American Journal of Therapeutics 28, e434–e460 (2021)

OPEN

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

Andrew Bryant, MSc,[1]* Theresa A. Lawrie, MBBCh, PhD,[2] Therese Dowswell, PhD,[2] Edmund J. Fordham, PhD,[2] Scott Mitchell, MBChB, MRCS,[3] Sarah R. Hill, PhD,[1] and Tony C. Tham, MD, FRCP[4]

Background: Repurposed medicines may have a role against the SARS-CoV-2 virus. The antiparasitic ivermectin, with antiviral and anti-inflammatory properties, has now been tested in numerous clinical trials.

Areas of uncertainty: We assessed the efficacy of ivermectin treatment in reducing mortality, in secondary outcomes, and in chemoprophylaxis, among people with, or at high risk of, COVID-19 infection.

Data sources: We searched bibliographic databases up to April 25, 2021. Two review authors sifted for studies, extracted data, and assessed risk of bias. Meta-analyses were conducted and certainty of the evidence was assessed using the GRADE approach and additionally in trial sequential analyses for mortality. Twenty-four randomized controlled trials involving 3406 participants met review inclusion.

Therapeutic Advances: Meta-analysis of 15 trials found that ivermectin reduced risk of death compared with no ivermectin (average risk ratio 0.38, 95% confidence interval 0.19–0.73; n = 2438; I^2 = 49%; moderate-certainty evidence). This result was confirmed in a trial sequential analysis using the same DerSimonian–Laird method that underpinned the unadjusted analysis. This was also robust against a trial sequential analysis using the Biggerstaff–Tweedie method. Low-certainty evidence found that ivermectin prophylaxis reduced COVID-19 infection by an average 86% (95% confidence interval 79%–91%). Secondary outcomes provided less certain evidence. Low-certainty evidence suggested that there may be no benefit with ivermectin for "need for mechanical ventilation,"

[1]*Population Health Sciences Institute, Newcastle University, Newcastle Upon Tyne, United Kingdom;* [2]*Evidence-based Medicine Consultancy, Bath, United Kingdom;* [3]*Emergency Department, Princess Elizabeth Hospital, Guernsey, United Kingdom; and* [4]*Division of Gastroenterology, Ulster Hospital, Dundonald, Belfast, Northern Ireland, United Kingdom.*

The preprint of this review received no funding. This updated version was funded by the crowdfunding initiative https://www.gofundme.com/f/help-us-get-lifesaving-drug-approved-for-covid19

The authors have no conflicts of interest to declare.

T. A. Lawrie and A. Bryant cowrote the review; they also sifted the search and classified studies for inclusion and entered and checked the data in RevMan and performed analyses. Data extraction was divided among T. A. Lawrie, A. Bryant, and T. Dowswell. T. Dowswell and A. Bryant graded the evidence. E. J. Fordham prepared the text on ivermectin mechanisms, use in pregnancy, and among the elderly. S. R. Hill prepared the brief economic commentary. Clinicians S. Mitchell and T. C. Tham contributed to the interpretation of the evidence in the discussion and conclusions. All authors reviewed and approved the final version of the manuscript.

This article discusses off-label use of the FDA-approved medication ivermectin against COVID-19.

**Address for correspondence: Population Health Sciences Institute, Newcastle University, Baddiley-Clark Building, Richardson Road, Newcastle Upon Tyne NE2 4AX, United Kingdom. E-mail: andy.bryant@ncl.ac.uk*

whereas effect estimates for "improvement" and "deterioration" clearly favored ivermectin use. Severe adverse events were rare among treatment trials and evidence of no difference was assessed as low certainty. Evidence on other secondary outcomes was very low certainty.

Conclusions: Moderate-certainty evidence finds that large reductions in COVID-19 deaths are possible using ivermectin. Using ivermectin early in the clinical course may reduce numbers progressing to severe disease. The apparent safety and low cost suggest that ivermectin is likely to have a significant impact on the SARS-CoV-2 pandemic globally.

Keywords: ivermectin, prophylaxis, treatment, COVID-19, SARS-CoV-2

INTRODUCTION

To date, very few treatments have been demonstrated to reduce the burden of morbidity and mortality from COVID-19. Although corticosteroids have been proven to reduce mortality in severe disease,[1] there has been little convincing evidence on interventions that may prevent disease, reduce hospitalizations, and reduce the numbers of people progressing to critical disease and death.

