled and randomly assigned to receive SIPL-PCV (n=220), PHiD-CV (n=220), or PCV13 (n=220). 602 infants (91%) were included in the per protocol immunogenicity population. The median age at vaccination was 46 days (range 42-56). 342 infants (52%) were female and 318 (48%) were male. Post-booster serotype-specific IgG GMCs generated by SIPL-PCV ranged from 1.54 µg/mL (95% CI 1.38-1.73) for serotype 5 to 12.46 µg/mL (11.07-14.01) for serotype 6B. Post-booster GMCs against shared serotypes generated by PHiD-CV ranged from 0.80 µg/mL (0.72-0.88) for serotype 5 to 17.31 µg/mL (14.83-20.20) for serotype 19F. Post-booster GMCs generated by PCV13 ranged from 2.04 µg/mL (1.86-2.24) for serotype 5 to 15.54 µg/mL (13.71-17.60) for serotype 6B. Post-booster IgG GMCs generated by SIPL-PCV were higher than those generated by PHiD-CV for seven of the eight shared serotypes (1, 5, 6B, 7F, 9V, 14, and 23F). The GMC generated by serotype 19F was higher after PHiD-CV. The SIPL-PCV to PHiD-CV GMC ratios for shared serotypes ranged from 0.64 (95% CI 0.52-0.79) for serotype 19F to 2.91 (2.47-3.44) for serotype 1. The serotype 1 GMC generated by SIPL-PCV was higher than that generated by PCV13, whereas serotype 5, 6A, 19A, and 19F GMCs were higher after PCV13. The SIPL-PCV to PCV13 GMC ratios ranged from 0.72 (0.60-0.87) for serotype 19A to 1.44 (1.23-1.69) for serotype 1.

**Interpretation:** SIPL-PCV was safe and immunogenic when given to infants in The Gambia according to a 2 + 1 schedule. This PCV is expected to provide similar protection against invasive and mucosal pneumococcal disease to the protection provided by PCV13 and PHiD-CV, for which effectiveness data are available. Generating post-implementation data on the impact of SIPL-PCV on pneumococcal disease endpoints remains important.

Hum Vaccin Immunother. 2022 Dec 31;18(1):2019498.

doi: 10.1080/21645515.2021.2019498. Epub 2022 Feb 22.

[\*\*Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine administered in a prime-boost regimen among Chinese infants: a randomized, double blind phase III clinical trial\*\*](#)

[Wenjuan Wang<sup>1</sup>](#), [Qi Liang<sup>1</sup>](#), [Jiahong Zhu<sup>2</sup>](#), [Junxia Zhang<sup>3</sup>](#), [Junsheng Chen<sup>4</sup>](#), [Sulan Xie<sup>5</sup>](#), [Yuemei Hu<sup>1</sup>](#), [Guifan Li<sup>6</sup>](#)

**Abstract**



This study aimed to evaluate the immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine (PCV13). In total, 1200 infants were randomized into two groups with a 1:1 allocation and received a three-dose series of tested PCV13 or control PCV13 at ages 2, 4 and 6 months, respectively, and a booster dose at 12-15 months. Blood samples were collected before and 30 days after primary and booster vaccination. Serotype-specific antibodies were measured using ELISA for immunoglobulin G (IgG) and OPA for functional antibodies. Safety data were collected for 30 days after each inoculation. Results showed that post primary vaccination seropositive rates of all 13 serotypes except type 3 were not significantly different between two groups. The seropositive rate for type 3 in Group T was significantly higher than Group C ( $P < .0001$ ). For all 13 serotypes except type 7 F, the GMCs in Group T were significantly higher than Group C. The GMC for type 7 F in Group T ( $P < .0009$ ) was significantly lower than Group C. The frequencies of overall adverse events ( $P = .0064$ ) and solicited adverse reactions ( $P = .0019$ ) in Group T were significantly lower than Group C. Post booster vaccination, seropositive rates for all serotypes in Group T were 100.00%. For all serotypes except type 23 F, IgG GMCs in Group T were significantly higher than Group C. Totally, 21 subjects reported SAEs and all but one were considered irrelevant or probably irrelevant to vaccination. In conclusion, the tested PCV13 showed non-inferior immunogenicity and had a good safety profile compared with control vaccine.

Vaccine. 2023 Apr 7;S0264-410X(23)00370-5.

doi: 10.1016/j.vaccine.2023.03.063. Online ahead of print.

**[A systematic review of pneumococcal conjugate vaccine impact on pneumococcal nasopharyngeal colonisation density in children under 5 years of age](#)**

[Isatou Jagne<sup>1</sup>](#), [Claire von Mollendorf<sup>2</sup>](#), [Ashleigh Wee-Hee<sup>3</sup>](#), [Belinda Ortika<sup>3</sup>](#), [Catherine Satzke<sup>4</sup>](#), [Fiona M Russell<sup>5</sup>](#)

**Abstract**

**Background:** High pneumococcal carriage density has been associated with severe pneumonia in some settings. The impact of pneumococcal conjugate vaccines (PCVs) on pneumococcal carriage density has been variable. The aim of this systematic literature review is to describe the effect of PCV7, PCV10 and PCV13 on pneumococcal colonisation density in children under five years old.

**Methods:** We included peer reviewed English literature published between 2000 and 2021 to identify relevant articles using Embase, Medline and PubMed. Original research articles of any study design in countries where PCV has been introduced/studied were included. Quality (risk) assessment was performed using tools developed by the National Heart Brain and Lung Institute for inclusion in this review. We used a narrative synthesis to present results.

**Results:** Ten studies were included from 1941 articles reviewed. There were two randomised controlled trials, two cluster randomised trials, one case control study, one retrospective cohort study and four cross sectional studies. Three studies used semiquantitative culture methods to determine density while the remaining studies used quantitative molecular techniques. Three studies reported an increase in density and three studies found a decrease in density among vaccinated compared with unvaccinated children. Four studies found no effect. There was considerable heterogeneity in the study populations, study design and laboratory methods.

**Conclusion:** There was no consensus regarding the impact of PCV on pneumococcal nasopharyngeal density. We recommend the use of standardised methods to evaluate PCV impact on density.

## Polio vaccine

Open Forum Infect Dis. 2022 Jul 27;9(8):ofac340.

doi: 10.1093/ofid/ofac340. eCollection 2022 Aug.

### [Stopping Oral Polio Vaccine \(OPV\) After Defeating Poliomyelitis in Low- and Middle-Income Countries: Harmful Unintended Consequences? Review of the Nonspecific Effects of OPV](#)

[Peter Aaby<sup>1</sup>](#), [Sebastian Nielsen<sup>1</sup>](#), [Ane B Fisker<sup>1</sup>](#), [Line M Pedersen<sup>1</sup>](#), [Paul Welaga<sup>2</sup>](#), [Syed M A Hanifi<sup>3</sup>](#), [Cesario L Martins<sup>1</sup>](#), [Amabelia Rodrigues<sup>1</sup>](#), [Konstantin Chumakov<sup>4</sup>](#), [Christine S Benn<sup>5</sup>](#)

#### **Abstract**

**Background:** The live vaccines bacille Calmette-Guérin (BCG) and measles vaccine have beneficial nonspecific effects (NSEs) reducing mortality, more than can be explained by prevention of tuberculosis or measles infection. Live oral polio vaccine (OPV) will be stopped after polio eradication; we therefore reviewed the potential NSEs of OPV.

**Methods:** OPV has been provided in 3 contexts: (1) coadministration of OPV and diphtheria-tetanus-pertussis (DTP) vaccine at 6, 10, and 14 weeks of age; (2) at birth (OPV0) with BCG; and (3) in OPV campaigns (C-OPVs) initiated to eradicate polio infection. We searched PubMed and Embase for studies of OPV with mortality as an outcome. We used meta-analysis to obtain the combined relative risk (RR) of mortality associated with different uses of OPV.

**Results:** First, in natural experiments when DTP was missing, OPV-only compared with DTP + OPV was associated with 3-fold lower mortality in community studies (RR, 0.33 [95% confidence interval {CI}, .14-.75]) and a hospital study (RR, 0.29 [95% CI, .11-.77]). Conversely, when OPV was missing, DTP-only was associated with 3-fold higher mortality than DTP + OPV (RR, 3.23 [95% CI, 1.27-8.21]). Second, in a randomized controlled trial, BCG + OPV0 vs BCG + no OPV0 was associated with 32% (95% CI, 0-55%) lower infant mortality. Beneficial NSEs were stronger with early use of OPV0. Third, in 5 population-based studies from Guinea-Bissau and Bangladesh, the mortality rate was 24% (95% CI, 17%-31%) lower after C-OPVs than before C-OPVs.

**Conclusions:** There have been few clinical polio cases reported in this century, and no confounding factors or bias would explain all these patterns. The only consistent interpretation is that OPV has beneficial NSEs, reducing nonpolio child mortality.

Lancet. 2023 Jan 14;401(10371):131-139.

doi: 10.1016/S0140-6736(22)02397-2. Epub 2022 Dec 7.

### [Evaluation of the safety, immunogenicity, and faecal shedding of novel oral polio vaccine type 2 in healthy newborn infants in Bangladesh: a randomised, controlled, phase 2 clinical trial](#)

[Khaelqu Zaman<sup>1</sup>](#), [Ananda S Bandyopadhyay<sup>2</sup>](#), [Masuma Hoque<sup>1</sup>](#), [Christopher Gast<sup>3</sup>](#), [Mohammad Yunus<sup>1</sup>](#), [Khondoker M Jamil<sup>4</sup>](#), [Bernardo A Mainou<sup>5</sup>](#), [Jennifer L Konopka-Anstadt<sup>3</sup>](#), [William S Hendley<sup>5</sup>](#), [Annelet Vincent<sup>5</sup>](#), [Ralf Clemens<sup>6</sup>](#), [Sue Ann Costa Clemens<sup>7</sup>](#), [Allen G Ross<sup>8</sup>](#), [John D Clemens<sup>9</sup>](#), [Erman Tritama<sup>10</sup>](#)

## Abstract

**Background:** Type 2 circulating vaccine-derived polioviruses (cVDPV2) from Sabin oral poliovirus vaccines (OPVs) are the leading cause of poliomyelitis. A novel type 2 OPV (nOPV2) has been developed to be more genetically stable with similar tolerability and immunogenicity to that of Sabin type 2 vaccines to mitigate the risk of cVDPV2. We aimed to assess these aspects of nOPV2 in poliovirus vaccine-naïve newborn infants.

**Methods:** In this randomised, double-blind, controlled, phase 2 trial we enrolled newborn infants at the Matlab Health Research Centre, Chandpur, Bangladesh. We included infants who were healthy and were a single birth after at least 37 weeks' gestation. Infants were randomly assigned (2:1) to receive either two doses of nOPV2 or placebo, administered at age 0-3 days and at 4 weeks. Exclusion criteria included receipt of rotavirus or any other poliovirus vaccine, any infection or illness at the time of enrolment (vomiting, diarrhoea, or intolerance to liquids), diagnosis or suspicion of any immunodeficiency disorder in the infant or a close family member, or any contraindication for venipuncture. The primary safety outcome was safety and tolerability after one and two doses of nOPV2, given 4 weeks apart in poliovirus vaccine-naïve newborn infants and the primary immunogenicity outcome was the seroconversion rate for neutralising antibodies against type 2 poliovirus, measured 28 days after the first and second vaccinations with nOPV2. Study staff recorded solicited and unsolicited adverse events after each dose during daily home visits for 7 days. Poliovirus neutralising antibody responses were measured in sera drawn at birth and at age 4 weeks and 8 weeks. This study is registered on ClinicalTrials.gov, [NCT04693286](#).

**Findings:** Between Sept 21, 2020, and Aug 16, 2021, we screened 334 newborn infants, of whom three (<1%) were found to be ineligible and one (<1%) was withdrawn by the parents; the remaining 330 (99%) infants were assigned to receive nOPV2 (n=220 [67%]) or placebo (n=110 [33%]). nOPV2 was well tolerated; 154 (70%) of 220 newborn infants in the nOPV2 group and 78 (71%) of 110 in the placebo group had solicited adverse events, which were all mild or moderate in severity. Severe unsolicited adverse events in 11 (5%) vaccine recipients and five (5%) placebo recipients were considered unrelated to vaccination. 306 (93%) of 330 infants had seroprotective maternal antibodies against type 2 poliovirus at birth, decreasing to 58 (56%) of 104 in the placebo group at 8 weeks. In the nOPV2 group 196 (90%) of 217 infants seroconverted by week 8 after two doses, when 214 (99%) had seroprotective antibodies.

**Interpretation:** nOPV2 was well tolerated and immunogenic in newborn infants, with two doses, at birth and 4 weeks, resulting in almost 99% of infants having protective neutralising antibodies.

J Infect Dis. 2022 Oct 17;226(8):1319-1326.

doi: 10.1093/infdis/jiac205.

