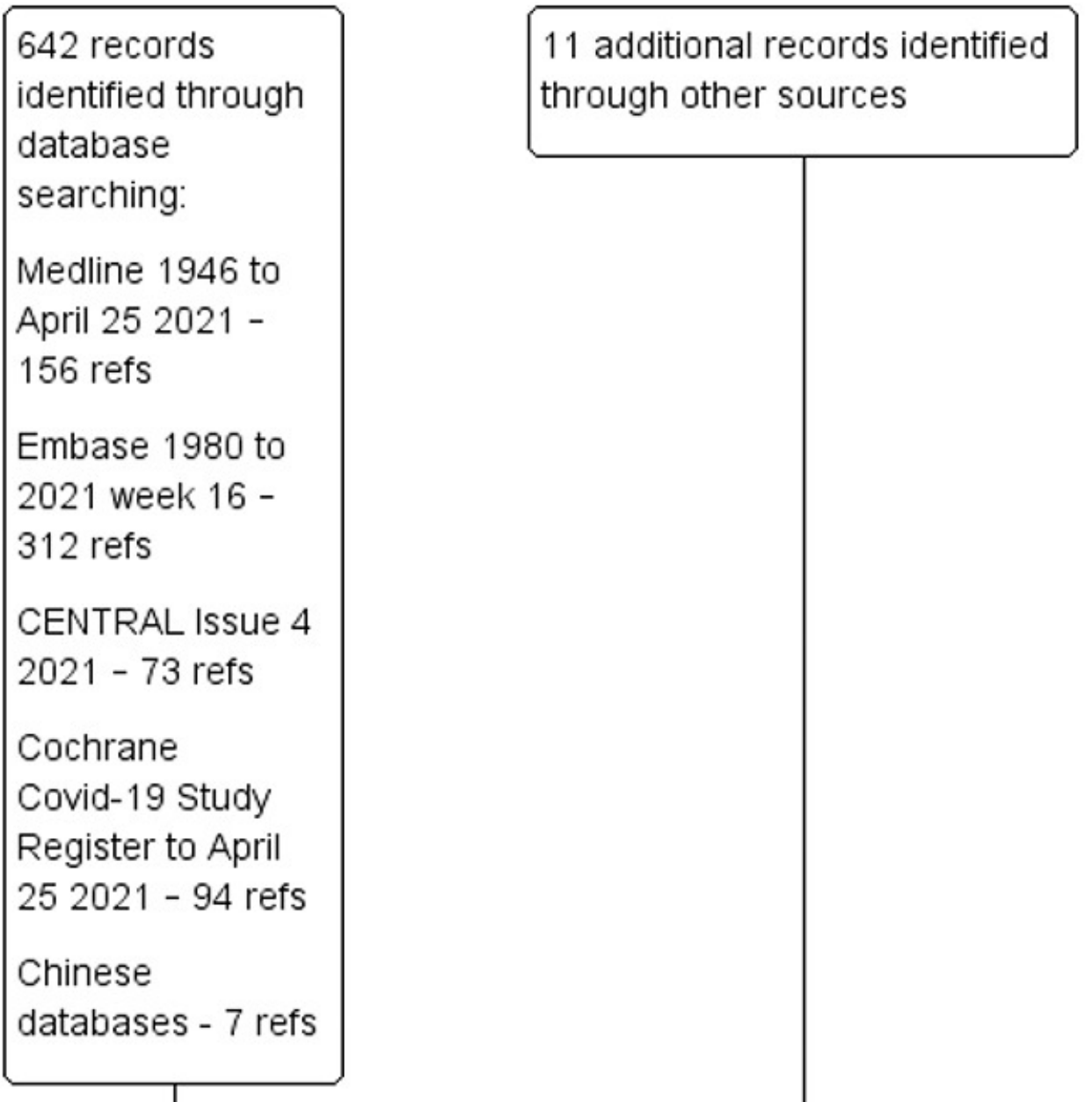
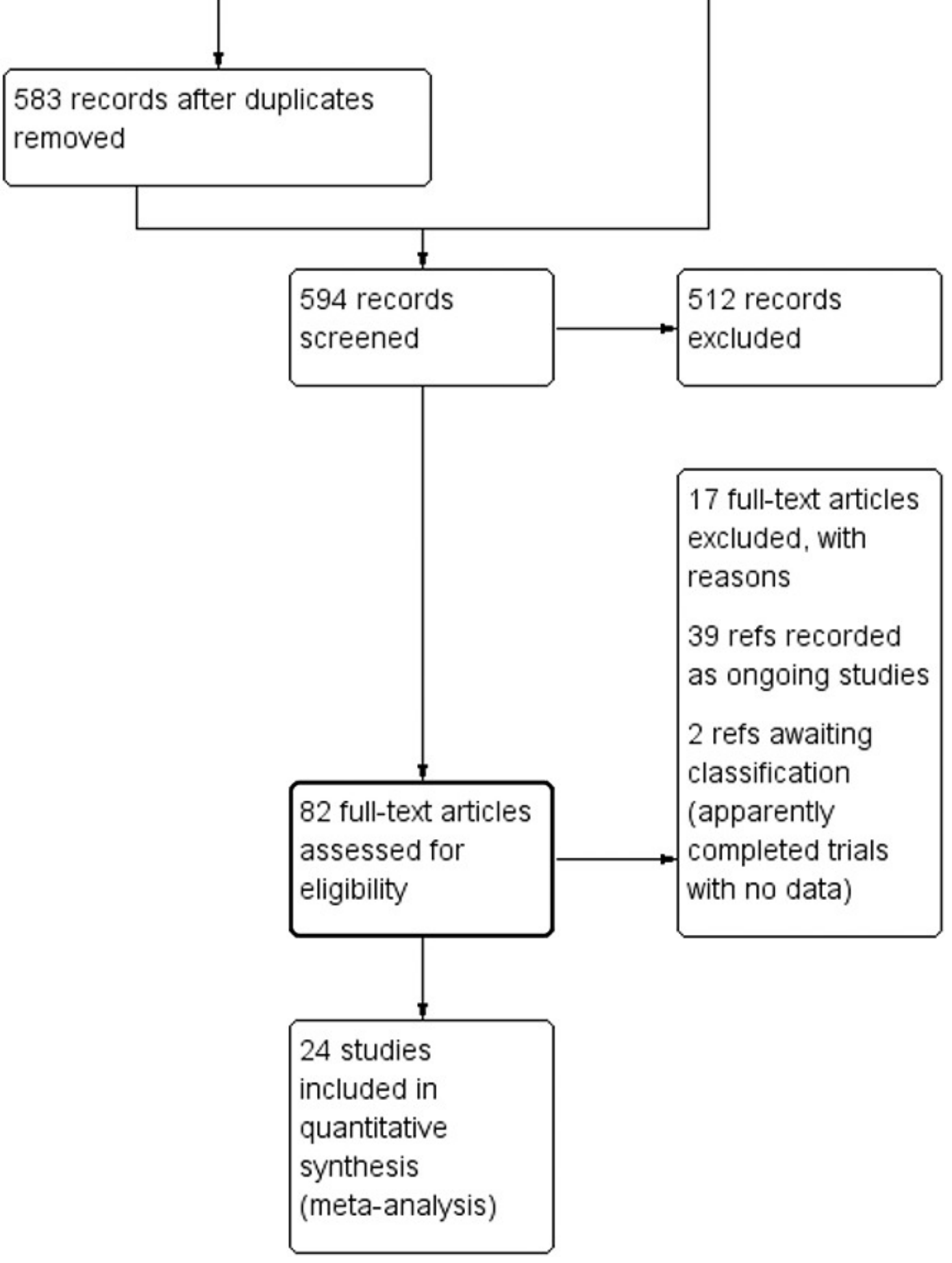
Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines





Trial sequential analysis

When a meta-analysis is subjected to repeated statistical evaluation, there is an exaggerated risk that “naive” point estimates and confidence intervals will yield spurious inferences. In a meta-analysis, it is important to minimize the risk of making a false-positive or false-negative conclusion. There is a trade-off between the risk of observing a false-positive result (type I error) and the risk of observing a false-negative result (type II error). Conventional meta-analysis methods (eg, in RevMan) also do not take into account the amount of available evidence. Therefore, we examined the reliability and conclusiveness of the available evidence using trial sequential analyses (TSA).[41–43] The DerSimonian–Laird (DL) method was used because this is most often used in meta-analytic practice and was also used in the primary meta-analysis.[30]

The TSA was used to calculate the required information size (IS) to demonstrate or reject a relative reduction in the risk (RRR) of death in the ivermectin group, as found in the primary meta-analysis. We assumed the estimated event proportion in the control group from the meta-analysis because this is the best and most representative available estimate. Recommended type I and II error rates of 5% and 10% were used, respectively (power of 90%),[43] powering the result on the effect observed in the primary meta-analyses. We did not identify any large COVID-19 trials powered on all-cause mortality, so powering on some

external meaningful difference was not possible. Any small RRR is meaningful in this context, given the scale of the pandemic, but the required IS would be unfeasibly high for this analysis if powered on a small difference. The only reliable data on ivermectin in its repurposed role for treatment against COVID-19 will be from the primary meta-analysis. Therefore, assuming it does not widely deviate from other published systematic reviews, a pragmatic decision was therefore made to power on the pooled meta-analysis effect estimate for all-cause mortality a priori. This is more reflective of a true meaningful difference. We used a model variance-based estimate to correct for heterogeneity. A continuity correction of 0.01 was used in trials that reported zero events in one or both arms. The required IS is the sample size required for a reliable and conclusive meta-analysis and is at least as large as that needed in a single powered RCT. The heterogeneity corrected required IS was used to construct sequential monitoring boundaries based on the O'Brien–Fleming type alpha-spending function for the cumulative z-scores (corresponding to the cumulative meta-analysis),[43] analogous to interim monitoring in an RCT, to determine when sufficient evidence had been accrued. These monitoring boundaries are relatively insensitive to the number of repeated significance tests. They can be used to further contextualize the original meta-analysis and enhance our certainty around its conclusions. We used a two-sided test, so also considered futility boundaries (to test for no

statistically significant difference) and the possibility that ivermectin could harm. Sensitivity analyses were performed excluding the trial of Fonseca,[44] which was a cause of substantial heterogeneity (but retained in the core analysis because it was at low risk of bias). Its removal dramatically reduced I^2 and D^2 (diversity) estimates, thus reducing the model variance-based estimate to correct for heterogeneity. Two further sensitivity analyses were performed using 2 alternative random effect models, namely the Biggerstaff–Tweedie (BT) and Sidik–Jonkman (SJ) methods.[43]

All outcomes have been assessed independently by 2 review authors (T.D. and A.B.) using the GRADE approach,[45] which ranks the quality and certainty of the evidence. The results of the TSAs will also form part of the judgment for the primary all-cause mortality outcome. The results are presented in a summary of findings table. Any differences in judgments were resolved by discussion with the wider group. We used Cochrane Effective Practice and Organisation of Care guidance to interpret the evidence.[46]