Ivermectin is a well-known medicine that is approved as an antiparasitic by the World Health Organization and the US Food and Drug Administration. It is widely used in low- and middle-income countries (LMICs) to treat worm infections.[2,3] Also used for the treatment of scabies and lice, it is one of the World Health Organization's Essential Medicines.[4] With total doses of ivermectin distributed apparently equaling one-third of the present world population,[5] ivermectin at the usual doses (0.2–0.4 mg/kg) is considered extremely safe for use in humans.[6,7] In addition to its antiparasitic activity, it has been noted to have antiviral and anti-inflammatory properties, leading to an increasing list of therapeutic indications.[8]

Since the start of the SARS-CoV-2 pandemic, both observational and randomized studies have evaluated ivermectin as a treatment for, and as prophylaxis against, COVID-19 infection. A review by the Front Line COVID-19 Critical Care Alliance summarized findings from 27 studies on the effects of ivermectin for the prevention and treatment of COVID-19 infection, concluding that ivermectin "demonstrates a strong signal of therapeutic efficacy" against COVID-19.[9] Another recent review found that ivermectin reduced deaths by 75%.[10] Despite these findings, the National Institutes of Health in the United States recently stated that "there are insufficient data to recommend either for or against the use of ivermectin for the treatment of COVID-19,"[11] and the World Health Organization recommends against its use outside of clinical trials.[12]

Ivermectin has exhibited antiviral activity against a wide range of RNA and some DNA viruses, for example, Zika, dengue, yellow fever, and others.[13] Caly et al[14] demonstrated specific action against SARS-CoV-2 in vitro with a suggested host-directed mechanism of action being the blocking of the nuclear import of viral proteins[14,15] that suppress normal immune responses. However, the necessary cell culture EC_{50} may not be achievable in vivo.[16] Other conjectured mechanisms include inhibition of SARS-CoV-2 3CLPro activity[17,18] (a protease essential for viral replication), a variety of anti-inflammatory effects,[19] and competitive *binding* of ivermectin with the viral S protein as shown in multiple *in silico* studies.[20] The latter would inhibit viral binding to ACE-2 receptors suppressing infection. Hemagglutination via viral binding to sialic acid receptors on erythrocytes is a recently proposed pathologic mechanism[21] that would be similarly disrupted. Both host-directed and virus-directed mechanisms have thus been proposed, the clinical mechanism may be multimodal, possibly dependent on disease stage, and a comprehensive review of mechanisms of action is warranted.

Developing new medications can take years; therefore, identifying existing drugs that can be repurposed against COVID-19 that already have an established safety profile through decades of use could play a critical role in suppressing or even ending the SARS-CoV-2 pandemic. Using repurposed medications may be especially important because it could take months, possibly years, for much of the world's population to get vaccinated, particularly among LMIC populations.

Currently, ivermectin is commercially available and affordable in many countries globally.[6] A 2018 application for ivermectin use for scabies gives a direct cost of $2.90 for 100 12-mg tablets.[22] A recent estimate from Bangladesh[23] reports a cost of US$0.60—US$1.80 for a 5-day course of ivermectin. For these reasons, the exploration of ivermectin's potential effectiveness against SARS-CoV-2 may be of particular importance

for settings with limited resources.[24] If demonstrated to be effective as a treatment for COVID-19, the cost-effectiveness of ivermectin should be considered against existing treatments and prophylaxes.

The aim of this review was to assess the efficacy of ivermectin treatment among people with COVID-19 infection and as a prophylaxis among people at higher risk of COVID-19 infection. In addition, we aimed to prepare a brief economic commentary (BEC) of ivermectin as treatment and as prophylaxis for COVID-19.[25]

METHODS

The conduct of this review was guided by a protocol that was initially written using Cochrane's rapid review template and subsequently expanded to a full protocol for a comprehensive review.[26]

Search strategy and selection criteria

Two reviewers independently searched the electronic databases of Medline, Embase, CENTRAL, Cochrane COVID-19 Study Register, and Chinese databases for randomized controlled trials (RCTs) up to April 25, 2021 (see **Appendix 1–3**, **Supplemental digital content 1**, http://links.lww.com/AJT/A95); current guidance[25] for the BEC was followed for a supplementary search of economic evaluations. There were no language restrictions, and translations were planned to be performed when necessary.

We searched the reference list of included studies, and of two other 2021 literature reviews on ivermectin,[9] as well as the recent WHO report, which included analyses of ivermectin.[12] We contacted experts in the field (Drs. Andrew Hill, Pierre Kory, and Paul Marik) for information on new and emerging trial data. In addition, all trials registered on clinical trial registries were checked, and trialists of 39 ongoing trials or unclassified studies were contacted to request information on trial status and data where available. Many preprint publications and unpublished articles were identified from the preprint servers MedRχiv and *Research Square*, and the International Clinical Trials Registry Platform. This is a rapidly expanding evidence base, so the number of trials are increasing quickly. Reasons for exclusion were recorded for all studies excluded after full-text review.

Data analysis

We extracted information or data on study design (including methods, location, sites, funding, study author declaration of interests, and inclusion/exclusion criteria), setting, participant characteristics (disease severity, age, gender, comorbidities, smoking, and occupational risk), and intervention and comparator characteristics (dose and frequency of ivermectin/comparator). The primary outcome for the intervention component of the review included death from any cause and presence of COVID-19 infection (as defined by investigators) for ivermectin prophylaxis. Secondary outcomes included time to polymerase chain reaction (PCR) negativity, clinical recovery, length of hospital stay, admission to hospital (for outpatient treatment), admission to ICU or requiring mechanical ventilation, duration of mechanical ventilation, and severe or serious adverse events, as well as post hoc assessments of improvement and deterioration. All of these data were extracted as measured and reported by investigators. Numerical data for outcomes of interest were extracted according to intention to treat.