[One Full or Two Fractional Doses of Inactivated Poliovirus Vaccine for Catch-up Vaccination in Older Infants: A Randomized Clinical Trial in Bangladesh](#)

[Asma B Aziz<sup>1,2</sup>](#), [Harish Verma<sup>3</sup>](#), [Visalakshi Jeyaseelan<sup>3</sup>](#), [Mohammad Yunus<sup>1</sup>](#), [Samarea Nowrin<sup>1</sup>](#), [Deborah D Moore<sup>4</sup>](#), [Bernardo A Mainou<sup>4</sup>](#), [Ondrej Mach<sup>3</sup>](#), [Roland W Sutter<sup>3</sup>](#), [Khalequ Zaman<sup>1</sup>](#)

## Abstract

**Background:** The polio eradication endgame called for the removal of trivalent oral poliovirus vaccine (OPV) and introduction of bivalent (types 1 and 3) OPV and inactivated poliovirus vaccine (IPV). However, supply shortages have delayed IPV administration to tens of millions of infants, and immunogenicity data are currently lacking to guide catch-up vaccination policies.

**Methods:** We conducted an open-label randomized clinical trial assessing 2 interventions, full or fractional-dose IPV (fIPV, one-fifth of IPV), administered at age 9-13 months with a second dose given 2 months later. Serum was collected at days 0, 60, 67, and 90 to assess seroconversion, priming, and antibody titer. None received IPV or poliovirus type 2-containing vaccines before enrolment.

**Results:** A single fIPV dose at age 9-13 months yielded 75% (95% confidence interval [CI], 6%-82%) seroconversion against type 2, whereas 2 fIPV doses resulted in 100% seroconversion compared with 94% (95% CI, 89%-97%) after a single full dose ( $P < .001$ ). Two doses of IPV resulted in 100% seroconversion.

**Conclusions:** Our study confirmed increased IPV immunogenicity when administered at an older age, likely due to reduced interference from maternally derived antibodies. Either 1 full dose of IPV or 2 doses of fIPV could be used to vaccinate missed cohorts, 2 fIPV doses being antigen sparing and more immunogenic.

Lancet Infect Dis. 2023 May 10;S1473-3099(23)00139-1.

doi: 10.1016/S1473-3099(23)00139-1. Online ahead of print.

## [Immunogenicity of novel oral poliovirus vaccine type 2 administered concomitantly with bivalent oral poliovirus vaccine: an open-label, non-inferiority, randomised, controlled trial](#)

[Amanda L Wilkinson<sup>1</sup>](#), [Khalequ Zaman<sup>2</sup>](#), [Masuma Hoque<sup>2</sup>](#), [Concepcion F Estivariz<sup>3</sup>](#), [Cara C Burns<sup>3</sup>](#), [Jennifer L Konopka-Anstadt<sup>3</sup>](#), [Bernardo A Mainou<sup>3</sup>](#), [Stephanie D Kovacs<sup>3</sup>](#), [Qian An<sup>3</sup>](#), [Jacquelyn S Lickness<sup>3</sup>](#), [Mohammad Yunus<sup>2</sup>](#), [Cynthia J Snider<sup>3</sup>](#), [Yiting Zhang<sup>3</sup>](#), [Elizabeth Coffee<sup>3</sup>](#), [Talha Abid<sup>3</sup>](#), [Steven G F Wassilak<sup>3</sup>](#), [Mark A Pallansch<sup>3</sup>](#), [M Steven Oberste<sup>3</sup>](#), [John F Vertefeuille<sup>3</sup>](#), [Abhijeet Anand<sup>3</sup>](#)

## Abstract

**Background:** Novel oral poliovirus vaccine type 2 (nOPV2) was developed by modifying the Sabin strain to increase genetic stability and reduce risk of seeding new circulating vaccine-derived poliovirus type 2 outbreaks. Bivalent oral poliovirus vaccine (bOPV; containing Sabin types 1 and 3) is the vaccine of choice for type 1 and type 3 outbreak responses. We aimed to assess immunological interference between nOPV2 and bOPV when administered concomitantly.

**Methods:** We conducted an open-label, non-inferiority, randomised, controlled trial at two clinical trial sites in Dhaka, Bangladesh. Healthy infants aged 6 weeks were randomly assigned (1:1:1) using block randomisation, stratified by site, to receive nOPV2 only, nOPV2 plus bOPV, or bOPV only, at the ages of 6 weeks, 10 weeks, and 14 weeks. Eligibility criteria included singleton and full term ( $\geq 37$  weeks' gestation) birth and parents intending to remain

in the study area for the duration of study follow-up activities. Poliovirus neutralising antibody titres were measured at the ages of 6 weeks, 10 weeks, 14 weeks, and 18 weeks. The primary outcome was cumulative immune response for all three poliovirus types at the age of 14 weeks (after two doses) and was assessed in the modified intention-to-treat population, which was restricted to participants with adequate blood specimens from all study visits. Safety was assessed in all participants who received at least one dose of study product. A non-inferiority margin of 10% was used to compare single and concomitant administration. This trial is registered with ClinicalTrials.gov, [NCT04579510](https://clinicaltrials.gov/ct2/show/study/NCT04579510).

**Findings:** Between Feb 8 and Sept 26, 2021, 736 participants (244 in the nOPV2 only group, 246 in the nOPV2 plus bOPV group, and 246 in the bOPV only group) were enrolled and included in the modified intention-to-treat analysis. After two doses, 209 (86%; 95% CI 81-90) participants in the nOPV2 only group and 159 (65%; 58-70) participants in the nOPV2 plus bOPV group had a type 2 poliovirus immune response; 227 (92%; 88-95) participants in the nOPV2 plus bOPV group and 229 (93%; 89-96) participants in the bOPV only group had a type 1 response; and 216 (88%; 83-91) participants in the nOPV2 plus bOPV group and 212 (86%; 81-90) participants in the bOPV only group had a type 3 response. Co-administration was non-inferior to single administration for types 1 and 3, but not for type 2. There were 15 serious adverse events (including three deaths, one in each group, all attributable to sudden infant death syndrome); none were attributed to vaccination.

**Interpretation:** Co-administration of nOPV2 and bOPV interfered with immunogenicity for poliovirus type 2, but not for types 1 and 3. The blunted nOPV2 immunogenicity we observed would be a major drawback of using co-administration as a vaccination strategy.

J Infect Dis. 2022 Aug 24;226(2):292-298.

doi: 10.1093/infdis/jiaa704.

### [Immunogenicity of Reduced-Dose Monovalent Type 2 Oral Poliovirus Vaccine in Mocuba, Mozambique](#)

[Nilza de Deus<sup>1</sup>](#), [Igor Paulo Ubisse Capitine<sup>1</sup>](#), [Adilson Fernando Loforte Bauhofer<sup>1,2</sup>](#), [Selma Marques<sup>1</sup>](#), [Marta Cassocera<sup>1,2</sup>](#), [Assucênio Chissaque<sup>1,2</sup>](#), [Diocreciano Matias Bero<sup>1</sup>](#), [José Paulo Langa<sup>1</sup>](#), [Fernando Manuel Padama<sup>3</sup>](#), [Visalakshi Jeyaseelan<sup>4</sup>](#), [M Steven Oberste<sup>5</sup>](#), [Concepcion F Estivariz<sup>5</sup>](#), [Harish Verma<sup>4</sup>](#), [Ilesh Jani<sup>1</sup>](#), [Ondrej Mach<sup>4</sup>](#), [Roland W Sutter<sup>4</sup>](#)

#### **Abstract**

**Background:** The monovalent type 2 oral poliovirus vaccine (mOPV2) stockpile is low. One potential strategy to stretch the existing mOPV2 supply is to administer a reduced dose: 1 drop instead of 2.

**Methods:** We conducted a randomized, controlled, open-label, noninferiority trial (10% margin) to compare immunogenicity after administration of 1 versus 2 drops of mOPV2. We enrolled 9-22-month-old infants from Mocuba district of Mozambique. Poliovirus neutralizing antibodies were measured in serum samples collected before and 1 month after mOPV2 administration. Immune response was defined as seroconversion from seronegative (<1:8) at baseline to seropositive ( $\geq$ 1:8) after vaccination or boosting titers by  $\geq$ 4-fold for those with titers between 1:8 and 1:362 at baseline. The trial was registered at anzctr.org.au (no. ACTRN12619000184178p).

**Results:** We enrolled 378 children, and 262 (69%) completed per-protocol requirements. The immune response of mOPV2 was 53.6% (95% confidence interval, 44.9%-62.1%) and 60.6% (52.2%-68.4%) in 1-drop and 2-drop recipients, respectively. The noninferiority margin of the 10% was not reached (difference, 7.0%; 95% confidence interval, -5.0% to 19.0%).

**Conclusion:** A small loss of immunogenicity of reduced mOPV2 was observed. Although the noninferiority target was not achieved, the Strategic Advisory Group of Experts on Immunization recommended the 1-drop strategy as a dose-sparing measure if mOPV2 supplies deteriorate further.

J Infect Dis. 2022 Aug 24;226(2):299-307.

doi: 10.1093/infdis/jiaa726.

### **Randomized Controlled Clinical Trial of Bivalent Oral Poliovirus Vaccine and Inactivated Poliovirus Vaccine in Nigerian Children**

[Beckie N Tagbo](#)<sup>1</sup>, [Harish Verma](#)<sup>2</sup>, [Zubairu M Mahmud](#)<sup>3</sup>, [Kolade Ernest](#)<sup>4</sup>, [Roosevelt O Nnani](#)<sup>5</sup>, [Chinedu Chukwubike](#)<sup>5</sup>, [Kehinde T Craig](#)<sup>6</sup>, [Abdullahi Hamisu](#)<sup>6</sup>, [William C Weldon](#)<sup>7</sup>, [Steven M Oberste](#)<sup>7</sup>, [Visalakshi Jeyaseelan](#)<sup>2</sup>, [Fiona Braka](#)<sup>6</sup>, [Pascal Mkanda](#)<sup>8</sup>, [Dorothy Esangbedo](#)<sup>9</sup>, [Adebiyi Olowu](#)<sup>9</sup>, [Eric Nwaze](#)<sup>3</sup>, [Roland W Sutter](#)<sup>2</sup>

#### **Abstract**

**Background:** We conducted a trial in Nigeria to assess the immunogenicity of the new bivalent oral poliovirus vaccine + inactivated poliovirus vaccine (bOPV+IPV) immunization schedule and gains in type 2 immunity with addition of second dose of IPV. The trial was conducted in August 2016-March 2017, well past the trivalent OPV-bOPV switch in April 2016.

**Methods:** This was an open-label, 2-arm, noninferiority, multicenter, randomized, controlled trial. We enrolled 572 infants aged  $\leq 14$  days and randomized them into 2 arms. Arm A received bOPV at birth, 6, and 10 weeks, bOPV+IPV at week 14, and IPV at week 18. Arm B received IPV each at 6, 10, and 14 weeks and bOPV at 18 weeks of age.

**Results:** Seroconversion rates for poliovirus types 1 and 3, respectively, were 98.9% (95% confidence interval [CI], 96.7-99.8) and 98.1% (95% CI, 88.2-94.8) in Arm A and 89.6% (95% CI, 85.4-93.0) and 98.5% (95% CI, 96.3-99.6) in Arm B. Type 2 seroconversion with 1 dose IPV in Arm A was 72.0% (95% CI, 66.2-77.3), which increased significantly with addition of second dose to 95.9% (95% CI, 92.8-97.9).

**Conclusions:** This first trial on the new Expanded Program on Immunization (EPI) schedule in a sub-Saharan African country demonstrated excellent immunogenicity against poliovirus types 1 and 3 and substantial/enhanced immunogenicity against poliovirus type 2 after 1 to 2 doses of IPV, respectively.

J Infect Dis. 2022 Sep 13;226(5):852-861.

doi: 10.1093/infdis/jiab507.

### **Fecal Shedding of 2 Novel Live Attenuated Oral Poliovirus Type 2 Vaccine Candidates by Healthy Infants Administered Bivalent Oral Poliovirus Vaccine/Inactivated Poliovirus Vaccine: 2 Randomized Clinical Trials**

[Christopher Gast](#)<sup>1</sup>, [Ananda S Bandyopadhyay](#)<sup>2</sup>, [Xavier Sáez-Llorens](#)<sup>3,4</sup>, [Tirza De Leon](#)<sup>5</sup>, [Rodrigo DeAntonio](#)<sup>5</sup>, [José Jimeno](#)<sup>6</sup>, [Gabriela Aguirre](#)<sup>7</sup>, [Larin M McDuffie](#)<sup>8</sup>, [Elizabeth Coffee](#)<sup>8</sup>, [Demetrius L Mathis](#)<sup>8</sup>, [M Steven Oberste](#)<sup>9</sup>, [William C Weldon](#)<sup>9</sup>, [Jennifer L Konopka](#)



[Anstadt<sup>9</sup>](#), [John Modlin<sup>2</sup>](#), [Novilia S Bachtiar<sup>10</sup>](#), [Alan Fix<sup>1</sup>](#), [John Konz<sup>1</sup>](#), [Ralf Clemens<sup>11</sup>](#), [Sue Ann Costa Clemens<sup>12</sup>](#), [Ricardo Rüttimann<sup>7</sup>](#)

## Abstract

**Background:** Primary intestinal immunity through viral replication of live oral vaccine is key to interrupt poliovirus transmission. We assessed viral fecal shedding from infants administered Sabin monovalent poliovirus type 2 vaccine (mOPV2) or low and high doses of 2 novel OPV2 (nOPV2) vaccine candidates.