1. Horby P, Lim WS, Emberson J, et al. . Dexamethasone in hospitalized patients with covid-19. *NEJM*. 2021;384:693–704. [PMC free article] [PubMed] [Google Scholar]
2. Barrows NJ, Campos RK, Powell ST, et al. . A screen of FDA-approved drugs for inhibitors of zika virus infection. *Cell Host Microbe*. 2016;20:259–270. [PMC free article]

[PubMed] [Google Scholar]
3. Conterno LO, Turchi MD, Corrêa I, et al. . Anthelmintic drugs for treating ascariasis. *Cochrane Database Syst Rev.* 2020;1. doi: 10.1002/14651858.CD010599.pub2. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
4. World Health Organization. *21st Model List of Essential Medicines*. Geneva, Switzerland; 2019. Available at: https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06. Accessed January 26, 2021. [Google Scholar]
5. Nicolas P, Maia MF, Bassat Q, et al. . Safety of oral ivermectin during pregnancy: a systematic review and meta-analysis. *Lancet Glob Health.* 2020;8:e92–e100. [PubMed] [Google Scholar]
6. Banerjee K, Nandy M, Dalai CK, et al. . The battle against covid 19 pandemic: what we need to know before we "test fire" ivermectin. *Drug Res (Stuttg).* 2020;70:337–340. [PMC free article] [PubMed] [Google Scholar]
7. Navarro M, Camprubí D, Requena-Méndez A, et al. . Safety of high-dose ivermectin: a systematic review and meta-analysis. *J Antimicrob Chemother.* 2020;75:827–834. [PubMed] [Google Scholar]
8. Kircik LH, Del Rosso JQ, Layton AM, et al. . Over 25 Years of clinical experience with ivermectin: an overview of safety for an increasing number of indications. *J Drugs Dermatol.* 2016;15:325–332. [PubMed] [Google Scholar]
9. Kory P, GU M, Varon J, et al. . Review of the emerging evidence demonstrating the efficacy of ivermectin in the

prophylaxis and treatment of COVID-19. *Am J Ther*. 2021;28:e299–e318. [Google Scholar]
10. Hill A, Abdulamir A, Ahmed S, et al. . Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection, 19. *Res Square*. 2021. doi: 10.21203/rs.3.rs-148845/v1.Preprint. [CrossRef] [Google Scholar]
11. National Institute of Health. *The Covid-19 Treatment Guidelines Panel's Statement on the Use of Ivermectin for the Treatment of Covid-19*. 2021. [Google Scholar]
12. World Health Organization. *Therapeutics and COVID-19: Living Guideline*. Geneva, Switzerland: WHO; 2021. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.1. Accessed April 8, 2021. [Google Scholar]
13. Heidary H, Gharebaghi R. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. *J Antibiot*. 2020;73:593–602. [PMC free article] [PubMed] [Google Scholar]
14. Caly L, Druce JD, Catton MG, et al. . The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antivir Res*. 2020;178:104787. [PMC free article] [PubMed] [Google Scholar]
15. Jans DA, Wagstaff KM. Ivermectin as a broad-spectrum host-directed anti-viral: the real deal? *Cells*. 2020;9:2100. [PMC free article] [PubMed] [Google Scholar]
16. Schmith VD, Zhou J, Lohmer LRL. The approved dose of ivermectin alone is not the ideal dose for the treatment of

Covid-19. *Clin Pharmacol Ther.* 2020;108:762–765. [PMC free article] [PubMed] [Google Scholar]
17. Anand K, Ziebuhr J, Wadhwani P, et al. . Coronavirus main proteinase (3CLpro) structure: basis for design of anti-SARS drugs. *Science.* 2003;300:1763–1767. [PubMed] [Google Scholar]
18. Mody V, Ho J, Wills S, et al. . Identification of 3-chymotrypsin like protease (3CLPro) inhibitors as potential anti-SARS-CoV-2 agents. *Nat Commun Biol.* 2021;4:93. [PMC free article] [PubMed] [Google Scholar]
19. DiNicolantonio JJ, Barroso J, McCarty. Ivermectin may be a clinically useful anti-inflammatory agent for late-stage covid-19. *Open Heart.* 2020;7:e001350–e. [PMC free article] [PubMed] [Google Scholar]
20. Lehrer A, Rheinstein PH. Ivermectin docks to the SARS-CoV-2 spike receptor binding domain attached to ACE2. *vivo*. 2020;34:3023–3026. [PMC free article] [PubMed] [Google Scholar]
21. Scheim D. From cold to killer: how SARS-CoV-2 evolved without hemagglutinin esterase to agglutinate, then clot blood Cells in pulmonary and systemic microvasculature. *SSRN.* 2020. doi: 10.2139/ssrn.3706347.Preprint. [CrossRef] [Google Scholar]
22. *WHO Expert Committee on the Selection and Use of Essential Medicines. Application for Inclusion of Ivermectin on the WHO Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc) for the*

Indication of Scabies. 2018. Available at: https://www.who.int/selection_medicines/committees/expert/22/applications/s6.6_ivermectin.pdf. Accessed February 21, 2021. [Google Scholar]
23. Ahmed S, Karim MM, Ross AG, et al. . A five day course of ivermectin for the treatment of covid-19 may reduce the duration of illness. *Int J Infect Dis*. 2020;103:214–216. [PMC free article] [PubMed] [Google Scholar]
24. Chaccour C, Casellas A, Blanco-Di Matteo A, et al. . The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial. *EClinical Med*. 2021;32:100720. doi: 10.1016/j.eclinm.2020.100720 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
25. Aluko P, Graybill E, Craig D, et al. . Chapter 20: economic evidence. In: Higgins J, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions (Version 61). Cochrane*; 2020. [Google Scholar]
26. Bryant A, Lawrie T, Dowsell T, et al. . *Ivermectin for Prevention and Treatment of Covid-19 (Protocol)*. The Evidence-Based Medical Consultancy Ltd; 2021. Available at: https://tinyurl.com/cx7pnaxa. Accessed February 27, 2021. [Google Scholar]
27. Higgins JPT, Thomas J, Chandler J, et al. . *Cochrane Handbook for Systematic Reviews of Interventions Version 6. 0 Cochrane*. 2019. [Google Scholar]