If there was a conflict between data reported across multiple sources for a single study (eg, between a published article and a trial registry record), we contacted the authors for clarification. Assessments were conducted by 2 reviewers (T.L., T.D., A.B., or G.G.) using the Cochrane RCT risk-of-bias tool.[27] Discrepancies were resolved by discussion.

Continuous outcomes were measured as the mean difference and 95% confidence intervalss (CI), and dichotomous outcomes as risk ratio (RR) and 95% CI.

We did not impute missing data for any of the outcomes. Authors were contacted for missing outcome data and for clarification on study methods, where possible, and for trial status for ongoing trials.

We assessed heterogeneity between studies by visual inspection of forest plots, by estimation of the I^2 statistic ($I^2 \geq 60\%$ was considered substantial heterogeneity),[28] by a formal statistical test to indicate statistically significant heterogeneity,[29] and, where possible, by subgroup analyses (see below). If there was evidence of substantial heterogeneity, the possible reasons for this were investigated and reported. We assessed reporting biases using funnel plots if more than 10 studies contributed to a meta-analysis.

We meta-analyzed data using the random effects model (DerSimonian and Laird method)[30] using RevMan 5.4.1 software.[27,31] The results used the inverse variance method for weighting.[27] Some sensitivity analyses used other methods that are outlined below and some calculations were performed in *R*[32] through an interface[33] to the *netmeta* package.[34] Where possible, we performed subgroup analyses grouping trials by disease severity, inpatients versus outpatients, and single dose versus multiple doses. We performed sensitivity analyses by excluding studies at high risk of bias. We conducted further post hoc sensitivity analyses using alternative methods to test the robustness of results in the presence of zero events in both arms in a number of trials[35] and estimated odds ratios [and additionally RR for the Mantel–Haenszel

(MH) method] using a fixed effects model. The models incorporate evidence from single-zero studies without having to resort to continuity corrections. However, double-zero studies are excluded from the analysis; so, the risk difference was also assessed using the MH method as this approach can adequately incorporate trials with double-zero events. This method can also use a random-effects component. A "treatment-arm" continuity correction was used, where the values 0.01, 0.1, and 0.25 were added where trials reported zero events in both arms. It has been shown that a nonfixed continuity correction is preferable to the usual 0.5.[35] Other methods are available but were not considered due to difficulty in interpretation, sensitivity of assumptions, or the fact they are rarely used in practice.[36–40]

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]

RESULTS

Search results and risk-of-bias assessment

The combined and preliminary deduplicated total was n = 583. We also identified 11 records from other sources (reference lists, etc). See PRISMA flow diagram for inclusion and exclusion details of these references (Figure 1).

The supplementary search for the BEC identified 17 studies, of which 4 were retrieved in full. No full trial- or model-based economic evaluations (cost–utility analyses, cost–effectiveness analyses, or cost–benefit analyses) were identified.

Twenty-one trials in treatment and 2 trials in prophylaxis of COVID-19 met review inclusion. One further study[47] reported separate treatment and prophylaxis components; we label this study "Elgazzar" under both questions. In effect, there were 22 trials in treatment and 3 in prophylaxis. All of these contributed data to at least one review outcome and meta-analysis. Fifteen trials contributed data for the primary outcome for ivermectin treatment (death); 3 studies reported the primary outcome for prophylaxis (COVID-19 infection). Characteristics of included studies are given in Table 1. Seventeen studies[47–63] were excluded as they were not RCTs and we identified 39 ongoing studies[64–102] and 2 studies[103,104] are awaiting classification.

A risk-of-bias summary graph is given in Figure 2. Eleven studies[23,24,44,47,105,106–111] used satisfactory random sequence generation and allocation concealment. Two trials described satisfactory sequence generation, but it was unclear whether allocation was concealed.[112,113]

Ten trials reported adequate blinding of the participants/personnel and/or the outcome assessors.[23,24,44,105,107,109,110,111,113,114] The others were either unclear or high risk for blinding. We considered blinding to be a less important criterion for evaluation of evidence related to the review's primary outcomes, namely death and laboratory-confirmed COVID-19 infection, which are objective outcomes.

We did not consider publication on preprint web sites to constitute a risk of bias because all studies were scrutinized and peer reviewed by us during the review process and, where additional information was needed, we contacted the authors for clarification.

Main findings

Twenty-four RCTs (including 3 quasi-RCTs) involving 3406 participants were included, with sample sizes ranging from 24 to 476 participants. Twenty-two trials in treatment and 3 trials in prophylaxis met review inclusion, including the trial of Elgazzar et al, which reported both components. For trials of COVID-19 treatment, 16 evaluated ivermectin among participants with mild to moderate COVID-19 only; 6 trials included patients with severe COVID-19. Most compared ivermectin with placebo or no ivermectin; 3 trials included an active comparator (Table 1). Three RCTs involving 738 participants were included in the prophylaxis trials. Most trials were registered, self-funded, and undertaken by clinicians working in the field. There were no obvious conflicts of interest noted, with the exception of two trials.[85,139]