**Methods:** In 2 randomized clinical trials in Panama, a control mOPV2 study (October 2015 to April 2016) and nOPV2 study (September 2018 to October 2019), 18-week-old infants vaccinated with bivalent oral poliovirus vaccine/inactivated poliovirus vaccine received 1 or 2 study vaccinations 28 days apart. Stools were assessed for poliovirus RNA by polymerase chain reaction (PCR) and live virus by culture for 28 days postvaccination.

**Results:** Shedding data were available from 621 initially reverse-transcription PCR-negative infants (91 mOPV2, 265 nOPV2-c1, 265 nOPV2-c2 recipients). Seven days after dose 1, 64.3% of mOPV2 recipients and 31.3%-48.5% of nOPV2 recipients across groups shed infectious type 2 virus. Respective rates 7 days after dose 2 decreased to 33.3% and 12.9%-22.7%, showing induction of intestinal immunity. Shedding of both nOPV2 candidates ceased at similar or faster rates than mOPV2.

**Conclusions:** Viral shedding of either nOPV candidate was similar or decreased relative to mOPV2, and all vaccines showed indications that the vaccine virus was replicating sufficiently to induce primary intestinal mucosal immunity.

## Rabies vaccine

Hum Vaccin Immunother. 2023 Dec 31;19(1):2211896.

doi: 10.1080/21645515.2023.2211896. Epub 2023 May 30.

### **Safety and immunogenicity of rabies vaccine (PVRV-WIBP) in healthy Chinese aged 10-50 years old: Randomized, blinded, parallel controlled phase III clinical study**

[Xiaoyuan Huang<sup>1,2</sup>](#), [Jing Liang<sup>1,2</sup>](#), [Lili Huang<sup>3</sup>](#), [Xuanxuan Nian<sup>1,2</sup>](#), [Wei Chen<sup>1,2</sup>](#), [Jiayou Zhang<sup>1,2</sup>](#), [Xiao Xu<sup>1,2</sup>](#), [Xuan Lin<sup>1,2</sup>](#), [Yue Wang<sup>1,2</sup>](#), [Jinrong Shi<sup>1,2</sup>](#), [Lanxin Jia<sup>1,2</sup>](#), [Qingliang Li<sup>1,2</sup>](#), [Qianxi Wang<sup>1,2</sup>](#), [Kai Duan<sup>1,2</sup>](#), [Xinguo Li<sup>1,2</sup>](#), [Yaqi Ji<sup>1,2</sup>](#), [Feixia Peng<sup>1,2</sup>](#), [Wei Zhang<sup>3</sup>](#), [Zhiqiang Xie<sup>3</sup>](#), [Yanxia Wang<sup>3</sup>](#), [Xiaoming Yang<sup>1,4</sup>](#)

## Abstract

This phase III clinical trial aimed to assess the safety and demonstrate the immunogenicity of a candidate freeze-dried purified Vero cell-based rabies vaccine (PVRV-WIBP) developed for human use. A cohort of 40 participants in stage 1 and 1956 subjects in stage 2 with an age range of 10-50 years were recruited for the phase III clinical trial. For safety analysis in stage 1, 20 participants received either 4-dose or 5-dose regimen of PVRV-WIBP. In stage 2, 1956 subjects were randomly divided into the 5-dose PVRV-WIBP, 5-dose PVRV-LNCD, and 4-dose PVRV-WIBP groups. The serum neutralizing antibody titer against rabies was determined on day 7 or 14 and day 35 or 42. Adverse reactions were recorded for more than 6 months. Most adverse reactions, which were mild and moderate in severity, occurred and resolved within 1 week after each injection in the PVRV-WIBP (4 and 5 doses) and PVRV-LNCD (5 doses) groups.

All three groups achieved complete seroconversion 14 days after the initial dose and 14 days after completing the full vaccination schedule, the susceptible subjects in the PVRV-WIBP group (4-dose or 5-dose regimen) displayed higher neutralizing antibody titers against the rabies virus compared to those in the PVRV-LNCD group (5-dose regimen). PVRV-WIBP induced non-inferior immune responses versus PVRV-LNCD as assessed by seroconversion rate. PVRV-WIBP was well tolerated and non-inferior to PVRV-LNCD in healthy individuals aged 10-50 years. The results indicated that PVRV-WIBP (both 4- and 5-dose schedules) could be an alternative to rabies post-exposure prophylaxis.

## Respiratory syncytial virus vaccine

J Infect Dis. 2023 Feb 1;jiad024.

doi: 10.1093/infdis/jiad024. Online ahead of print.

### [Safety and immunogenicity of an investigational respiratory syncytial virus vaccine \(RSVPreF3\) in mothers and their infants: a phase 2 randomized trial](#)

[Zourab Bebia](#)<sup>1</sup>, [Osvaldo Reyes](#)<sup>2</sup>, [Robert Jeanfreau](#)<sup>3</sup>, [Anu Kantele](#)<sup>4</sup>, [Ruth Graciela De Leon](#)<sup>5</sup>, [Marta García Sánchez](#)<sup>6</sup>, [Peyman Banooni](#)<sup>7</sup>, [Glenn J Gardener](#)<sup>8</sup>, [José Luis Bartha Rasero](#)<sup>9</sup>, [Maria Begoña Encinas Pardilla](#)<sup>10</sup>, [Joanne M Langley](#)<sup>11</sup>, [Claudio Maañón Di Leo](#)<sup>12</sup>, [Elisabeth Botelho-Nevers](#)<sup>13</sup>, [Jim Buttery](#)<sup>14</sup>, [Helene Laurichesse](#)<sup>15</sup>, [Shabir A Madhi](#)<sup>16</sup>, [Adrián Martín García](#)<sup>17</sup>, [Thorsten Stanley](#)<sup>18</sup>, [Tiphaine Barjat](#)<sup>19</sup>, [Rebecca Griffith](#)<sup>20</sup>, [Maria Mercedes Castrejón-Alba](#)<sup>21</sup>, [Magali de Heusch](#)<sup>22</sup>, [Ilse Dieussaert](#)<sup>23</sup>, [Melanie Hercor](#)<sup>22</sup>, [Patricia Lese](#)<sup>1</sup>, [Hui Qian](#)<sup>1</sup>, [Antonella N Tullio](#)<sup>1</sup>, [Ouzama Henry](#)<sup>1</sup>

#### Abstract

**Background:** In a phase I/II study, a maternal respiratory syncytial virus vaccine candidate (RSVPreF3) demonstrated an acceptable safety profile and efficiently increased RSV-specific humoral immune responses in non-pregnant women.

**Methods:** In this phase II observer-blind, placebo-controlled, randomized clinical trial ([NCT04126213](#)), the safety of RSVPreF3 (60 or 120 µg), administered during late second or third trimester, was evaluated in 213 18-40-year-old healthy pregnant women through six months post-delivery and their offspring through infancy; immunogenicity was evaluated through day 43 post-delivery and day 181 post-birth, respectively.

**Results:** RSVPreF3 was well tolerated. No pregnancy-related or neonatal adverse events of special interest were considered vaccine/placebo-related. In the 60 and 120 µg RSVPreF3 groups: (i) neutralizing antibody (nAb) titers in mothers increased 12.7- and 14.9-fold against RSV-A and 10.6- and 13.2-fold against RSV-B, respectively, one month post-vaccination and remained 8.9-10.0-fold over pre-vaccination at day 43 post-delivery, (ii) nAb titers were consistently higher compared to placebo recipients, (iii) placental transfer ratios for anti-RSVPreF3 antibodies at birth were 1.62 and 1.90, respectively, and (iv) nAb levels in infants were highest at birth and declined through day 181 post-birth.

**Conclusions:** RSVPreF3 maternal vaccination had an acceptable safety risk profile and induced robust RSV-specific immune responses with successful antibody transfer to their newborns.

## Rotavirus vaccine

Lancet Infect Dis. 2022 Nov;22(11):1606-1616.

doi: 10.1016/S1473-3099(22)00368-1. Epub 2022 Aug 9.

### [Head-to-head comparison of the immunogenicity of RotaTeq and Rotarix rotavirus vaccines and factors associated with seroresponse in infants in Bangladesh: a randomised, controlled, open-label, parallel, phase 4 trial](#)

[Daniel E Velasquez-Portocarrero<sup>1</sup>](#), [Xiaoqian Wang<sup>1</sup>](#), [Margaret M Cortese<sup>1</sup>](#), [Cynthia J Snider<sup>1</sup>](#), [Abhijeet Anand<sup>1</sup>](#), [Veronica P Costantini<sup>1</sup>](#), [Md Yunus<sup>2</sup>](#), [Asma B Aziz<sup>2</sup>](#), [Warda Haque<sup>2</sup>](#), [Umesh Parashar<sup>1</sup>](#), [Zufan Sisay<sup>1</sup>](#), [Heidi M Soeters<sup>1</sup>](#), [Terri B Hyde<sup>1</sup>](#), [Baoming Jiang<sup>3</sup>](#), [Khalequ Zaman<sup>2</sup>](#)

#### Abstract

**Background:** A head-to-head comparison of the most widely used oral rotavirus vaccines has not previously been done, particularly in a high child mortality setting. We therefore aimed to compare the immunogenicity of RotaTeq (Merck, Kenilworth, NJ, USA) and Rotarix (GlaxoSmithKline, Rixensart, Belgium) rotavirus vaccines in the same population and examined risk factors for low seroresponse.

**Methods:** We did a randomised, controlled, open-label, parallel, phase 4 trial in urban slums within Mirpur and Mohakahli (Dhaka, Bangladesh). We enrolled eligible participants who were healthy infants aged 6 weeks and full-term (ie, >37 weeks' gestation). We randomly assigned participants (1:1), using block randomisation via a computer-generated electronic allocation with block sizes of 8, 16, 24, and 32, to receive either three RotaTeq vaccine doses at ages 6, 10, and 14 weeks or two Rotarix doses at ages 6 and 10 weeks without oral poliovirus vaccine. Coprimary outcomes were the rotavirus-specific IgA seroconversion in both vaccines, and the comparison of the rotavirus IgA seroconversion by salivary secretor phenotype in each vaccine arm. Seroconversion at age 18 weeks in the RotaTeq arm and age of 14 weeks in the Rotarix arm was used to compare the complete series of each vaccine. Seroconversion at age 14 weeks was used to compare two RotaTeq doses versus two Rotarix doses. Seroconversion at age 22 weeks was used to compare the immunogenicity at the same age after receiving the full vaccine series. Safety was assessed for the duration of study participation. This study is registered with ClinicalTrials.gov, [NCT02847026](#).

**Findings:** Between Sept 1 and Dec 8, 2016, a total of 1144 infants were randomly assigned to either the RotaTeq arm (n=571) or Rotarix arm (n=573); 1080 infants (531 in the RotaTeq arm and 549 in the Rotarix arm) completed the study. Rotavirus IgA seroconversion 4 weeks after the full series occurred in 390 (73%) of 531 infants age 18 weeks in the RotaTeq arm and 354 (64%) of 549 infants age 14 weeks in the Rotarix arm (p=0.01). At age 14 weeks, 4 weeks after two doses, RotaTeq recipients had lower seroconversion than Rotarix recipients (268 [50%] of 531 vs 354 [64%] of 549; p<0.0001). However, at age 22 weeks, RotaTeq recipients had higher seroconversion than Rotarix recipients (394 [74%] of 531 vs 278 [51%] of 549; p<0.0001). Among RotaTeq recipients, seroconversion 4 weeks after the third dose was higher than after the second dose (390 [73%] of 531 vs 268 [50%] of 531; p<0.0001). In the RotaTeq arm, rotavirus IgA seroconversion was lower in non-secretors than in secretors at ages 14 weeks (p=0.08), 18 weeks (p=0.01), and 22 weeks (p=0.02). Similarly, in the Rotarix arm, rotavirus IgA seroconversion was lower in non-secretors than in secretors at ages 14 weeks (p=0.02) and 22 weeks (p=0.01). 65 (11%) of 571 infants had adverse events in the RotaTeq arm compared with 63 (11%) of 573 infants in the Rotarix arm; no adverse events

were attributed to the use of either vaccine. One death due to aspiration occurred in the RotaTeq arm, which was not related to the vaccine.

**Interpretation:** RotaTeq induced a higher magnitude and longer duration of rotavirus IgA response than Rotarix in this high child mortality setting. Additional vaccination strategies should be evaluated to overcome the suboptimal performance of current oral rotavirus vaccines in these settings.

Lancet Infect Dis. 2022 Aug;22(8):1191-1199.

doi: 10.1016/S1473-3099(22)00161-X. Epub 2022 May 16.