28. Higgins JP, Thompson SG, Deeks JJ, et al. . Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560. [PMC free article] [PubMed] [Google Scholar]
29. Deeks JJ, Altman DG, Bradburn MJ. Chapter 15: statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: *Systematic Reviews in Health Care: Meta-Analysis in Context*. London, United Kingdom: BMJ Publication Group; 2001. [Google Scholar]
30. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clin Trials*. 1986;7:177–188. [PubMed] [Google Scholar]
31. *RevMan. Review Manager 5*. The Cochrane Collaboration; 2020. [Google Scholar]
32. *R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing V, Austria*. R Foundation for Statistical Computing. Vienna, Austria; 2021. [Google Scholar]
33. Owen RK, Bradbury N, Xin Y, et al. . MetaInsight: an interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. *Res Syn Meth*. 2019;10:569–581. [PMC free article] [PubMed] [Google Scholar]
34. Rücker G, Schwarzer G, Krahn U, et al. . *Network Meta-Analysis Using Frequentist Methods*; 2017. [Google Scholar]
35. Efthimiou O. Practical guide to the meta-analysis of rare events. *Evid Based Ment Health*. 2018;21:72–76. [PubMed]

[Google Scholar]
36. Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. *Stat Med.* 2010;29:3046–3067. [PubMed] [Google Scholar]
37. Chen Y, Chu H, Luo S, et al. . Bayesian analysis on meta-analysis of casecontrol studies accounting for within-study correlation. *Stat Methods Med Res.* 2015;24:836–855. [PMC free article] [PubMed] [Google Scholar]
38. Rücker G, Schwarzer G, Carpenter J, et al. . Why add anything to nothing? The arcsine difference as a measure of treatment effect in meta-analysis with zero cells. *Stat Med.* 2009;28:721–738. [PubMed] [Google Scholar]
39. Tian L, Cai T, Pfeffer MA, et al. . Exact and efficient inference procedure for meta-analysis and its application to the analysis of independent 2 x 2 tables with all available data but without artificial continuity correction. *Biostatistics.* 2009;10:275–281. [PMC free article] [PubMed] [Google Scholar]
40. Cai T, Parast L, Ryan L. Meta-analysis for rare events. *Stat Med.* 2010;29:2078–2089. [PMC free article] [PubMed] [Google Scholar]
41. Brok J, Thorlund K, Gluud C, et al. . Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *J Clin Epidemiol.* 2008;61:763–769. [PubMed] [Google Scholar]

42. Wetterslev J, Thorlund K, Brok J, et al. . Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Med Res Methodol*. 2009;9:86. [PMC free article] [PubMed] [Google Scholar]
43. Thorlund K, Engstrøm J, Wetterslev J, et al. . *User Manual for Trial Sequential Analysis (TSA)*. 2011. Available at: www.ctu.dk/tsa. Accessed April 8, 2021. [Google Scholar]
44. Fonseca AJ. *The Effect of Chloroquine, Hydroxychloroquine OR Ivermectin in Patients with Severe Manifestations of Coronavirus*. 2021. Available at: https://ensaiosclinicos.gov.br/rg/RBR-8h7q82/. Accessed January 20, 2021. [Google Scholar]
45. Schünemann H, Vist G, Higgins J, et al. . Chapter 15: interpreting results and drawing conclusions. In: Higgins J, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 61. Cochrane*; 2020.updated September 2020. [Google Scholar]
46. Cochrane Effective Practice and Organisation of Care (EPOC). *EPOC Resources for Review Authors*; 2017. Available at: www.epoc.cochrane.org/epoc-specific-resources-review-authors. Accessed February 1, 2021. [Google Scholar]
47. Elgazzar A, Eltaweel A, Youssef SA, et al. . Efficacy and safety of ivermectin for treatment and prophylaxis of covid-19 pandemic. *Res Square*. 2020. doi: 10.21203/rs.3.rs-100956/v2.Preprint. [CrossRef] [Google Scholar]
48. Alam MT, Murshe R, Bhiuyan E, et al. . A case series of

100 covid-19 positive patients treatedwith combination of ivermectin and doxycycline. *J Bangladesh Coll Physicians Surgeons*. 2020;38:10–15. [Google Scholar]
49. Behera P, Patro BK, Singh AK, et al. . Role of ivermectin in the prevention of covid-19 infection among healthcare workers in India: a matched case-control study. *PLoS One*. 2020;16:e0247163. [PMC free article] [PubMed] [Google Scholar]
50. Bernigaud C, Guillemot D, Ahmed-Belkacem A, et al. . Oral ivermectin for a scabies outbreak in a long-term–care facility: potential value in preventing COVID-19 and associated mortality? *Br J Dermatol*. 2021. doi: 10.1111/bjd.19821. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
51. Budhiraja S, Soni A, Jha V, et al. . Clinical Profile of First 1000 Covid-19 Cases Admitted at Tertiary Care Hospitals and the Correlates of Their Mortality: An Indian Experience. *medRxiv*. 2020. doi: 10.1101/2020.11.16.20232223.Preprint. [CrossRef] [Google Scholar]
52. Cadegiani FA, Goren A, Wambier CG, et al. . Early covid-19 therapy with azithromycin plus nitazoxanide, ivermectin orHydroxychloroquine in outpatient settings significantly reduced SymptomsCompared to known outcomes in untreated patients. *medRxiv*. 2020. doi: 10.1101/2020.10.31.20223883.Preprint. [CrossRef] [Google Scholar]
53. Camprubí D, Almuedo-Riera A, Martí-Soler H, et al. .