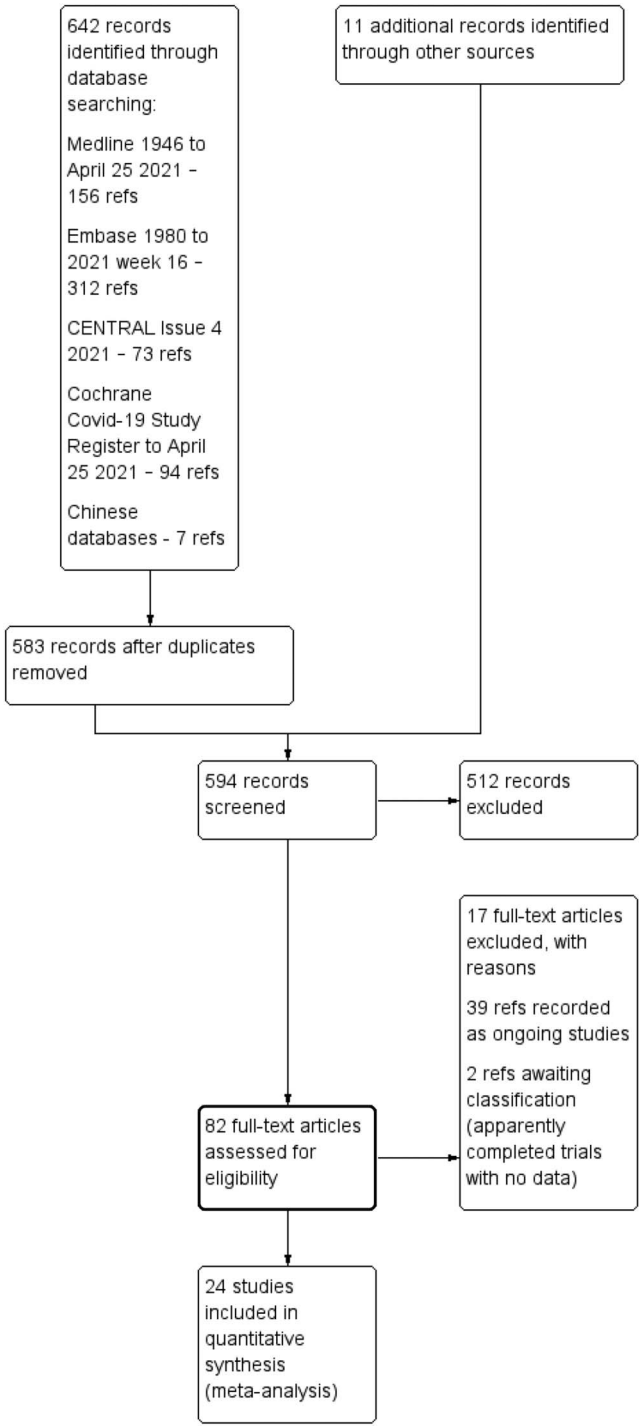


FIGURE 1. Study flow diagram from search on 25 April 2021.

Table 1. Summary of study characteristics.