**Safety and immunogenicity of the Rotavac and Rotasiil rotavirus vaccines administered in an interchangeable dosing schedule among healthy Indian infants: a multicentre, open-label, randomised, controlled, phase 4, non-inferiority trial**

[Suman Kanungo](#)<sup>1</sup>, [Pranab Chatterjee](#)<sup>2</sup>, [Ashish Bavdekar](#)<sup>3</sup>, [Manoj Murhekar](#)<sup>4</sup>, [Sudhir Babji](#)<sup>5</sup>, [Richa Garg](#)<sup>1</sup>, [Sandip Samanta](#)<sup>6</sup>, [Ranjan K Nandy](#)<sup>7</sup>, [Anand Kawade](#)<sup>8</sup>, [Kangusamy Boopathi](#)<sup>4</sup>, [Kaliaperumal Kanagasabai](#)<sup>4</sup>, [Vineet Kumar Kamal](#)<sup>4</sup>, [Velusamy Saravana Kumar](#)<sup>4</sup>, [Nivedita Gupta](#)<sup>9</sup>, [Shanta Dutta](#)<sup>10</sup>

**Abstract**

**Background:** Rotavirus is the leading cause of severe dehydrating gastroenteritis among children younger than 5 years in low-income and middle-income countries. Two vaccines-Rotavac and Rotasiil-are used in routine immunisation in India. The safety and immunogenicity of these vaccines administered in a mixed regimen is not documented. We therefore aimed to compare the safety and seroresponse of recipients of a mixed regimen versus a single regimen.

**Methods:** We did a multicentre, open-label, randomised, controlled, phase 4, non-inferiority trial at two sites in India. We recruited healthy infants aged 6-8 weeks. Infants with systemic disorders, weight-for-height Z scores of less than minus three SDs, or a history of persistent diarrhoea were excluded. Eligible infants were randomly allocated to six groups in equal numbers to receive either the single vaccine regimen (ie, Rotavac-Rotavac-Rotavac [group 1] or Rotasiil-Rotasiil-Rotasiil [group 2]) or the mixed vaccine regimen (ie, Rotavac-Rotasiil-Rotavac [group 3], Rotasiil-Rotavac-Rotasiil [group 4], Rotavac-Rotasiil-Rotasiil [group 5], or Rotasiil-Rotavac-Rotavac [group 6]). Randomisation was done using an online software by site in blocks of at least 12. The primary outcome was seroresponse to rotavirus vaccine, measured using rotavirus-specific serum IgA antibodies 4 weeks after the third dose. The seroresponse rates were compared between recipients of the four mixed vaccine regimens (consisting of various combinations of Rotavac and Rotasiil) with recipients of the single vaccine regimens (consisting of Rotavac or Rotasiil only for all three doses). The non-inferiority margin was set at 10%. Safety follow-ups were done for the duration of study participation. This trial was registered with the Clinical Trials Registry India, number CTRI/2018/08/015317.

**Findings:** Between March 25, 2019, and Jan 15, 2020, a total of 1979 eligible infants were randomly assigned to receive a single vaccine regimen (n=659; 329 in group 1 and 330 in group 2) or a mixed vaccine regimen (n=1320; 329 each in groups 3 and 4, and 331 each in groups 5 and 6). All eligible participants received the first dose, 1925 (97.3%) of 1979 received the second dose, and 1894 (95.7%) received all three doses of vaccine. 1852 (93.6%) of 1979 participants completed the follow-up. The immunogenicity analysis consisted of 1839 infants (1238 [67.3%] in the mixed vaccine regimen and 601 [32.7%] in the single vaccine regimen; 13

samples were insufficient in quantity) who completed vaccination and provided post-vaccination sera. The seroresponse rate in the mixed vaccine regimen group (33.5% [95% CI 30.9-36.2]) was non-inferior compared with the single vaccine regimen group (29.6% [26.1-33.4]); the seroresponse rate difference was 3.9% (95% CI -0.7 to 8.3). The proportion of participants with any type of solicited adverse events was 90.9% (95% CI 88.4-93.0) in the single vaccine regimen group and 91.1% (89.5-92.6) in the mixed vaccine regimen group. No vaccine-related serious adverse events or intussusception were reported during the study.

**Interpretation:** Rotavac and Rotasiil can be safely used in an interchangeable manner for routine immunisation since the seroresponse was non-inferior in the mixed vaccine regimen compared with the single vaccine regimen. These results allow for flexibility in administering the vaccines, helping to overcome vaccine shortages and supply chain issues, and targeting migrant populations easily.

## Salmonella typhi vaccine

## Schistosomiasis vaccine

## Tuberculosis vaccine

BMC Infect Dis. 2023 Feb 24;23(1):120.

doi: 10.1186/s12879-023-08092-4.

### [Safety and efficacy of tuberculosis vaccine candidates in low- and middle-income countries: a systematic review of randomised controlled clinical trials](#)

[Lydia Wilson](#)<sup>#1</sup>, [Lara Gracie](#)<sup>#2</sup>, [Farah Kidy](#)<sup>3</sup>, [G Neil Thomas](#)<sup>3</sup>, [Krishnarajah Nirantharakumar](#)<sup>3</sup>, [Sheila Greenfield](#)<sup>3</sup>, [Semira Manaseki-Holland](#)<sup>3</sup>, [Derek J Ward](#)<sup>#3</sup>, [Tiffany E Gooden](#)<sup>#4</sup>

#### **Abstract**

**Background:** Tuberculosis (TB) remains a leading cause of death worldwide, with 98% of cases occurring in low- and middle-income countries (LMICs). The only vaccine licenced for the prevention of TB has limited protection for adolescents, adults and vulnerable populations. A safe and effective vaccine for all populations at risk is imperative to achieve global elimination of TB. We aimed to systematically review the efficacy and safety of TB vaccine candidates in late-phase clinical trials conducted in LMICs.

**Methods:** Medline, Embase, CENTRAL, PubMed, Clinicaltrials.gov and GreyLit.org were searched in June 2021 to identify phase 2 or later clinical randomised controlled trials that report the efficacy or safety (adverse events) of TB vaccine candidates with participants of any age living in an LMIC. TB vaccine candidates listed in the 2020 WHO Global TB Report were eligible for inclusion aside from BCG revaccination. Trials were excluded if all

participants had active TB at baseline. Two reviewers independently assessed papers for eligibility, and for bias and quality using the Risk of Bias 2 tool and GRADE guidelines, respectively. We report efficacy rates and frequencies of adverse events from each included trial where available and qualitatively synthesise the findings.

**Results:** Thirteen papers representing eleven trials met our inclusion criteria. Seven vaccine candidates were reviewed across seven countries: M72/AS01, RUTI, VPM1002, H56:IC31, MTBVAC, DAR-901 and ID93 + GLA-SE. Two trials reported on efficacy: an efficacy rate of 54% (95% CI 11.5, 76.2) was reported for M72/AS01 in adults with latent TB and 3% (95% CI -13.9, 17.7) for DAR-901 in healthy adolescents. However, the latter trial was underpowered. All vaccine candidates had comparable occurrences of adverse events between treatment arms and demonstrated acceptable safety profiles; though, RUTI resulted in one serious complication in a person living with HIV. M72/AS01 was the only vaccine considered safe across a diverse group of people including people living with HIV or latent TB and healthy infants and adolescents.

**Conclusion:** Further efficacy trials for M72/AS01 are warranted to include additional populations at risk where safety has been demonstrated. Further safety trials are needed for the remaining vaccine candidates to confirm safety in vulnerable populations.

## Typhoid vaccine

Hum Vaccin Immunother. 2022 Dec 30;18(7):2150030.

doi: 10.1080/21645515.2022.2150030. Epub 2022 Dec 7.

### [Safety, immunogenicity and non-interference of concomitant Typhoid Vi capsular polysaccharide-tetanus toxoid conjugate vaccine \(Typbar-TCV®\) and measles or measles-mumps-rubella vaccines in 8-9 months-old Indian children](#)

[Krishna Mohan Vadrevu<sup>1</sup>](#), [Raju Dugyala<sup>1</sup>](#), [Niranjana Shamulinga Mahantashetti<sup>2</sup>](#), [Vasant Khalatkar<sup>3</sup>](#), [Krishna Murthy<sup>4</sup>](#), [Sandeep Mogre<sup>5</sup>](#), [Monjori Mitra<sup>6</sup>](#)

#### **Abstract**

We evaluated safety, reactogenicity, and immunogenicity when the WHO-prequalified single-dose Typhoid Vi-polysaccharide conjugate vaccine, Typbar-TCV®, was administered concomitantly with measles (MV) or measles-mumps-rubella (MMR) vaccines in 8- or 9-month-old children. We enrolled 493 children who were randomized 2:1:1:1 to four groups to receive either TCV (0.5 mL intramuscularly) and MV (0.5 ml subcutaneously) concomitantly at 9 months of age (Group 1) with two subgroups given TCV booster 28 days (Group 1A) or 180 days (Group 1B) later, or MV on Day 0 and TCV on Day 28 (Group 2); or TCV at 8 months of age and MV 28 days later (Group 3), or MV only at 9 months of age (Group 4). All children received MMR at 15 months of age. We observed no statistically significant differences between group rates of solicited or unsolicited adverse events assessed throughout the study.

Seroconversion rates for measles, mumps, and rubella antibodies were unaffected by concomitant administration with TCV, being similar in Groups 1, 2, and 3 and comparable to Group 4 (Control). IgG anti-Vi antibody titers were similar in all groups after primary Typbar-TCV® vaccination and were not increased by a second dose 28 days later. A small response to a booster dose of Typbar-TCV® given at 180 days did not achieve the high titers observed after the first dose, suggesting that booster vaccination may be more effective after a longer



interval than 6 months. Typbar-TCV® can be safely co-administered with measles and MMR vaccines in children aged ≥9 months.

Lancet Glob Health. 2022 Sep;10(9):e1326-e1335.

doi: 10.1016/S2214-109X(22)00275-3.

**Safety and immunogenicity of a typhoid conjugate vaccine among children aged 9 months to 12 years in Malawi: a nested substudy of a double-blind, randomised controlled trial**

[Nginache Nampota-Nkomba<sup>1</sup>](#), [Oswald M Nyirenda<sup>1</sup>](#), [Lameck Khonde<sup>1</sup>](#), [Victoria Mapemba<sup>1</sup>](#), [Maurice Mbewe<sup>2</sup>](#), [John M Ndaferankhande<sup>2</sup>](#), [Harrison Msuku<sup>2</sup>](#), [Clemens Masesa<sup>2</sup>](#), [Theresa Misiri<sup>2</sup>](#), [Felistas Mwakiseghile<sup>2</sup>](#), [Priyanka D Patel<sup>2</sup>](#), [Pratiksha Patel<sup>2</sup>](#), [Ifayet Johnson-Mayo<sup>3</sup>](#), [Marcela F Pasetti<sup>3</sup>](#), [Robert S Heyderman<sup>4</sup>](#), [J Kathleen Tracy<sup>3</sup>](#), [Shrimati Datta<sup>3</sup>](#), [Yuanyuan Liang<sup>3</sup>](#), [Kathleen M Neuzil<sup>3</sup>](#), [Melita A Gordon<sup>5</sup>](#), [Matthew B Laurens<sup>6</sup>](#), [Typhoid Vaccine Acceleration Consortium team](#)

**Abstract**

**Background:** Typhoid fever is a substantial public health problem in Africa, yet there are few clinical trials of typhoid conjugate vaccine (TCV). We assessed immunogenicity and safety of Typbar TCV in Malawi.

**Methods:** This substudy was nested within a phase 3, double-blind, parallel design, randomised controlled trial of TCV in children from Ndirande Health Centre in Ndirande township, Blantyre, Malawi. To be eligible, participants had to be aged between 9 months and 12 years with no known immunosuppression or chronic health conditions, including HIV or severe malnutrition; eligible participants were enrolled into three strata of approximately 200 children (9-11 months, 1-5 years, and 6-12 years), randomly assigned (1:1) to receive TCV or control (meningococcal serogroup A conjugate vaccine [MCV-A]) intramuscularly. Serum was collected before vaccination and at 28 days and 730-1035 days after vaccination to measure anti-Vi antibodies by ELISA. Because of COVID-19, day 730 visits were extended up to 1035 days. This nested substudy evaluated reactogenicity, safety, and immunogenicity by age stratum. Safety outcomes, analysed in the intention-to-treat population, included solicited adverse events within 7 days of vaccination (assessed on 3 separate days) and unsolicited adverse events within 28 days of vaccination. This trial is registered with ClinicalTrials.gov, [NCT03299426](#).