Lack of efficacy of standard doses of ivermectin in severe covid-19 patients. *PLoS One*. 2020;15:e0242184. [PMC free article] [PubMed] [Google Scholar]
54. Carvallo H, Hirsch R, Farinella M. Safety and efficacy of the combined use of ivermectin, dexamethasone, enoxaparin and aspirin against covid 19. *medRxiv*. 2020. doi: 10.1101/2020.09.10.20191619.Preprint. [CrossRef] [Google Scholar]
55. Rajter JC, Sherman MS, Fatteh N, et al. . Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019. *CHEST*. 2021;159:85–92. [PMC free article] [PubMed] [Google Scholar]
56. Espitia-Hernandez G, Munguia L, Diaz-Chiguer D, et al. . Effects of Ivermectin-azithromycin-cholecalciferol combined therapy on COVID-19 infected patients: a proof of concept study. *Biomed Res*. 2020;31:129–133. [Google Scholar]
57. Gorial FI, Mashhadani S, Sayaly HM, et al. . Effectiveness of ivermectin as add-on therapy in covid-19 management (pilot trial). *medRxiv*. 2020. doi: 10.1101/2020.07.07.20145979.Preprint. [CrossRef] [Google Scholar]
58. Hellwig MD, Maia A. A covid-19 Prophylaxis? Lower incidence associated withprophylactic administration of Ivermectin. *Int J Antimicrob Agent*. 2021;57:106248. [PMC free article] [PubMed] [Google Scholar]
59. Khan M, Khan M, Debnath C, et al. . Ivermectin treatment

may improve the prognosis of patients with covid-19. *Archivos de Bronconeumología*. 2020;56:832. [PMC free article] [PubMed] [Google Scholar]
60. Morgenstern J, Redondo JN, De León A, et al. . The use of compassionate ivermectin in the management of symptomatic outpatients and hospitalized patients with clinical diagnosis of covid-19 at the medical center bournigal and the medical center punta cana, rescue group, Dominican Republic. *medRxiv*. 2020. doi: 10.1101/2020.10.29.20222505.Preprint. [CrossRef] [Google Scholar]
61. Portmann-Baracco A, Bryce-Alberti M, Accinelli RA. Antiviral and anti-inflammatory properties ofivermectin and its potential use in Covid-19. *Arch Bronconeumol*. 2020;56:831. [PMC free article] [PubMed] [Google Scholar]
62. Shokati Z. *A Randomized Clinical Trial Study, Comparison of the Therapeutic Effects of Ivermectin, Kaletra and Chloroquine with Kaletra and Chloroquine in the Treatment of Patients with Coronavirus [Protocol]*. 2019. Available at: https://en.irct.ir/trial/48444. Accessed January 2021. [Google Scholar]
63. Spoorthi V, Sasank S. Utility of ivermectin and doxycycline combination for the treatment of SARS- CoV-2. *Int Arch Integrated Med*. 2020;7:177–182. [Google Scholar]
64. Abd-Elsalam S. *The Efficacy of Ivermectin and Nitazoxanide in Covid-19 Treatment*. 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04351347. Accessed

January 2021. [Google Scholar]
65. Abd-Elsalam S. *Ivermectin as a Novel Therapy in Covid-19 Treatment*. 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04403555. Accessed January 2021. [Google Scholar]
66. Alam MT. *Safety and Efficacy of Ivermectin and Doxycycline in Treatment of Covid-19*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04551755. Accessed January 2021. [Google Scholar]
67. Arnold S. *Novel Agents for Treatment of High-Risk Covid-19 Positive Patients*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04374019. Accessed January 2021. [Google Scholar]
68. Centenario Hospital Miguel Hidalgo. *Hydroxychloroquine and Ivermectin for the Treatment of Covid-19 Infection*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04391127. Accessed January 2021. [Google Scholar]
69. Ashraf S. *Efficacy of Subcutaneous Ivermectin with or without Zinc and Nigella Sativa in Covid-19 Patients (SINZ-Covid-PK)*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04472585. Accessed January 2021. [Google Scholar]
70. Ataee Z. *Evaluation of the Effect of Ivermectin in Hospitalized Patients with Covid-19 in Imam Reza Hospital in Mashhad*; 2020. Available at: https://en.irct.ir/trial/49180. Accessed January 2021. [Google Scholar]

71. Bisoffi Z. *COVidIVERmectin: Ivermectin for Treatment of Covid-19 (COVER)*. 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04438850. Accessed January 2021. [Google Scholar]
72. ProgenaBiom. *Trial of Combination Therapy to Treat Covid-19 Infection*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04482686. Accessed January 2021. [Google Scholar]
73. Perez A. *Efficacy, Safety and Tolerability of Ivermectin in Subjects Infected with SARS-CoV-2 with or without Symptoms (SILVERBULLET)*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04407507. Accessed January 2021. [Google Scholar]
74. Echeverri E. *Effectiveness and Safety of Ivermectin for the Prevention of Covid-19 Infection in Colombian Health Personnel (IveprofCovid19)*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04527211. Accessed January 2021. [Google Scholar]
75. Elalfy H. *New Antiviral Drugs for Treatment of Covid-19*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04392427. Accessed January 2021. [Google Scholar]
76. Exman P. *Early Treatment with Ivermectin and LosarTAN for Cancer Patients with Covid-19 Infection (TITAN)*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04447235. Accessed January 2021. [Google Scholar]