Study ID	Country	Design	Funding	Participants	Sample size	Ivermectin dose and frequency*	Comparator	Origin of data	Main outcomes reported
COVID-19 treatment studies									
Ahmed 2020[23]	Bangladesh	Double-blind	BPL(Pharma); Bangladesh, Canada, Sweden, and UK govt	Mild to moderate COVID (inpatients)	72	12 mg × 1 day or × 5 days (3 study arms)*	Placebo	Published in PR journal; emailed/ responded with data	Time to viral clearance (PCR –ve), remission of fever and cough within 7 days, duration of hospitalization, mortality, failing to maintain sats >93%, adverse events, PCR –ve at 7 and 14 days
Babalola 2020[105]	Nigeria	Double-blind	Self-funded	Asymptomatic, mild or moderate COVID (45 inpatients and 17 outpatients)	62	6 mg every 84 hrs × 2 wks (arm 1) or 12 mg every 84 hrs × 2 wks (arm 2)	Ritonavir/lopinavir	MedRxiv preprint: emailed/ responded with data. Paper accepted for publication	Time to PCR –ve, laboratory parameters (platelets, lymphocytes, clotting time), clinical symptom parameters
Bukhari 2021[135]	Pakistan	Open-label	None reported	Mild to moderate COVID (inpatients)	100	12 mg × 1 dose	SOC	MedRxiv preprint	Viral clearance, any adverse side effects, mechanical ventilation
Chaccour 2020[24]	Spain	Double-blind	Idapharma, ISGlobal, and the University of Navarra	Mild COVID (outpatients)	24	0.4 mg/kg × 1 dose	Placebo	Published in PR journal	PCR +ve at day 7, proportion symptomatic at day 4,7,14,21, progression, death, adverse events
Chachar 2020[112]	Pakistan	Open-label	Self-funded	Mild COVID (outpatients)	50	12 mg at 0, 12, and 24 hours (3 doses)	SOC	Published in PR journal	Symptomatic at day 7
Chowdhury 2020[136]	Bangladesh	Quasi-RCT	None reported	Outpatients with a +ve PCR (approx. 78% symptomatic)	116	0.2 mg/kg x1 dose*	HCQ 400 mg 1st day then 200 mg BID × 9 days + AZM 500 mg daily × 5 days	Research square preprint	Time to –ve PCR test; period to symptomatic recovery; adverse events
Elgazzar 2020[47]	Egypt	RCT	None reported	Mild to severe COVID (inpatients)	200	0.4 mg/kg daily × 4 days	HCQ 400 mg BID × 1 day then 200 mg BID × 9 days	Research square preprint: emailed/ responded with data	Improved, progressed, died. Also measured CRP, D-dimers, HB, lymphocyte, serum ferritin after one week of treatment
Fonseca 2021[44]	Brazil	Double-blind	Institution-funded	Moderate to severe (inpatients)	167	14 mg daily × 3 days (plus placebos × 2 additional days)	HCQ—400 mg BID on day 0 then daily × 4 days; CQ -450 mg BID day 0 then daily × 4 days	Prepublication data/ manuscript in progress obtained via email	Death, invasive mechanical ventilation
Gonzalez 2021[137]	Mexico	Double-blind	Institution-funded	Moderate to severe (inpatients)	108	12 mg × 1 dose	Placebo	MedRxiv preprint	Length of hospital stay, invasive mechanical ventilation, death, time to negative PCR
Hashim 2020[138]	Iran	Quasi-RCT	None reported	Mild to critical (inpatients)	140	0.2 mg/kg × 2 days* Some had a 3rd dose a week later	SOC	MedRxiv preprint	Death, mean time to recovery, disease progression (deterioration)
Krolewiecki 2020[106]	Argentina	Open-label	None reported	Mild to moderate (inpatients)	45	0.6 mg/kg/d × 5 days	Placebo	Research Gate and SSRN preprints	Viral load reduction in respiratory secretions day 5, IVM concentrations in plasma, severe adverse events
Lopez-Medina 2021[85]	Columbia	Double-blind	Institution-funded	Mild (outpatients)	476	0.3 mg/kg elixir × 5 days	Placebo	Published in a PR journal	Resolution of symptoms within 21 days, deterioration, clinical condition, hospitalization, adverse events
Mahmud 2020[107]	Bangladesh	Double-blind	None reported	Mild to moderate COVID (inpatients)	363	12 mg × 1 dose*	Placebo + SOC	Data published on clinical trial registry and clarification obtained via email	Improvement, deterioration, late clinical recovery, persistent PCR test +ve

(*Continued on next page*)

Table 1. (*Continued*) Summary of study characteristics.

Study ID	Country	Design	Funding	Participants	Sample size	Ivermectin dose and frequency*	Comparator	Origin of data	Main outcomes reported
Mohan 2021[110]	India	Double-blind	Institution-funded	Mild to moderate	152	12 mg or 24 mg elixir × 1 dose	Placebo	MedRxiv preprint research	Conversion of RT-PCR to negative result, decline of viral load at day 5 from enrollment
Niaee 2020[108]	Iran	Double-blind	Institution-funded	Mild to severe COVID	180	0.2 mg/kg × 1 and 3 other dosing options) ~ 14 mg tablet†	Placebo	Research Square preprint	Deaths, length of stay, biochemical parameters
Okumus 2021[115]	Turkey	Quasi-RCT	None reported	Severe COVID	66	0.2 mg/kg × 5 days	SOC	Prepublication data/ manuscript in progress obtained via email	Clinical improvement, deterioration, death, SOFA scores
Petkov 2021[139]	Bulgaria	Double-blind	Pharma-funded	Mild to moderate COVID	100	0.4 mg/kg × 3 days	Placebo	Prepublication data obtained from another source	Rate of conversion to PCR negative
Podder 2020[140]	Bangladesh	Open-label	Self-funded	Mild to moderate (outpatients)	62	0.2 mg/kg × 1 dose	SOC	Published in PR journal	Duration of symptoms, recovery time to symptom free from enrollment, recovery time to symptom free from symptom onset, repeat PCR result on day 10
Raad 2021[113]	Lebanon	Double-blind	Self-funded	Asymptomatic outpatients	100	9 mg PO if 45 kg–64 kg, 12 mg PO if 65 kg–84 kg and 0.15 mg/kg if body weight ≥85 kg	Placebo	Prepublication data/ manuscript in progress obtained via email	Viral load reduction, hospitalization, adverse effects
Ravikirti 2021[109]	India	Double-blind	Self-funded	Mild to moderate COVID (inpatients)	112	12 mg × 2 days + SOC	Placebo + SOC	Published in PR journal	A negative RT-PCR report on day 6, symptomatic on day 6, discharge by day 10, admission to ICU, need for invasive mechanical ventilation, mortality
Rezai 2020[111]	Iran	Double-blind	None reported	Mild to moderate (inpatient)	60	0.2 mg/kg × 1 dose	SOC	Prepublication data obtained from another source	Clinical symptoms, respiratory rate and O2 saturation
Schwartz 2021[114,141]	Israel	Double-blind	None reported	Mild to moderate (outpatients)	94	0.15–0.3 mg/kg × 3 days	Placebo	Prepublication data obtained from another source	Viral clearance at day 4, 6, 8 and 10), hospitalization
COVID-19 prophylaxis studies									
Chahla 2021[142]	Argentina	Open-label	None reported	Health care workers	234	12 mg (in drops) weekly + iota-carrageenan 6 sprays daily × 4 wk	SOC	Prepublication data/ manuscript in progress obtained via email	COVID-19 infection (not clear if measured by PCR or symptoms)
Elgazzar 2020[47]	Egypt	Open-label	Self-funded	Health care and family contacts	200	0.4 mg/kg, weekly × 2 weeks	SOC	Research square preprint: emailed/ responded with data	Positive PCR test
Shouman 2020[143]	Egypt	Open-label	Self-funded	Family contacts	304	2 doses (15–24 mg depending on weight) on day 1 and day 3	SOC	Published in PR journal	Symptoms and/or positive COVID-19 PCR test within 14 days; adverse events