**Findings:** Between Feb 22 and Sept 6, 2018, 664 participants were screened, and 631 participants were enrolled and randomly assigned (320 to the TCV group and 311 to the MCV-A group). 305 participants in the TCV group and 297 participants in the MCV-A group were vaccinated. Among TCV recipients, anti-Vi IgG geometric mean titres increased more than 500 times from 4.2 ELISA units (EU)/mL (95% CI 4.0-4.4) at baseline to 2383.7 EU/mL (2087.2-2722.3) at day 28, then decreased to 48.0 EU/mL (39.9-57.8) at day 730-1035, remaining more than 11 times higher than baseline. Among MCV-A recipients, anti-Vi IgG titres remained unchanged: 4.3 EU/mL (4.0-4.5) at baseline, 4.4 EU/mL (4.0-4.7) on day 28, and 4.6 EU/mL (4.2-5.0) on day 730-1035. TCV and MCV-A recipients had similar solicited local (eight [3%] of 304, 95% CI 1.3-5.1 and three [1%] of 293, 0.4-3.0) and systemic (27 [9%] of 304, 6.2-12.6 and 27 [9%] of 293, 6.4-13.1) reactogenicity. Related unsolicited adverse events occurred similarly in TCV and MCV-A recipients in eight (3%) of 304 (1.3-5.1) and eight (3%) of 293 (1.4-5.3).

**Interpretation:** This study provides evidence of TCV safety, tolerability, and immunogenicity up to 730-1035 days in Malawian children aged 9 months to 12 years.

Hum Vaccin Immunother. 2023 Dec 31;19(1):2203634.

doi: 10.1080/21645515.2023.2203634.

**[A randomized, observer-blind, controlled phase III clinical trial assessing safety and immunological non-inferiority of Vi-diphtheria toxoid versus Vi-tetanus toxoid typhoid conjugate vaccine in healthy volunteers in eastern Nepal](#)**

[Shipra Chaudhary](#)<sup>1</sup>, [Gauri Shankar Shah](#)<sup>1</sup>, [Nisha Keshary Bhatta](#)<sup>1</sup>, [Prakash Poudel](#)<sup>1</sup>, [Basant Rai](#)<sup>1</sup>, [Surendra Uranw](#)<sup>1</sup>, [Prashant Mani Tripathi](#)<sup>1</sup>, [Basudha Khanal](#)<sup>1</sup>, [Anup Ghimire](#)<sup>1</sup>, [Nikita Rai](#)<sup>1</sup>, [Birendra Prasad Gupta](#)<sup>2</sup>, [Sridhar Vemula](#)<sup>2</sup>, [T Anh Wartel](#)<sup>2</sup>, [Sushant Sahastrabuddhe](#)<sup>2</sup>, [Tarun Saluja](#)<sup>2</sup>

**Abstract**

Typhoid remains one of the major serious health concerns for children in developing countries. With extremely drug-resistant cases emerging, preventative measures like sanitation and vaccination, including typhoid conjugate vaccines (TCV) remain the mainstay in its prevention and control. Different types of TCVs are being developed to meet the global demand. This report outlines the results from a study done to assess the immunogenicity and safety of Vi-Diphtheria toxoid (Vi-DT) TCV in Nepal. The study was a randomized, active-controlled, immunological non-inferiority and safety study. Eligible participants from Sunsari and Morang districts of eastern Nepal were randomized into 4 study groups (A-D) within 3 age strata (6 months to <2 years, 2 to <18 years, and 18 to 45 years). Groups A to C received a single dose (25 µg) of Vi-DT test vaccine from any of the 3 lots, while group D received the comparator, Typbar-TCV<sup>®</sup>, Vi-tetanus toxoid (Vi-TT) vaccine (25 µg) in 1:1:1:1 ratio and evaluated at 4 weeks postvaccination with 6 months follow-up. Amongst 400 randomized participants, anti-Vi-IgG seroconversion rates for all age strata in Vi-DT pooled groups (A+B+C) were 100.00% (97.5% CI 98.34-100.00) vs 98.99% (97.5% CI 93.99-99.85) in Vi-TT group (D) at 4 weeks. Comparable safety events were reported between the groups. Three serious adverse events (1 in Vi-DT; 2 in Vi-TT group) were reported during the 6 months follow-up, none being related to the investigational product. Thus, Vi-DT vaccine is safe, immunogenic, and immunologically non-inferior to Vi-TT when analyzed at 4 weeks postvaccination.

Vaccine. 2023 Mar 3;41(10):1753-1759.

doi: 10.1016/j.vaccine.2022.12.007. Epub 2023 Feb 9.

**[A Phase II/III, Multicenter, Observer-blinded, Randomized, Non-inferiority and Safety, study of typhoid conjugate vaccine \(EuTCV\) compared to Typbar-TCV<sup>®</sup> in healthy 6 Months-45 years aged participants](#)**

[Yeong Ok Baik](#)<sup>1</sup>, [Youngjin Lee](#)<sup>1</sup>, [Chankyu Lee](#)<sup>2</sup>, [Soo Kyung Kim](#)<sup>2</sup>, [Jooyoung Park](#)<sup>1</sup>, [Meixiang Sun](#)<sup>2</sup>, [DaYe Jung](#)<sup>1</sup>, [Jin Young Jang](#)<sup>2</sup>, [Tae Jun Yong](#)<sup>2</sup>, [Jeong Woo Park](#)<sup>3</sup>, [Sungho Jeong](#)<sup>3</sup>, [Suwon Lim](#)<sup>3</sup>, [Seung Hyun Han](#)<sup>3</sup>, [Seuk Keun Choi](#)<sup>4</sup>

**Abstract**

The typhoid conjugate vaccine (TCV) ensures a long-lasting protective immune response, requires fewer doses and is fit for children under 2 years of age. From Phase I study, EuTCV displayed considerable immunogenicity and reliable safety, thus endorsing further examination in Phase II/III trials. Therefore, a clinical Phase II/III study ([NCT04830371](#)) was conducted to evaluate its efficacy in healthy Filipino participants aged 6 months to 45 years through administration of the test vaccine (Arm A, B, and C) or comparator vaccine Typbar-TCV<sup>®</sup> (Arm D). Sera samples were collected pre-vaccination (Visit 1) and post-vaccination (Visit 4, Day 28) to assess the immunogenicity of EuTCV and Typbar-TCV<sup>®</sup>. During the study, participants were regularly monitored through scheduled visits to the clinic to report any adverse events associated with the vaccine. For vaccine safety, the proportion of solicited and unsolicited Treatment-Emergent Adverse Events was all comparable between EuTCV and Typbar-TCV<sup>®</sup> groups. A single dose of EuTCV produced seroconversion in 99.4% of treated participants, with seroconversion rates non-inferior to that of Typbar-TCV<sup>®</sup>. Batch-to-batch consistency was concluded based on the 90% Confidence Interval of the geometric mean ratio (EuTCV Arm A, B, and C) at Week 4, lying within the equivalence margin of 0.5 to 2.0 for all batches. Results from this Phase II/III clinical trial of EuTCV in healthy volunteers show comparable safety and considerable immunogenicity, compared to Typbar-TCV<sup>®</sup>, meeting the objectives of this pivotal study.

Lancet Glob Health. 2022 Nov 25;11(1):e136-e144.

doi: 10.1016/S2214-109X(22)00466-1. Online ahead of print.

**[Typhoid conjugate vaccine effectiveness in Malawi: evaluation of a test-negative design using randomised, controlled clinical trial data](#)**

[Yuanyuan Liang](#)<sup>1</sup>, [Amanda J Driscoll](#)<sup>2</sup>, [Priyanka D Patel](#)<sup>3</sup>, [Shrimati Datta](#)<sup>2</sup>, [Merryn Voysey](#)<sup>4</sup>, [Neil French](#)<sup>5</sup>, [Leslie P Jamka](#)<sup>2</sup>, [Marc Y R Henrion](#)<sup>3</sup>, [Latif Ndeketa](#)<sup>3</sup>, [Matthew B Laurens](#)<sup>2</sup>, [Robert S Heyderman](#)<sup>6</sup>, [Melita A Gordon](#)<sup>7</sup>, [Kathleen M Neuzil](#)<sup>8</sup>

**Abstract**

**Background:** Typhoid conjugate vaccines are being introduced in low-income and middle-income countries to prevent typhoid illness in children. Vaccine effectiveness studies assess vaccine performance after introduction. The test-negative design is a commonly used method to estimate vaccine effectiveness that has not been applied to typhoid vaccines because of concerns over blood culture insensitivity. The overall aim of the study was to evaluate the appropriateness of using a test-negative design to assess typhoid Vi polysaccharide-tetanus toxoid conjugate vaccine (Vi-TT) effectiveness using a gold standard randomised controlled trial database.

**Methods:** Using blood culture data from a randomised controlled trial of Vi-TT in Malawi, we simulated a test-negative design to derive vaccine effectiveness estimates using three different approaches and compared these to randomised trial efficacy results. In the randomised trial, 27 882 children aged 9 months to 12 years were randomly assigned (1:1) to receive a single dose of Vi-TT or meningococcal capsular group A conjugate vaccine between Feb 21 and Sept 27, 2018, and were followed up for blood culture-confirmed typhoid fever until Sept 30, 2021.

**Findings:** For all three test-negative design approaches, vaccine effectiveness estimates (test-negative design A, 80.3% [95% CI 66.2 to 88.5] vs test-negative design B, 80.5% [66.5 to 88.6] vs test-negative design C, 80.4% [66.9 to 88.4]) were almost identical to the randomised

trial results (80.4% [95% CI 66.4 to 88.5]). Receipt of Vi-TT did not affect the risk of non-typhoid fever (vaccine efficacy against non-typhoid fever -0.4% [95% CI -4.9 to 3.9] vs -1% [-5.6 to 3.3] vs -2.5% [-6.4 to 1.3] for test-negative design A, test-negative design B, and test-negative design C, respectively).

**Interpretation:** This study validates the test-negative design core assumption for typhoid vaccine effectiveness estimation and shows the accuracy and precision of the estimates compared with the randomised controlled trial. These results show that the test-negative design is suitable for assessing typhoid conjugate vaccine effectiveness in post-introduction studies using blood culture surveillance.

Vaccine. 2023 May 5;41(19):3137-3140.

doi: 10.1016/j.vaccine.2023.04.014. Epub 2023 Apr 13.

### [Immune responses in children after vaccination with a typhoid Vi-tetanus toxoid conjugate vaccine in Bangladesh](#)

[Farhana Khanam<sup>1</sup>](#), [Golap Babu<sup>2</sup>](#), [Nazia Rahman<sup>2</sup>](#), [Xinxue Liu<sup>3</sup>](#), [Nazmul Hasan Rajib<sup>2</sup>](#), [Shams Uddin Ahmed<sup>2</sup>](#), [Md Ismail Hossen<sup>2</sup>](#), [Prasanta Kumar Biswas<sup>2</sup>](#), [Sarah Kelly<sup>3</sup>](#), [Katherine Thesis-Nyland<sup>3</sup>](#), [Yama Mujadidi<sup>3</sup>](#), [Nigel A J McMillan<sup>4</sup>](#), [Andrew J Pollard<sup>3</sup>](#), [John D Clemens<sup>5</sup>](#), [Firdausi Qadri<sup>6</sup>](#)

#### **Abstract**

A cluster-randomized trial of Vi-TT was conducted in Dhaka, Bangladesh, using JE vaccine as the control. A subset of 1,500 children were randomly selected on 2:1 basis (Vi-TT vs JE) to assess immune response. Blood was collected before vaccination, and on days 28, 545 and 730 post-vaccination and plasma anti-Vi-IgG response was measured. A robust, persistent antibody response was induced after single dose of Vi-TT, even after 2 years of vaccination. While there is no accepted serological antibody threshold of protection, analyzing the antibodies of children who received Vi-TT provides evidence that may later be useful in predicting population protection.

Clin Infect Dis. 2022 Nov 14;75(10):1681-1687.

doi: 10.1093/cid/ciac289.

### [Prevention of Typhoid by Vi Conjugate Vaccine and Achievable Improvements in Household Water, Sanitation, and Hygiene: Evidence From a Cluster-Randomized Trial in Dhaka, Bangladesh](#)

[Birkneh Tilahun Tadesse<sup>1</sup>](#), [Farhana Khanam<sup>2</sup>](#), [Faisal Ahmmed<sup>2</sup>](#), [Justin Im<sup>1</sup>](#), [Md Taufiqul Islam<sup>2</sup>](#), [Deok Ryun Kim<sup>1</sup>](#), [Sophie S Y Kang<sup>1</sup>](#), [Xinxue Liu<sup>3</sup>](#), [Fahima Chowdhury<sup>2</sup>](#), [Tasnuva Ahmed<sup>2</sup>](#), [Asma Binte Aziz<sup>1</sup>](#), [Masuma Hoque<sup>2</sup>](#), [Juyeon Park<sup>1,4</sup>](#), [Gideok Pak<sup>1</sup>](#), [Khalequ Zaman<sup>2</sup>](#), [Ashraf Islam Khan<sup>2</sup>](#), [Andrew J Pollard<sup>3</sup>](#), [Jerome H Kim<sup>1</sup>](#), [Florian Marks<sup>1,4,5,6</sup>](#), [Firdausi Qadri<sup>2</sup>](#), [John D Clemens<sup>1,2,7</sup>](#)

#### **Abstract**

**Background:** Typhoid fever contributes to approximately 135 000 deaths annually. Achievable improvements in household water, sanitation, and hygiene (WASH) combined with vaccination using typhoid conjugate vaccines (TCVs) may be an effective preventive

strategy. However, little is known about how improved WASH and vaccination interact to lower the risk of typhoid.