77. Fathalipour M. *The Efficacy and Safety of Ivermectin in Patients with Covid-19: A Randomized Clinical Trial*; 2020. Available at: https://www.irct.ir/trial/49501. Accessed January 2021. [Google Scholar]
78. George B. *A Phase IIB Open Label Randomized Controlled Trial to Evaluate the Efficacy and Safety of Ivermectin in Reducing Viral Loads in Patients with Hematological Disorders Who Are Admitted with Covid 19 Infection*; 2020. Available at: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=43449. Accessed January 2021. [Google Scholar]
79. Gheibi N. *Dose-Finding Study of Ivermectin Treatment on Patients Infected with Covid-19:A Clinical Trial*; 2020. Available at: https://en.irct.ir/trial/47012. Accessed January 2021. [Google Scholar]
80. Gheibi N. *Determination the Therapeutic Effect of Ivermectin and Sovodak on Patients Infected with Covid-19: A Clinical Trial*; 2020. Available at: https://en.irct.ir/trial/51007. Accessed January 2021. [Google Scholar]
81. Temple University. *Outpatient Use of Ivermectin in Covid-19*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04530474. Accessed January 2021. [Google Scholar]
82. Pott Junior H, Bastos Paoliello MM, Miguel AQC, et al. . Use of ivermectin in the treatment of Covid-19: a pilot trial. *Toxicol Rep*. 2021;8:505–510. [PMC free article] [PubMed]

[Google Scholar]
83. Kamal E. *Ivermectin in Treatment of Covid 19 Patients*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04425707. Accessed January 2021. [Google Scholar]
84. Saibannavar A. *An Open Label, Prospective Comparative Study to Evaluate the Proposed Therapy in Adults with Mild Symptomatic Covid-19 Patients Receiving the Standard Treatment of Covid Infection*; 2020. Available at: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=46392. Accessed January 2021. [Google Scholar]
85. López-Medina E, López P, Hurtado IC. Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial. *J Am Med Assoc.* 2021;325:1426–1435. [PMC free article] [PubMed] [Google Scholar]
86. García Funegra P. *Randomized Phase IIA Clinical Trial to Evaluate the Efficacy of Ivermectin to Obtain Negative PCR Results in Patients with Early Phase Covid-19 (SAINT-PERU)*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04635943. Accessed January 2021. [Google Scholar]
87. Okasha K. *Ivermectin and Nitazoxanide Combination Therapy for Covid-19*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04360356. Accessed January 2021. [Google Scholar]
88. Okasha K. *Ivermectin Nasal Spray for Covid19 Patients*;

2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04510233. Accessed January 2021. [Google Scholar]
89. Rathi S. *Study to Efficacy of Ivermectin in Patients of Covid-19*; 2020. Available at: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=43728. Accessed January 2021. [Google Scholar]
90. Pathak R. *Effectiveness of Ivermectin in Preventing Development of Symptomatic Covid-19 Among Primary Contacts of Newly Diagnosed Covid-19 Positive Patients at a Tertiary Care Hospital in North India—an Interventional Study*; 2020. Available at: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=46676. Accessed January 2021. [Google Scholar]
91. Prakash A. *A Clinical Trial to Study the Effects of Hydroxychloroquine, Ciclesonide and Ivermectin in Treatment of Moderate Covid-19 Illness*. 2020. Available at: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=43364. Accessed January 2021. [Google Scholar]
92. Ochoa-Jaramillo F. *Ivermectin in Adults with Severe Covid-19*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04602507. Accessed January 2021. [Google Scholar]
93. Saxena R. *Assessment of Response of Ivermectin on Virological Clearance in Covid 19 Patients*; 2020. Available at: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=46873. Accessed January 2021. [Google Scholar]

94. Hidalgo C. *Pragmatic Study "CORIVER": Ivermectin as Antiviral Treatment for Patients Infected by SARS-COV2 (Covid-19)*; 2020. Available at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001971-33/. Accessed January 2021. [Google Scholar]
95. Shahbazi F. *Evaluation Effects of the Standard Regimen along with Ivermectin on Treatment of Corona Virus Type 2 Pneumonia*; 2020. Available at: https://www.irct.ir/trial/49280. Accessed January 2021. [Google Scholar]
96. Stein M. *A Randomized Double-Blind Placebo-Controlled Trial of Oral Ivermectin for Outpatient Treatment of Those at High Risk for Hospitalization Due to Covid-19*; 2020. Available at: https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=380506&isReview=true. Accessed January 2021. [Google Scholar]
97. Suputtamongkol Y. *Ivermectin vs Combined Hydroxychloroquine and Antiretroviral Drugs (ART) Among Asymptomatic Covid-19 Infection (IDRA-Covid19)*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04435587. Accessed January 2021. [Google Scholar]
98. Fundació Assistencial Mútua Terrassa. *Randomised Clinical Trial of Ivermectin for Treatment and Prophylaxis of Covid-19*; 2020. Available at: https://www.clinicaltrialsregister.eu/ctr-search/search?