*Also administered doxycycline.
†multiarm trial.
SOC, standard of care; PR, peer review.

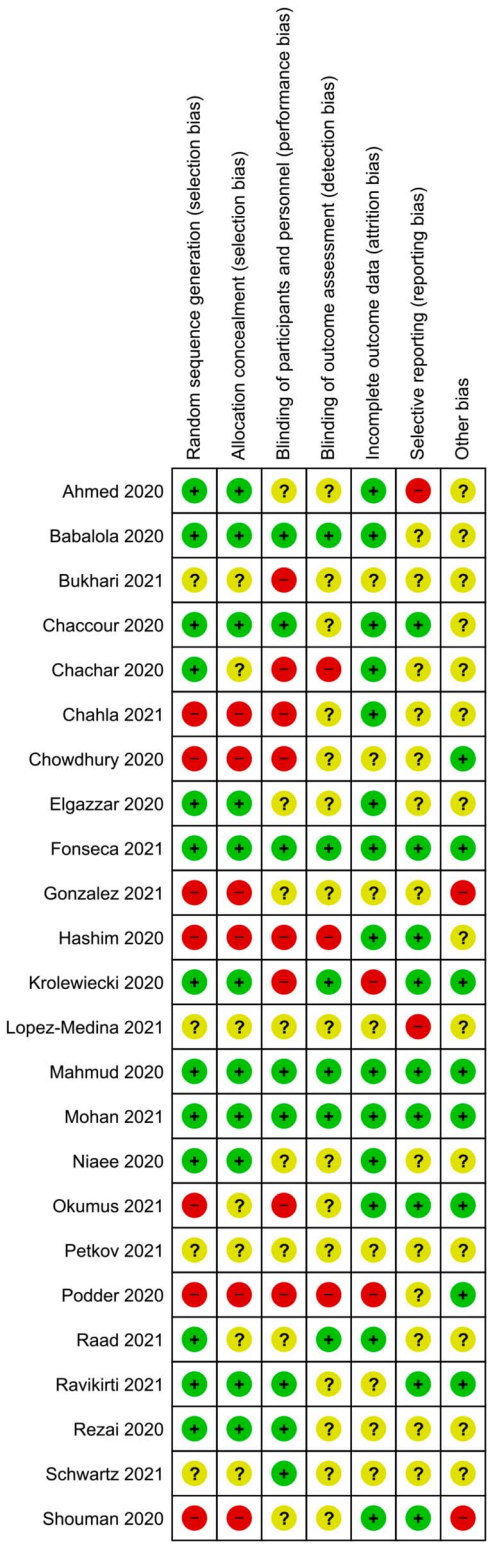


FIGURE 2. Risk-of-bias summary: review authors' judgments about each risk of bias item for each included study.

Ivermectin treatment versus no ivermectin treatment

Twenty-two trials (2668 participants) contributed data to the comparison ivermectin treatment versus no ivermectin treatment for COVID-19 treatment.

All-cause mortality

Meta-analysis of 15 trials, assessing 2438 participants, found that ivermectin reduced the risk of death by an average of 62% (95% CI 27%–81%) compared with no ivermectin treatment [average RR (aRR) 0.38, 95% CI 0.19 to 0.73; $I^2 = 49\%$]; risk of death 2.3% versus 7.8% among hospitalized patients in this analysis, respectively (SoF Table 2 and Figure 3). Much of the heterogeneity was explained by the exclusion of one trial[44] in a sensitivity analysis (average RR 0.31, 95% CI 0.17–0.58, n = 2196, $I^2 = 22\%$), but because this trial was at low risk of bias, it was retained in the main analysis. The source of heterogeneity may be due to the use of active comparators in the trial design. The results were also robust to sensitivity analyses excluding 2 other studies with an active treatment comparator (average RR 0.41, 95% CI 0.23–0.74, n = 1809, $I^2 = 8\%$). The results were also not sensitive to the exclusion of studies that were potentially at higher risk of bias (average RR 0.29, 95% CI 0.10–0.80, 12 studies, n = 2095, $I^2 = 61\%$), but in subgroup analysis, it was unclear as to whether a single dose would be sufficient. The effect on reducing deaths was consistent across mild to moderate and severe disease subgroups. Subgrouping data according to inpatient and outpatient trials was not informative because few outpatient studies reported this serious outcome. The conclusions of the primary outcome were also robust to a series of alternative post hoc analyses that explored the impact of numerous trials that reported no deaths in either arm. Extreme sensitivity analyses using a treatment arm continuity correction of between 0.01 and 0.5 did not change the certainty of the evidence judgments (Table 3).