**Methods:** A total of 61 654 urban Bangladeshi children aged 9 months to <16 years, residing in 150 clusters with a baseline population of 205 760 residents, were randomized 1:1 by cluster to Vi-tetanus toxoid TCV or Japanese encephalitis (JE) vaccine. Surveillance for blood culture-confirmed typhoid fever was conducted over 2 years. Existing household WASH status was assessed at baseline as Better or Not Better using previously validated criteria. The reduction in typhoid risk among all residents associated with living in TCV clusters, Better WASH households, or both was evaluated using mixed-effects Poisson regression models.

**Results:** The adjusted reduced risk of typhoid among all residents living in the clusters assigned to TCV was 55% (95% confidence interval [CI], 43%-65%;  $P < .001$ ), and that of living in Better WASH households, regardless of cluster, was 37% (95% CI, 24%-48%;  $P < .001$ ). The highest risk of typhoid was observed in persons living in households with Not Better WASH in the JE clusters. In comparison with these persons, those living in households with Better WASH in the TCV clusters had an adjusted reduced risk of 71% (95% CI, 59%-80%;  $P < .001$ ).

**Conclusions:** Implementation of TCV programs combined with achievable and culturally acceptable household WASH practices were independently associated with a significant reduction in typhoid risk.

Hum Vaccin Immunother. 2022 Nov 30;18(5):2043103.

doi: 10.1080/21645515.2022.2043103. Epub 2022 Mar 25.

[\*\*A multicenter, single-blind, randomized, phase-2/3 study to evaluate immunogenicity and safety of a single intramuscular dose of biological E's Vi-capsular polysaccharide-CRM<sub>197</sub> conjugate typhoid vaccine \(TyphiBEV™\) in healthy infants, children, and adults in comparison with a licensed comparator\*\*](#)

[Subhash Thuluva<sup>1</sup>, Vikram Paradkar<sup>1</sup>, Ramesh Matur<sup>1</sup>, Kishore Turaga<sup>1</sup>, Subba Reddy Gv<sup>1</sup>](#)

### **Abstract**

The current scenario of typhoid fever warrants early prevention with typhoid conjugate vaccines in susceptible populations to provide lifelong protection. We conducted a multicenter, single-blind, randomized, Phase 2/3 study to assess the immunogenicity and safety of Biological E's Typhoid Vi-CRM<sub>197</sub> conjugate vaccine (TyphiBEV™) compared to Vi-TT conjugate vaccine manufactured by Bharat Biotech International Limited (Typbar-TCV; licensed comparator) in healthy infants, children, and adults from India. The study's primary objective was to assess the non-inferiority of TyphiBEV™ in terms of the difference in the proportion of subjects seroconverted with a seroconversion threshold value of  $\geq 2.0$   $\mu\text{g/mL}$  against Typbar-TCV. A total of 622 healthy subjects (311 each in both vaccine groups) were randomized and received the single dose of the study vaccine. The TyphiBEV™ group demonstrated noninferiority compared to the Typbar-TCV group at Day 42. The lower 2-sided 95% confidence interval limit of the group difference was  $-.34\%$ , which met the non-inferiority criteria of  $\geq 10.0\%$ . The geometric mean concentration (24.79  $\mu\text{g/mL}$  vs. 26.58  $\mu\text{g/mL}$ ) and proportion of subjects who achieved  $\geq 4$ -fold increase in antiVi IgG antibody concentrations (96.95% vs. 97.64%) at Day 42 were comparable between the TyphiBEV™ and Typbar-TCV vaccine groups. No apparent difference was observed in the safety profile between both vaccine groups. All adverse events reported were mild or moderate in intensity

in all age subsets. This data demonstrates that TyphiBEV™ is non-inferior to TypbarTCV in terms of immunogenicity, and the overall safety and reactogenicity in healthy infants, children, and adults studied from India was comparable.

Vaccine. 2022 Sep 22;40(40):5828-5834.

doi: 10.1016/j.vaccine.2022.08.034. Epub 2022 Sep 3.

[\*\*Immune non-interference and safety study of Vi-DT typhoid conjugate vaccine with a measles, mumps and rubella containing vaccine in 9-15 months old Nepalese infants\*\*](#)

[Tarun Saluja<sup>1</sup>](#), [Ganesh Kumar Rai<sup>2</sup>](#), [Shipra Chaudhary<sup>3</sup>](#), [Piush Kanodia<sup>4</sup>](#), [Bishnu Rath Giri<sup>2</sup>](#), [Deok Ryun Kim<sup>5</sup>](#), [Jae Seung Yang<sup>5</sup>](#), [Il-Yeon Park<sup>5</sup>](#), [Seung-Eun Kyung<sup>5</sup>](#), [Sridhar Vemula<sup>5</sup>](#), [Jagadeesh Reddy E<sup>5</sup>](#), [Bomi Kim<sup>5</sup>](#), [Birendra Prasad Gupta<sup>5</sup>](#), [Sue Kyoung Jo<sup>5</sup>](#), [Ji Hwa Ryu<sup>6</sup>](#), [Ho Keun Park<sup>6</sup>](#), [Jong Hoon Shin<sup>6</sup>](#), [Yoonyeong Lee<sup>6</sup>](#), [Hun Kim<sup>6</sup>](#), [Jerome H Kim<sup>5</sup>](#), [Zenaida Reynoso Mojares<sup>5</sup>](#), [T Anh Wartel<sup>5</sup>](#), [Sushant Sahastrabuddhe<sup>5</sup>](#)

**Abstract**

**Background:** Typhoid fever is a common disease in developing countries especially in the Indian subcontinent and Africa. The available typhoid conjugate vaccines (TCV) have been found to be highly immunogenic in infants and children less than 2 years of age. Many countries are planning to adopt TCV in their routine EPI programs around 9 months of age when measles containing vaccines are given. Therefore, Vi-DT TCV was tested in 9-15 months aged healthy infants in Nepal to demonstrate non-interference with a measles containing vaccine.

**Methods:** This was a randomized, open label, phase III study to assess the immune non-interference, safety, and reactogenicity of Vi-DT typhoid conjugate vaccine when given concomitantly with measles, mumps and rubella (MMR) vaccine. A total of 360 participants aged 9-15 months were enrolled and randomized equally into Vi-DT + MMR (180 participants) or MMR alone (180 participants) group and were evaluated for immunogenicity and safety 28 days post vaccination.

**Results:** Using the immunogenicity set, difference between proportions (95% CI) of the Vi-DT + MMR group vs MMR alone group were -2.73% (-8.85, 3.38), -3.19% (-11.25, 4.88) and 2.91% (-3.36, 9.18) for sero-positivity rate of anti-measles, anti-mumps and anti-rubella, respectively. Only the lower bound of the range in difference of the proportions for sero-positivity rate of anti-mumps did not satisfy the non-inferiority criteria as it was above the -10% limit, which may not be of clinical significance. These results were confirmed in the per protocol set. There were no safety concerns reported from the study and both Vi-DT + MMR and MMR alone groups were comparable in terms of solicited and unsolicited adverse events.

**Conclusions:** Results indicated that there is non-interference of MMR vaccine with Vi-DT and Vi-DT conjugate vaccine could be considered as an addition to the EPI schedule among children at risk of contracting typhoid.

Hum Vaccin Immunother. 2022 Nov 30;18(5):2043104.

doi: 10.1080/21645515.2022.2043104. Epub 2022 Mar 3.

[\*\*Public engagement during a typhoid conjugate vaccine trial in Lalitpur, Nepal- experience, challenges and lessons learnt\*\*](#)



[Ashata Dahal<sup>1</sup>](#), [Mila Shakya<sup>1</sup>](#), [Dikshya Pant<sup>2</sup>](#), [Anup Adhikari<sup>3</sup>](#), [Rachel Colin-Jones<sup>4</sup>](#), [Katherine Theiss-Nyland<sup>4</sup>](#), [Andrew J Pollard<sup>4</sup>](#), [Buddha Basnyat<sup>1</sup>](#), [Shrijana Shrestha<sup>2</sup>](#)

## Abstract

Typhoid is a public health problem in Nepal. To generate evidence on the impact of Typhoid Conjugate Vaccine (TCV), a phase 3, double-blind, randomized controlled trial was conducted in Lalitpur, Nepal. 20,000 children aged between 9 months and ≤16 years were vaccinated with a new TCV, or control vaccine. Participants were actively followed for safety and efficacy over 2 years through passive surveillance (PS) clinics. Several challenges were encountered during vaccination and PS stemming from misinformation, misconception, and fear around clinical trials in the community. Public engagement (PE) activities were conducted across various tiers moving from decision makers in the first tier; to elected local representatives in the second tier; ending with interaction in community with parents/guardians of the targeted population. Prior and during vaccination, engagement was conducted to inform about the study and discuss the importance of vaccination. Post-vaccination, engagement was conducted to inform about PS clinics, alleviate study concerns and share study updates. Direct and continuous interaction with community stakeholders, including parents/guardians of the targeted population contributed to build trust around the study and community willingness to be involved. It helped to raise awareness, drive away misconceptions, and allowed adaptation according to feedback from community members.

## Varicella vaccine

## Zika virus vaccine

Lancet Infect Dis. 2023 May;23(5):621-633.

doi: 10.1016/S1473-3099(22)00764-2. Epub 2023 Jan 19.

[\*\*The safety and immunogenicity of two Zika virus mRNA vaccine candidates in healthy flavivirus baseline seropositive and seronegative adults: the results of two randomised, placebo-controlled, dose-ranging, phase 1 clinical trials\*\*](#)

[Brandon Essink<sup>1</sup>](#), [Laurence Chu<sup>2</sup>](#), [William Seger<sup>3</sup>](#), [Elizabeth Barranco<sup>4</sup>](#), [Nancy Le Cam<sup>5</sup>](#), [Hamilton Bennett<sup>5</sup>](#), [Veronica Faughnan<sup>5</sup>](#), [Rolando Pajon<sup>5</sup>](#), [Yamuna D Paila<sup>5</sup>](#), [Brooke Bollman<sup>5</sup>](#), [Steven Wang<sup>5</sup>](#), [Jacqueline Dooley<sup>5</sup>](#), [Shiva Kalidindi<sup>5</sup>](#), [Brett Leav<sup>6</sup>](#)

## Abstract

**Background:** Developing a safe and immunogenic vaccine against Zika virus remains an unmet medical need. We did two phase 1 studies that evaluated the safety and immunogenicity of two mRNA-based Zika virus vaccines (mRNA-1325 and mRNA-1893) in adults.

**Methods:** Two randomised, placebo-controlled, dose-ranging, multicentre, phase 1 trials, one of mRNA-1325 (mRNA-1325 trial) and one of mRNA-1893 (mRNA-1893 trial), were done. For both studies, eligible participants were healthy adults (aged 18-49 years) who were flavivirus seronegative or flavivirus seropositive at baseline. Participants in the mRNA-1325 trial, which was done at three centres in the USA, were randomly assigned centrally (1:4), using a randomisation table, to the placebo group or one of three mRNA-1325 dose groups (10, 25, or 100 µg). All participants received two doses. The mRNA-1325 vaccine encoded the

premembrane and envelope E structural proteins (prME) from a Micronesia 2007 Zika virus isolate. Participants in the mRNA-1893 trial, which was done at three centres in the USA and one centre in Puerto Rico, were randomly assigned (1:4) to the placebo group or one of four mRNA-1893 dose groups (10, 30, 100, or 250 µg) using centralised interactive response technology. All participants in the mRNA-1893 trial received dose one on day 1 and then dose two on day 29. The mRNA-1893 vaccine encoded the prME from the RIO-U1 Zika virus isolate. Safety was the primary outcome of each study, which was evaluated in the respective safety populations (mRNA-1325 trial: participants who received at least one dose and provided safety data; mRNA-1893 trial: participants who received at least one dose) and the solicited safety population (mRNA-1893 trial only: received at least 1 dose and contributed solicited adverse reaction data). Endpoints in both trials included solicited adverse reactions within 7 days after vaccination and unsolicited adverse events within 28 days after vaccination. The secondary outcome of both trials was immunogenicity assessed by Zika virus-specific neutralising antibodies (nAbs) in the per-protocol populations in either trial (participants with no major protocol deviations received full dose[s] of assigned dose level within the acceptable time window, had samples drawn within acceptable time window, and had prevaccination and corresponding post-vaccination serum samples for testing). These were descriptive studies, with no formal hypothesis testing in either trial. Both trials are registered with ClinicalTrials.gov, [NCT03014089](#) (mRNA-1325 trial) and [NCT04064905](#) (mRNA-1893 trial).