query=eudract_number:2020-001994-66. Accessed January 2021. [Google Scholar]
99. Ghandali M. *Evaluating the Efficacy and Safety of Ivermectin in the Treatment of Covid-19 Patients: A Double-Blind Randomized Controlled Trial, Phase II*; 2020. Available at: https://en.irct.ir/trial/49935. Accessed January 2021. [Google Scholar]
100. Yamaoka K. *Placebo-controlled Randomized, Double-Blind (Evaluator, Patient) Multicenter, Parallel-Group Comparative Study Investigating the Efficacy and Safety of Ivermectin in Patients with Covid-19*; 2020. Available at: https://jrct.niph.go.jp/en-latest-detail/jRCT2031200120. Accessed January 2021. [Google Scholar]
101. Zendehdel A. *Evaluation of the Effect of Oral Ivermectin on the Outcome of Patients with Covid-19 and Compare it with the Effect of Conucntional Therapics in Patients Admitted to Ziaeian, Baharloo, Imam Khomeini in the Spring and Summer 2020*; 2020. Available at: https://en.irct.ir/trial/50305. Acessed January 2021. [Google Scholar]
102. Instituto de Cardiología de Corrientes. *Ivermectin to Prevent Hospitalizations in Covid-19 (IVERCORcovid19)*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04529525. Accessed January 2021. [Google Scholar]
103. Asghar A. *Efficacy of Ivermectin in COVID-19*; 2020. Available at:

https://clinicaltrials.gov/ct2/show/NCT04392713. Accessed January 2021. [Google Scholar]
104. National University Hospital Singapore. *A Preventive Treatment for Migrant Workers at High-Risk of Covid-19*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04446104. Accessed January 2021. [Google Scholar]
105. Babalola OE, Bode CO, Ajayi AA, et al. . Ivermectin shows clinical benefits in mild to moderate COVID19: a randomised controlled double blind dose response study in Lagos. *Int J Med.* 2021. doi: 10.1093/qjmed/hcab035. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
106. Krolewiecki A, Lifschitz A, Moragas M, et al. . Antiviral effect of high-dose ivermectin in adults with COVID-19: a pilot randomised, controlled, open label, multicentre trial. *SSRN.* 2020. doi: 10.2139/ssrn.3714649.Preprint. [CrossRef] [Google Scholar]
107. Mahmud R. *Clinical Trial of Ivermectin Plus Doxycycline for the Treatment of Confirmed Covid-19 Infection*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04523831. Accessed January 2021). [Google Scholar]
108. Niaee MS, Gheibi N, Namdar P, et al. . Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: a randomized multi-center clinical trial. *Res Square.* 2020. doi: 10.21203/rs.3.rs-109670/v1. Preprint. [CrossRef] [Google Scholar]

109. Ravikirti, Roy R, Pattadar C, et al. . Ivermectin as a potential treatment for mild to moderate COVID-19 - a double blind randomized placebo-controlled trial. *medRxiv*. 2021. doi: 10.1101/2021.01.05.21249310.Preprint. [CrossRef] [Google Scholar]
110. Mohan A, Tiwari P, Suri T, et al. . Ivermectin in mild and moderate COVID-19 (RIVET-COV): a randomized, placebo-controlled trial. *Res Square*. 2021. doi: 10.21203/rs.3.rs-191648/v1.Preprint. [CrossRef] [Google Scholar]
111. Rezai M. *Effectiveness of Ivermectin in the Treatment of Coronavirus Infection in Patients Admitted to Educational Hospitals of Mazandaran in 2020*. 2020. Available at: https://en.irct.ir/trial/49174. Accessed January 2021. [Google Scholar]
112. Chachar AZK, Khan KA, Asif M, et al. . Effectiveness of ivermectin in SARS-CoV-2/COVID-19 patients. *Int J Sci*. 2020;9:31–35. [Google Scholar]
113. Raad H. *In Vivo Use of Ivermectin (IVR) for Treatment for Corona Virus Infected Patients (Covid-19): A Randomized Controlled Trial*; 2021. Available at: http://www.chictr.org.cn/showproj.aspx?proj=54707. Accessed January 2021. [Google Scholar]
114. Schwartz E. *Ivermectin vs. Placebo for the Treatment of Patients with Mild to Moderate Covid-19*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04429711. Accessed January 2021. [Google Scholar]
115. Okumus N, Demirtürk N, Çetinkaya RA, et al. . *Evaluation*

of the Effectiveness and Safety of Adding Ivermectin to Treatment in Severe COVID-19 Patients. Research Square; 2021. doi: 10.21203/rs.3.rs-224203/v1.Preprint. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
116. Guzzo C, Furtek C, Porras AC, et al. . Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. *J Clin Pharmacol*. 2002;42:1122–1133. [PubMed] [Google Scholar]
117. World Health Organization. *Developing Global Norms for Sharing Data and Results during Public Health Emergencies*; 2015. Available at: https://www.who.int/medicines/ebola-treatment/blueprint_phe_data-share-results/en/. Accessed January 2021. [Google Scholar]
118. Yagisawa M, Foster PJ, Hanaki H, et al. . Global trends in clinical studies of ivermectin in COVID-19. *Jpn J Antibiot*. 2021;74:44–95. [Google Scholar]
119. Castañeda-Sabogal A, Chambergo-Michilot D, Toro-Huamanchumo CJ, et al. . Outcomes of Ivermectin in the treatment of covid-19: a systematic review and meta-analysis. *medRxiv*. 2021. doi: 10.1101/2021.01.26.21250420. Preprint. [CrossRef] [Google Scholar]
120. Nardelli P, Zangrillo A, Sanchini G, et al. . Crying wolf in time of Corona: the strange case of ivermectin and hydroxychloroquine. Is the fear of failure withholding potential life-saving treatment from clinical use? *Signa Vitae*. 2021;17:3–4. [Google Scholar]
121. Shea BJ, Reeves BC, Wells G, et al. . AMSTAR 2: a

critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. [PMC free article] [PubMed] [Google Scholar]
122. Alam MT, Murshed R, Gomes PF, et al. . Ivermectin as pre-exposure prophylaxis for COVID-19 among healthcare providers in a selected tertiary hospital in dhaka - an observational study. *Eur J Med Health Sci.* 2020;2. doi: 10.24018/ejmed.2020.2.6.599. [CrossRef] [Google Scholar]
123. Carvallo H, Hirsch R, Alkis P, et al. . Study of the efficacy and safety of topical ivermectin + iona-Carrageenan in the prophylaxis against COVID-19 in health personnel. *J Biomed Res Clin Invest.* 2020;2:1007. [Google Scholar]
124. Behera P, Patro BK, Padhy BM, et al. . Prophylactic role of ivermectin in SARS-CoV-2 infection among healthcare workers. *Res Square.* 2021. doi: 10.21203/rs.3.rs-208785/v1.Preprint. [CrossRef] [Google Scholar]
125. Fesler ML, Stricker RB. Pre-exposure prophylaxis for covid-19 in pregnant women. *Int J Gen Med.* 2021;14:279–284. [PMC free article] [PubMed] [Google Scholar]
126. Stricker RB, Fesler ML. Flattening the risk: pre-exposure prophylaxis for COVID-19. *Infect Drug Resist.* 2020;13:3689–3694. [PMC free article] [PubMed] [Google Scholar]
127. Chesler DL. *Letter to Dr Bray at the National Institutes of Health*. 2021. Available at: https://tinyurl.com/dnemehxn. Accessed March 16, 2021. [Google Scholar]

128. Chamie J. Real-world evidence: the case of Peru. In: *Causality between Ivermectin and COVID-19 Infection Fatality Rate*. ResearchGate; 2020. Available at: https://www.researchgate.net/publication/344469305. Accessed March 8, 2021. [Google Scholar]
129. Chamie-Quintero J, Hibberd J, Scheim DE. Sharp reductions in COVID-19 case fatalities and excess deaths in Peru in close time conjunction, state-by-state, with ivermectin treatments. *SSRN*. 2021. doi: 10.2139/ssrn.3765018.Preprint. [CrossRef] [Google Scholar]
130. GRADE-DECIDE. *The DECIDE Project*. 2016. Available at: http://www.decide-collaboration.eu/. Accessed January 2021. [Google Scholar]
131. Roguski J. *Ivermectin*; 2020. Available at: https://www.thecompleteguidetohealth.com/Ivermectin.html#. Accessed January 2021. [Google Scholar]
132. Ministerio de Salud y Deportes. *Ministry of Health Authorizes the Use of Ivermectin against COVID-19 under Protocol*; 2020. Available at: https://www.minsalud.gob.bo/4157-ministerio-de-salud-autoriza-uso-de-ivermectina-contra-el-covid-19-bajo-protocolo. Accessed January 2021. [Google Scholar]
133. Despacho de Comunicaciones y Estrategia Presidencial. *Coronavirus COVID-19 in Honduras*; 2021. Available at: https://covid19honduras.org/. Accessed January 2021. [Google Scholar]
134. TrialSiteNews. *Slovakia Becomes the First EU Nation to*

Formally Approve Ivermectin for Both Prophylaxis and Treatment for COVID-19 Patients. 2021. Available at: https://trialsitenews.com/slovakia-becomes-the-first-eu-nation-to-formally-approve-ivermectin-for-both-prophylaxis-and-treatment-for-covid-19-patients/. Accessed February 2021. [Google Scholar]
135. Bukhari KHS, Asghar A, Perveen N, et al. . Efficacy of Ivermectin in COVID-19 Patients with Mild to Moderate Disease. *medRxiv*. 2021. doi: 10.1101/2021.02.02.21250840.Preprint. [CrossRef] [Google Scholar]
136. Chowdhury ATMM, Shahbaz M, Karim R, et al. . A randomized trial of ivermectin-doxycycline and hydroxychloroquine-azithromycin therapy on COVID19 patients. *Res Square*. 2020. doi: 10.21203/rs.3.rs-38896/v1.Preprint. [CrossRef] [Google Scholar]
137. Gonzalez JLB, González Gámez M, Enciso EAM, et al. . Efficacy and safety of Ivermectin and Hydroxychloroquine in patients with severe COVID-19. A randomized controlled trial. *medRxiv*. 2021. doi: 10.1101/2021.02.18.21252037.Preprint. [CrossRef] [Google Scholar]
138. Hashim HA, Maulood MF, Rasheed AM, et al. . Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating covid-19 patients in Baghdad, Iraq. *medRxiv*. 2020. doi: 10.1101/2020.10.26.20219345.Preprint. [CrossRef] [Google Scholar]

139. Petkov S. *Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Investigating Efficacy, Safety and Tolerability of Ivermectin HUVE-19 in Patients with Proven SARS-CoV-2 Infection (Covid-19) and Manifested Clinical Symptoms*. 2021. Available at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002091-12/BG. Accessed January 2021. [Google Scholar]
140. Podder CS, Chowdhury N, Mohim IS, et al. . Outcome of ivermectin treated mild to moderate covid-19 cases: a single-centre, open-label, randomised controlled study. *IMC J Med Sci*. 2020;14:2. [Google Scholar]
141. Schwartz E. Viral load and culture viability in mild COVID-19 patients treated with Ivermectin. *New England J Med*. 2021.Submitted. [Google Scholar]
142. Chahla RE, Ruiz LM, Ortega ES, et al. . A randomized trial: intensive treatment based in Ivermectin and iota-Carageenan as pre-exposure prophylaxis for COVID-19 in healthcare agents. *medRxiv*. 2021. doi: 10.1101/2021.03.26.21254398.Preprint. [CrossRef] [Google Scholar]
143. Shouman W, Hegazy AA, Nafae RM, et al. . Use of ivermectin as a potential chemoprophylaxis for COVID-19 in Egypt: a randomized clinical trial. *J Clin Diagn Res*. 2021;15:OC27–OC32. [Google Scholar]
144. Campbell M, McKenzie JE, Sowden A, et al. . Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ*. 2020;16:l6890. [PMC free article]

[PubMed] [Google Scholar]