Trial sequential analysis

TSA, using the DL random-effects method, showed that there may have been sufficient evidence accrued before the end of 2020 to show significant benefit of ivermectin over control for all-cause mortality. The cumulative z-curve in Figure 8 crossed the trial sequential monitoring boundaries after reaching the required IS, implying that there is firm evidence for a beneficial effect of ivermectin use over no ivermectin use in mainly hospitalized participants with mild to moderate COVID-19 infection.

Table 2. Summary of findings table of ivermectin versus no ivermectin for COVID-19 treatment in any setting.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk No ivermectin	Corresponding risk Ivermectin			
Death from any cause	78 per 1000 (all disease severity)	48 fewer deaths per 1000 (21–63)	RR = 0.38 (0.19–0.73)	2438 (15)	Moderate†
Recovery time to negative PCR test, in days	Absolute risks were not computed due to certainty of evidence being low and, in some cases, number of events being sparse		MD = −3.20 (−5.99 to −0.40)	375 (6)	Very low†,‡,§
Time to clinical recovery, in days (outpatients)			MD = −1.06 (−1.63 to −0.49)	176 (2)	Very low†,‡,§
Time to clinical recovery, in days (mild to moderate COVID-19 inpatients)			MD = −7.32 (−9.25 to −5.39)	96 (1)	Very low†,¶
Time to clinical recovery, in days (severe COVID-19 inpatients)			MD = −3.98 (−10.06 to 2.10)	33 (1)	Very low†,¶
Admission to ICU			RR=1.22 (0.75–2.00)	379 (2)	Very low¶,‖
Need for mechanical ventilation			RR=0.66 (0.14–3.00)	431 (3)	Low§,‖
Length of hospital stay, in days			MD= 0.13 (−2.04 to 2.30)	68 (1)	Very low†,¶
Admission to hospital			RR 0.16 (0.02–1.32)	194 (2)	Very low†,¶
Duration of mechanical ventilation	Not reported				
Improvement (mild to moderate COVID-19)*	635 improved per 1000	159 more per 1000 (from 51 more to 286 more)	RR 1.25 (1.08–1.45)	681 (5)	Low†,‡
Deterioration (any disease severity)	143 per 1000	93 fewer per 1000 (from 50 fewer to 116 fewer)	RR 0.35 (0.19–0.65)	1587 (7)	Low†,‡
Serious adverse events	7/867 (0.8%) had an SAE in ivermectin group and 2/666 (0.3%) in control		RR=1.65 (0.44–6.09)	1533 (11)	Low†,‡

*Only one study contributed to the "severe" COVID-19 subgroup and subgroup data were not pooled due to subgroup differences.
†Downgraded −1 for study design limitations.
‡Downgraded −1 for inconsistency.
§Downgraded −1 for imprecision.
¶Downgraded −2 for imprecision/sparse data.
‖Downgraded −1 for indirectness.

The TSA was used to calculate the IS required to demonstrate or reject a 62% RRR of death in the ivermectin group, as observed in the primary meta-analysis. This estimate is similar to effect estimates reported in other reviews.[10] We assumed a 7.8% event proportion in the control group, which was the average control group

Table 3. Sensitivity analyses for death from any cause considering methods for dealing with zero events in trials.