**Findings:** The mRNA-1325 trial was done from Dec 14, 2016, to Aug 16, 2018. 90 participants were enrolled: 53 (59%) participants were women and 37 (41%) were men; 84 (93%) were White; and 74 (82%) were not Hispanic or Latino. All three dose levels of mRNA-1325 (10, 25, and 100 µg) were generally well tolerated, but the vaccine elicited poor Zika virus-specific nAb responses. At 28 days after dose two, geometric mean titres (GMTs) were highest for mRNA-1325 10 µg (10·3 [95% CI 5·9-18·2]). The mRNA-1893 trial was done from July 23, 2019, to March 22, 2021. 120 participants (70 [58%] women and 50 [42%] men) were enrolled, most participants were White (89 [74%]), and not Hispanic or Latino (91 [76%]). In the mRNA-1893 trial, solicited adverse reactions in participants who received a vaccine were mostly grade 1 or 2 and occurred more frequently at higher dose levels and after dose two. No participants withdrew due to an unsolicited treatment-emergent adverse event and most of these events were not treatment related. On day 57, all evaluated mRNA-1893 dose levels induced robust Zika virus-specific nAb responses, independent of flavivirus serostatus, that persisted until month 13. At day 57 in participants who were flavivirus seronegative, plaque reduction neutralisation titre test nAb GMTs were highest for mRNA-1893 100 µg (454·2 [330·0-619·6]); in participants who were flavivirus seropositive, GMTs were highest for mRNA-1893 10 µg (224·1 [43·5-1153·5]) and mRNA-1893 100 µg (190·5 [19·2-1887·2]).

**Interpretation:** These findings support the continued development of mRNA-1893 against Zika virus, which was well tolerated at all evaluated dose levels and induced strong Zika virus-specific serum nAb responses after two doses, regardless of baseline flavivirus serostatus.

## Vitamin A

## Vitamin D

(See also Tuberculosis)

Eur J Pediatr. 2022 Sep;181(9):3473-3482.

doi: 10.1007/s00431-022-04533-5. Epub 2022 Jun 21.

### [800 IU versus 400 IU per day of vitamin D<sub>3</sub> in term breastfed infants: a randomized controlled trial from an LMIC](#)

[Bharti Yadav<sup>#1</sup>](#), [Neeraj Gupta<sup>#2</sup>](#), [Rohit Sasidharan<sup>1</sup>](#), [Sivam Thanigainathan<sup>1</sup>](#), [Purvi Purohit<sup>3</sup>](#), [Kuldeep Singh<sup>4</sup>](#), [Praveen Sharma<sup>3</sup>](#), [Arun Singh<sup>1</sup>](#)

#### Abstract

This open-label, block-randomized controlled trial compared the effect of 800 IU/day and 400 IU/day of oral vitamin D<sub>3</sub> supplementation in reducing vitamin D insufficiency (VDI) among healthy-term breastfed infants at 14 weeks of postnatal age. All eligible infants were randomized to receive either 800 or 400 IU/day of oral vitamin D<sub>3</sub> (starting within the first week until 14 weeks). The primary outcome was the proportion of infants with VDI (25-OH-D < 20 ng/ml) at 14 weeks. Secondary outcomes were vitamin D deficiency (VDD, < 12 ng/ml), severe VDD (< 5 ng/ml), anthropometry, biochemical or clinical rickets, and any adverse events related to vitamin D toxicity (VDT). Among 102 enrolled infants, the distribution of baseline variables (including cord 25-OH-D levels; 13.0 versus 14.2 ng/ml) was similar in both groups. On intention-to-treat analysis, the proportions of infants with VDI at 14 weeks were significantly lower in the 800 IU group compared to those in the 400 IU group [24% versus 55%; RR 0.44; 95% CI: 0.25-0.76]. The proportions of infants with elevated parathormone (6% versus 26.5%; p = 0.012) and severe VDD (0% versus 12.2%; p = 0.033) were significantly lower in the 800 IU group. Clinical rickets developed in three (6.2%) infants in the 400 IU group. No infant developed VDT. Conclusions: Daily oral supplementation with 800 IU of vitamin D<sub>3</sub> resulted in an almost 50% reduction in the proportion of infants with VDI and prevented the occurrence of severe VDD at 14 weeks of age compared to 400 IU with no evidence of vitamin D toxicity.

J Pediatr Endocrinol Metab. 2023 May 18.

doi: 10.1515/jpem-2023-0146. Online ahead of print.

### [Daily vs. monthly oral vitamin D<sub>3</sub> for treatment of symptomatic vitamin D deficiency in infants: a randomized controlled trial](#)

[Anupriya Gora<sup>1</sup>](#), [Preeti Singh<sup>2</sup>](#), [Ekta Debnath<sup>3</sup>](#), [Rajeev Kumar Malhotra<sup>4</sup>](#), [Anju Seth<sup>2</sup>](#)

#### Abstract

**Objectives:** Compare the efficacy and safety of daily vs. monthly oral vitamin D<sub>3</sub> in treating symptomatic vitamin D deficiency in infants.

**Methods:** 90 infants with symptomatic vitamin D deficiency were randomized into Daily (D) [46 infants] and Bolus (B) [44 infants] groups to receive oral vitamin D<sub>3</sub>, daily (2000 IU/day) and bolus (60,000 IU/month) for three months respectively. Both groups received daily oral calcium @50 mg/kg/day. 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 and 12 weeks. At the end of 12 weeks, 78 infants were available for evaluation of efficacy and safety of both regimens.

**Results:** Both regimens led to a statistically significant increase in Ca and P levels and fall in ALP and PTH levels from baseline to 4 and 12 weeks of therapy, with no inter-group difference. Infants in group D had statistically significant higher mean 25(OH)D levels as compared to group B at 4 weeks (group D  $130.89 \pm 43.43$  nmol/L, group B -  $108.25 \pm 32.40$  nmol/L;  $p = 0.012$ ) and 12 weeks (group D -  $193.69 \pm 32.47$  nmol/L, group B -  $153.85 \pm 33.60$  nmol/L;  $p < 0.001$ ). Eight infants [group D - 6/41 (14.6 %); group B - 2/37 (5.4 %),  $p = 0.268$ ] developed mild asymptomatic hypercalcemia without hypercalciuria at 12 weeks that corrected spontaneously within a week.

**Conclusions:** Both daily and monthly oral vitamin D<sub>3</sub> in equivalent doses are efficacious and safe for treating symptomatic vitamin D deficiency in infants.

Indian Pediatr. 2022 Nov 15;59(11):852-858.

Epub 2022 Sep 22.

**[Sunlight Exposure vs Oral Vitamin D Supplementation for Prevention of Vitamin D Deficiency in Infancy: A Randomized Controlled Trial](#)**

[Anisha Goyal](#)<sup>1</sup>, [Aashima Dabas](#)<sup>2</sup>, [Dheeraj Shah](#)<sup>1</sup>, [Rajeev Kumar Malhotra](#)<sup>3</sup>, [Pooja Dewan](#)<sup>1</sup>, [S V Madhu](#)<sup>4</sup>, [Piyush Gupta](#)<sup>5</sup>

**Abstract**

**Objective:** To compare the efficacy of sunlight exposure and oral vitamin D<sub>3</sub> supplementation to achieve vitamin D sufficiency in infants at 6 months of age.

**Design:** Open-label randomized controlled trial.

**Setting:** Public hospital in Northern India (28.7°N).

**Participant:** Breastfed infants at 6-8 weeks of age.

**Intervention:** Randomized to receive sunlight exposure (40% body surface area for a minimum of 30 minutes/week) or oral vitamin D<sub>3</sub> supplementation (400 IU/day) till 6 months of age.

**Outcome:** Primary - proportion of infants having vitamin D sufficiency ( $>20$  ng/mL).

Secondary - proportion of infants developing vitamin D deficiency ( $<12$  ng/mL) and rickets in both the groups at 6 months of age.

**Results:** Eighty (40 in each group) infants with mean (SD) age 47.8 (4.5) days were enrolled. The proportion of infants with vitamin D sufficiency increased after intervention in the vitamin D group from 10.8% to 35.1% ( $P = 0.01$ ) but remained the same in sunlight group (13.9%) and was significant on comparison between both groups ( $P = 0.037$ ). The mean (SD) compliance rate was 72.9 (3.4) % and 59.7 (23.6) % in the vitamin D and sunlight group, respectively ( $P = 0.01$ ). The geometric mean (95% CI) serum 25(OH) D levels in the vitamin D and sunlight group were 16.23 (13.58-19.40) and 11.89 (9.93-14.23) ng/mL, respectively; ( $P = 0.02$ ), after adjusting baseline serum 25(OH)D with a geometric mean ratio of 1.36 (1.06-1.76). Two infants in sunlight group developed rickets.

**Conclusion:** Oral vitamin D<sub>3</sub> supplementation is more efficacious than sunlight in achieving vitamin D sufficiency in breastfed infants during the first 6 months of life due to better compliance.

Front Pediatr. 2022 Jul 25;10:943529.

doi: 10.3389/fped.2022.943529. eCollection 2022.

### [Efficacy and safety of vitamin D supplementation in hospitalized COVID-19 pediatric patients: A randomized controlled trial](#)

[Jessie Zurita-Cruz<sup>1</sup>](#), [Jeffrey Fonseca-Tenorio<sup>2</sup>](#), [Miguel Villasís-Keever<sup>3</sup>](#), [Mardia López-Alarcón<sup>4</sup>](#), [Israel Parra-Ortega<sup>5</sup>](#), [Briceida López-Martínez<sup>6</sup>](#), [Guadalupe Miranda-Novales<sup>3</sup>](#)

#### **Abstract**

**Background:** Some studies suggested that adequate levels of vitamin D (VD) decrease the risk of severe COVID-19. Information about the effectiveness of VD supplementation in children is scarce.

**Objective:** To assess the efficacy and safety of VD supplementation compared to the standard of care in hospitalized children with COVID-19.

**Patients and methods:** An open-label randomized controlled single-blind clinical trial was carried out. We included patients from 1 month to 17 years, with moderate COVID-19, who required hospitalization and supplemental oxygen. They were randomized into two groups: the VD group, which received doses of 1,000 (children < 1 year) or 2,000 IU/day (from 1 to 17 years) and the group without VD (control). The outcome variables were the progression of oxygen requirement, the development of complications, and death.

**Statistical analysis:** For comparison between groups, we used the chi-squared test or Fisher's exact test and the Mann-Whitney *U* test. Absolute risk reduction (ARR) and the number needed to treat (NNT) were calculated.  $p \leq 0.05$  was considered statistically significant.

**Results:** From 24 March 2020 to 31 March 2021, 87 patients were eligible to participate in the trial; 45 patients were randomized: 20 to the VD group and 25 to the control group. There was no difference in general characteristics at baseline, including serum VD levels (median 13.8 ng/ml in the VD group and 11.4 ng/ml in the control group).

**Outcomes:** 2/20 (10%) in the VD group vs. 9/25 (36%) in the control group progressed to a superior ventilation modality ( $p = 0.10$ ); one patient in the VD group died (5%) compared to 6 (24%) patients in the control group ( $p = 0.23$ ). ARR was 26% (95% CI 8.8 to 60.2%) and NNT was 3 (2 to 11) for progression and ARR was 19% (95% CI -3.9 to 42.8%) and NNT was 6 (2 to 26) for death. None of the patients receiving VD had adverse effects. The trial was stopped for ethical reasons; since after receiving the results of the basal VD values, none of the patients had normal levels.

**Conclusion:** In this trial, VD supplementation in pediatric patients seems to decrease the risk of COVID-19 progression and death. More studies are needed to confirm these findings.

J Nutr. 2023 Apr;153(4):1189-1198.

doi: 10.1016/j.tjnut.2022.11.026. Epub 2023 Jan 9.

### [Increased Serum Total and Free 25-Hydroxyvitamin D with Daily Intake of Cholecalciferol-Fortified Skim Milk: A Randomized Controlled Trial in Colombian Adolescents](#)

[Eduardo Villamor<sup>1</sup>](#), [Henry Oliveros<sup>2</sup>](#), [Constanza Marín<sup>2</sup>](#), [Sandra López-Arana<sup>3</sup>](#), [Samantha Agudelo-Cañas<sup>4</sup>](#)

#### **Abstract**

**Background:** The efficacy of cholecalciferol (vitamin D3) food fortification in low- and middle-income countries near the Equator is unknown.

**Objectives:** We examined the effects of providing cholecalciferol-fortified skim milk to adolescents and their mothers on serum total 25(OH)D, free 25(OH)D, and vitamin D-binding protein (DBP) concentrations in a randomized controlled trial.

**Methods:** We randomly assigned 80 Colombian families each with a child aged 12-14.5 y and their mother 1 L of skim milk daily, either fortified with 2400 IU (60 µg) cholecalciferol or unfortified, for 6 wk. We prescribed 500 mL of milk daily to adolescents; mothers consumed the remainder ad libitum. We estimated intent-to-treat effects as the between-arm difference in the change in serum total and free 25(OH)D and DBP concentrations from baseline to the end of follow-up. Secondary analyses included stratification by baseline characteristics and per-protocol comparisons.

**Results:** Among adolescents, fortification effects (95% CI) on serum total 25(OH)D, free 25(OH)D, and DBP concentrations were 5.4 nmol/L (2.1, 8.8 nmol/L), 0.6 pmol/L (-0.2, 1.4 pmol/L), and -416 nmol/L (-944, 112 nmol/L), respectively. Effects on total 25(OH)D were stronger in adolescents with lower DBP concentrations, darker skin, less sunlight exposure, and higher compliance than in their respective counterparts. Fortification increased free 25(OH)D concentrations in high compliers. Among mothers, the effects (95% CI) on total 25(OH)D and DBP concentrations were 4.0 nmol/L (0.6, 7.5 nmol/L) and -128 nmol/L (-637, 381 nmol/L), respectively. There were no adverse events.

**Conclusions:** Provision of cholecalciferol-fortified skim milk increases serum total 25(OH)D concentrations in Colombian adolescents and adult women.

Eur J Pediatr. 2023 Mar 1.

doi: 10.1007/s00431-023-04889-2. Online ahead of print.

**[Oral vitamin D supplementation and body weight in children and adolescents: a systematic review and meta-analysis of randomized controlled trials](#)**

[Sepideh Soltani](#)<sup>1</sup>, [Sara Beigrezaei](#)<sup>2,3</sup>, [Shima Abdollahi](#)<sup>4</sup>, [Cain C T Clark](#)<sup>5</sup>, [Marziyeh Ashoori](#)<sup>6</sup>

**Abstract**

This study was designed to ascertain whether oral vitamin D supplementation (oral supplementation and fortified foods) is associated with changes in body weight measures in children and adolescents, using a systematic review and meta-analysis of randomized controlled trials (RCTs). PubMed, Scopus, Cochrane, and Web of Science databases were searched from inception to October 28, 2022. The mean difference and corresponding 95% confidence interval (CI) of interested outcomes were pooled using a random-effects model. Twenty-one RCTs were included in the meta-analysis, and the results showed a significant decrease in body mass index (BMI) following vitamin D supplementation in children and adolescents (n = 9 studies, 1029 participants; weighted mean difference: - 0.43 kg/m<sup>2</sup>, 95% CI: - 0.79, - 0.08; P = 0.02; I<sup>2</sup> = 58.5%). Overall, oral vitamin D supplementation had no significant effect on body weight and other anthropometric indices, including fat mass, lean mass, waist circumference, BMI Z-score, and height. Although results of body weight changed to significant after sensitivity analysis (WMD = 0.39 kg, 95% CI = 0.01, 0.78; P = 0.04; I<sup>2</sup> = 0%, P-heterogeneity = 0.71), we also found significant weight gain in healthy pediatric population, and when the dose of vitamin D supplementation was up to 600 IU/day, the certainty of evidence was very low for weight, moderate for height and BMI, and low for the remaining outcomes.



**Conclusion:** Our results suggest that vitamin D supplementation may lead to a statistically significant weight gain in children and adolescents, while BMI was reduced. Although no significant change was observed in height, it seems vitamin D supplementation may elicit these changes by increasing skeletal growth; however, this remains to be verified. Further high-quality RCTs, with longer duration and larger sample sizes, are needed to yield more certain evidence in this regard.

**What is known:** • Available evidence indicates an inverse association between body weight/fat mass and vitamin D status in children and adolescents; however, findings regarding the effect of vitamin D supplementation on anthropometric measurements in children are controversial.

**What is new:** • Our results showed a significant decrease in BMI following vitamin D supplementation in children. • A significant weight gain also was observed after sensitivity analysis, and in healthy pediatric population, and when the dose of vitamin D supplementation was up to 600 IU/day.

## Yaws

## Zinc

(see also: Acute respiratory infection, Diarrhoea, Nutrition, Sickle cell disease)

PLoS One. 2022 Sep 19;17(9):e0274870.

doi: 10.1371/journal.pone.0274870. eCollection 2022.

**[Bioequivalence of micronutrient powders to Corn-soy Blend on serum zinc concentration of children \(6-36 months\) with Moderate Acute Malnutrition in Thika urban slums, Kenya: A cluster-randomized controlled trial](#)**

[Juliana Kiio](#)<sup>1</sup>, [Sophie Ochola](#)<sup>1</sup>, [Ruth Nduati](#)<sup>2</sup>, [Elizabeth Kuria](#)<sup>1</sup>, [Scholastica Mathenge](#)<sup>3</sup>, [Judith Okoth](#)<sup>4</sup>

### Abstract

Zinc deficiency is common among children with Moderate Acute Malnutrition (MAM) and contributes to growth failure, increased morbidity and mortality. Diarrhoea and poor dietary practices are the main causes of zinc deficiency. Corn-soy Blend (CSB), the standard product in management of children with MAM has a limitation of poor micronutrient bioavailability. Micronutrient powders (MNPs) which are added at the point of consumption have a potential in improving micronutrient status however, scientific evidence on efficacy on improving the zinc status is scarce. A cluster-randomized clinical trial was designed to establish bioequivalence of MNPs to CSB on serum zinc status among children (6-36 months) with MAM in Thika informal settlements, Kenya. Sample size was calculated to show bioequivalence within  $\pm 20\%$  limit. Twelve villages were randomized to four study groups. Three experimental groups received different formulations of MNPs added to unfortified CSB porridge as; multiple micronutrients containing zinc (CSB-MNP-A n = 84), multiple micronutrients without zinc (CSB-MNP-B n = 88) and zinc only (CSB-MNP-C n = 94). Control group (n = 80) received standard CSB fortified with multiple micronutrients. Standard amount of CSB was consumed in feeding centres for six months. Serum zinc concentration was assessed pre- and post-intervention. Data was analyzed based on treatment assignment

regardless of adherence and drop-out status. Mixed effects linear regression was used to model pre-post change in serum zinc concentration, adjusting for clustering effect and baseline differences. Bioequivalence was assessed using two one-sided t-tests. At baseline, 84.4% were zinc deficient (serum zinc <65µg/dL) and zinc intake was sub-optimal (<3 mg/day) for 95.7% of children. Mean change in serum zinc concentration was significantly higher ( $p = 0.024$ ) in CSB-MNP-A ( $18.7 \pm 2.1$ ) µg/dL compared to control group ( $11.8 \pm 2.6$  µg/dL). MNPs are not bioequivalent to CSB within the  $\pm 20\%$  bioequivalence limit. MNPs are more effective in improving serum zinc status compared to CSB. Trials with larger sample sizes are recommended to validate the current findings.

Sci Rep. 2022 Sep 27;12(1):16084.

doi: 10.1038/s41598-022-20445-8.

**[Daily preventive zinc supplementation increases the antibody response against pathogenic Escherichia coli in children with zinc insufficiency: a randomised controlled trial](#)**

[Chidchamai Kewcharoenwong](#)<sup>#1</sup>, [Myint Myint Sein](#)<sup>#2</sup>, [Arnone Nithichanon](#)<sup>3</sup>, [Aranya Khongmee](#)<sup>2</sup>, [K Ryan Wessells](#)<sup>4</sup>, [Guy-Marino Hinnouho](#)<sup>4,5</sup>, [Maxwell A Barffour](#)<sup>4,6</sup>, [Sengchanh Kounnavong](#)<sup>7</sup>, [Sonja Y Hess](#)<sup>4</sup>, [Charles B Stephensen](#)<sup>4,8</sup>, [Ganjana Lertmemongkolchai](#)<sup>9,10</sup>

**Abstract**

Zinc deficiency impairs the antibody-mediated immune response and is common in children from lower-income countries. This study aimed to investigate the impact of different zinc supplementation regimens (7, 10 or 20 mg/day elemental zinc)-therapeutic dispersible zinc tablets (TZ), daily multiple micronutrient powder (MNP), daily preventive zinc tablets (PZ) and placebo powder (control)-and compare between baseline and endline antibody production against pathogenic Escherichia coli in Laotian children (aged 6-23 months). Fifty representative plasma samples of each treatment group were randomly selected from 512 children to determine anti-E. coli IgG antibody levels and avidity. Of the 200 children, 78.5% had zinc deficiency (plasma zinc concentration < 65 µg/dL) and 40% had anaemia before receiving zinc supplementation. After receiving the TZ, MNP or PZ regimen, the plasma anti-E. coli IgG levels were significantly increased compared with baseline; the effect on the antibody level was more pronounced in children with zinc deficiency. Interestingly, there was increased anti-E. coli IgG avidity in the control and PZ groups. This study suggests that PZ might be the optimal zinc supplementation regimen to increase both the quantity and quality of antibody responses in children with zinc deficiency.

Cochrane Database Syst Rev. 2023 Mar 30;3(3):CD009384.

doi: 10.1002/14651858.CD009384.pub3.

**[Zinc supplementation for preventing mortality, morbidity, and growth failure in children aged 6 months to 12 years](#)**

[Aamer Imdad](#)<sup>1</sup>, [Jaimie Rogner](#)<sup>2</sup>, [Rida N Sherwani](#)<sup>1</sup>, [Jasleen Sidhu](#)<sup>3</sup>, [Allison Regan](#)<sup>3</sup>, [Maya R Haykal](#)<sup>3</sup>, [Olivia Tsistinas](#)<sup>4</sup>, [Abigail Smith](#)<sup>4</sup>, [Xin Hui S Chan](#)<sup>5</sup>, [Evan Mayo-Wilson](#)<sup>6</sup>, [Zulfiqar A Bhutta](#)<sup>7,8</sup>

**Abstract**

**Background:** Zinc deficiency is prevalent in low- and middle-income countries, and is considered a significant risk factor for morbidity, mortality, and linear growth failure. The effectiveness of preventive zinc supplementation in reducing prevalence of zinc deficiency needs to be assessed.

**Objectives:** To assess the effects of zinc supplementation for preventing mortality and morbidity, and for promoting growth, in children aged 6 months to 12 years.

**Search methods:** A previous version of this review was published in 2014. In this update, we searched CENTRAL, MEDLINE, Embase, five other databases, and one trials register up to February 2022, together with reference checking and contact with study authors to identify additional studies.

**Selection criteria:** Randomized controlled trials (RCTs) of preventive zinc supplementation in children aged 6 months to 12 years compared with no intervention, a placebo, or a waiting list control. We excluded hospitalized children and children with chronic diseases or conditions. We excluded food fortification or intake, sprinkles, and therapeutic interventions.

**Data collection and analysis:** Two review authors screened studies, extracted data, and assessed the risk of bias. We contacted study authors for missing information and used GRADE to assess the certainty of evidence. The primary outcomes of this review were all-cause mortality; and cause-specific mortality, due to all-cause diarrhea, lower respiratory tract infection (LRTI, including pneumonia), and malaria. We also collected information on a number of secondary outcomes, such as those related to diarrhea and LRTI morbidity, growth outcomes and serum levels of micronutrients, and adverse events.

**Main results:** We included 16 new studies in this review, resulting in a total of 96 RCTs with 219,584 eligible participants. The included studies were conducted in 34 countries; 87 of them in low- or middle-income countries. Most of the children included in this review were under five years of age. The intervention was delivered most commonly in the form of syrup as zinc sulfate, and the most common dose was between 10 mg and 15 mg daily. The median duration of follow-up was 26 weeks. We did not consider that the evidence for the key analyses of morbidity and mortality outcomes was affected by risk of bias. High-certainty evidence showed little to no difference in all-cause mortality with preventive zinc supplementation compared to no zinc (risk ratio (RR) 0.93, 95% confidence interval (CI) 0.84 to 1.03; 16 studies, 17 comparisons, 143,474 participants). Moderate-certainty evidence showed that preventive zinc supplementation compared to no zinc likely results in little to no difference in mortality due to all-cause diarrhea (RR 0.95, 95% CI 0.69 to 1.31; 4 studies, 132,321 participants); but probably reduces mortality due to LRTI (RR 0.86, 95% CI 0.64 to 1.15; 3 studies, 132,063 participants) and mortality due to malaria (RR 0.90, 95% CI 0.77 to 1.06; 2 studies, 42,818 participants); however, the confidence intervals around the summary estimates for these outcomes were wide, and we could not rule out a possibility of increased risk of mortality. Preventive zinc supplementation likely reduces the incidence of all-cause diarrhea (RR 0.91, 95% CI 0.90 to 0.93; 39 studies, 19,468 participants; moderate-certainty evidence) but results in little to no difference in morbidity due to LRTI (RR 1.01, 95% CI 0.95 to 1.08; 19 studies, 10,555 participants; high-certainty evidence) compared to no zinc. There was moderate-certainty evidence that preventive zinc supplementation likely leads to a slight increase in height (standardized mean difference (SMD) 0.12, 95% CI 0.09 to 0.14; 74 studies, 20,720 participants). Zinc supplementation was associated with an increase in the number of participants with at least one vomiting episode (RR 1.29, 95% CI 1.14 to 1.46; 5 studies, 35,192 participants; high-certainty evidence). We report a number of other outcomes, including the effect of zinc supplementation on weight and serum markers such

as zinc, hemoglobin, iron, copper, etc. We also performed a number of subgroup analyses and there was a consistent finding for a number of outcomes that co-supplementation of zinc with iron decreased the beneficial effect of zinc.

**Authors' conclusions:** Even though we included 16 new studies in this update, the overall conclusions of the review remain unchanged. Zinc supplementation might help prevent episodes of diarrhea and improve growth slightly, particularly in children aged 6 months to 12 years of age. The benefits of preventive zinc supplementation may outweigh the harms in regions where the risk of zinc deficiency is relatively high.