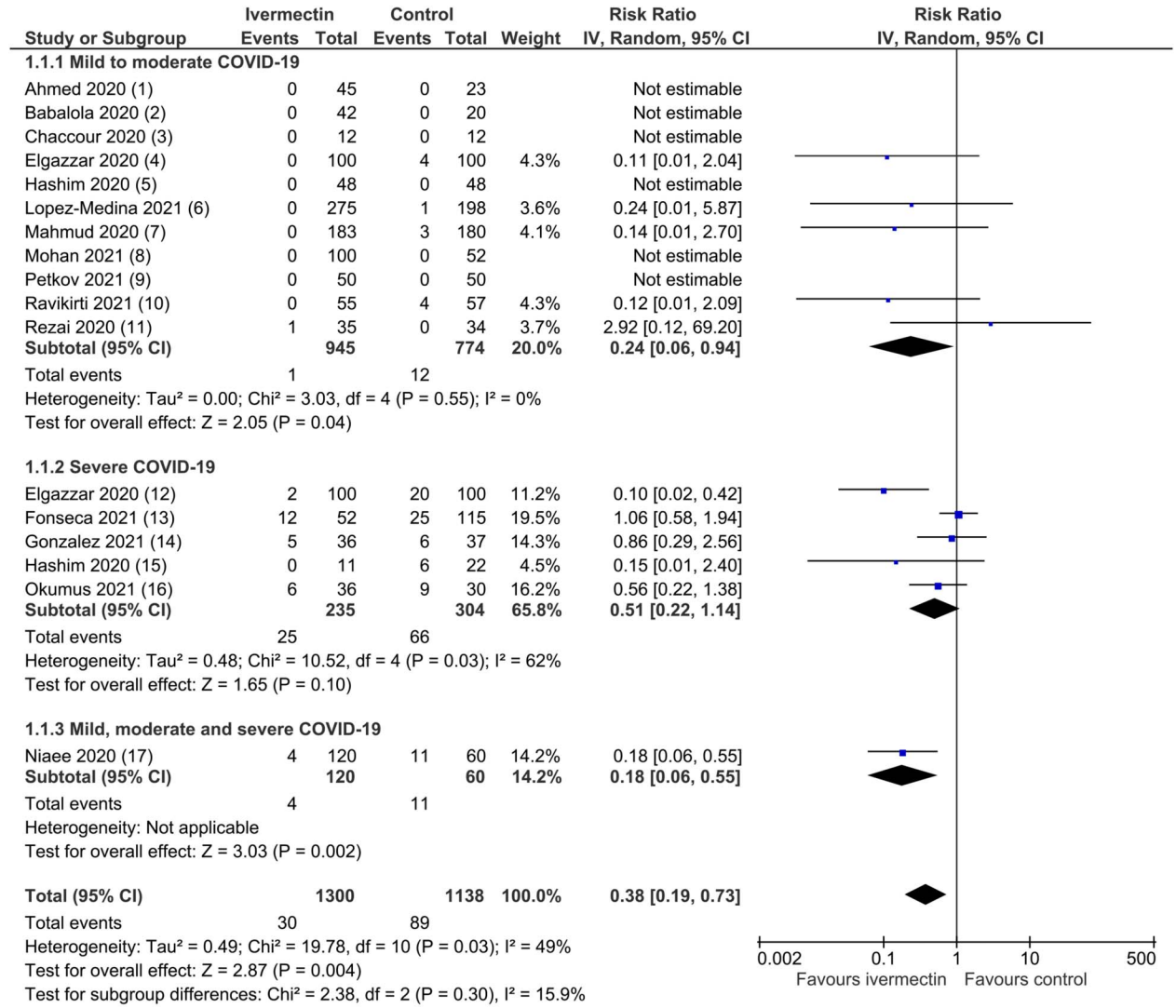
Method	Measure	Model	Effect size (95% CI)	Details
Peto	OR	FE	0.35 (0.24 to 0.53)	Handles single-zero trials
M-H	OR	FE	0.37 (0.24 to 0.56)	Handles single-zero trials
M-H	OR	RE	0.33 (0.16 to 0.68)	Handles single-zero trials
M-H	RR	FE	0.42 (0.29 to 0.60)	Handles single-zero trials
M-H	RR	RE	0.37 (0.19 to 0.74)	Handles single-zero trials
M-H	RD	FE	−0.04 (−0.06 to −0.02)	Handles double-zero trials
M-H	RD	RE	−0.03 (−0.06 to −0.00)	Handles double-zero trials
IV	RD	FE	−0.01 (−0.02 to −0.00)	Handles double-zero trials
IV	RD	RE	−0.02 (−0.04 to −0.00)	Handles double-zero trials
Treatment arm continuity correction methods using IV			Accounting for double zeros	Accounting for all zeros
0.01	RR	FE	0.54 (0.36 to 0.79)	0.58 (0.39–0.88)
0.01	RR	RE	0.43 (0.25 to 0.72)	0.58 (0.39–0.88)
0.1	RR	FE	0.54 (0.37 to 0.79)	0.56 (0.38–0.84)
0.1	RR	RE	0.43 (0.26 to 0.73)	0.46 (0.26–0.80)
0.25	RR	FE	0.54 (0.37 to 0.79)	0.55 (0.37–0.81)
0.25	RR	RE	0.44 (0.26 to 0.73)	0.45 (0.26–0.76)
0.5	RR	FE	0.54 (0.37 to 0.79)	0.55 (0.35–0.78)
0.5	RR	RE	0.45 (0.27 to 0.74)	0.47 (0.29–0.75)

FE, fixed effects; IV, inverse variance; M-H, Mantel-Haenszel; RD, risk difference; RE, random effects; TACC, treatment arm continuity correction.

event rate from the primary meta-analysis. We used a model variance-based estimate of 49.1% (diversity estimate) to correct for heterogeneity. The required IS was 1810 participants (Figure 8), which was exceeded by the total number of observed participants in the meta-analysis (n = 2438). In the TSA plots, the red dashed lines in Figure 8 represent the trial sequential monitoring boundaries using the O'Brien–Fleming alpha-spending function. The solid blue line is the cumulative z-curve and represents the observed trials in the cumulative meta-analysis. The adjusted significance boundaries for the cumulative z-curve were constructed under the assumption that significance testing may have been performed each time a new trial was added to the meta-analysis. In Figure 8, the z-curve crosses the boundary after reaching the required IS, thereby supporting the previous conclusion in RevMan 5.4.1[31] using the DL method that ivermectin is superior to control in reducing the risk of death.

Sensitivity analyses

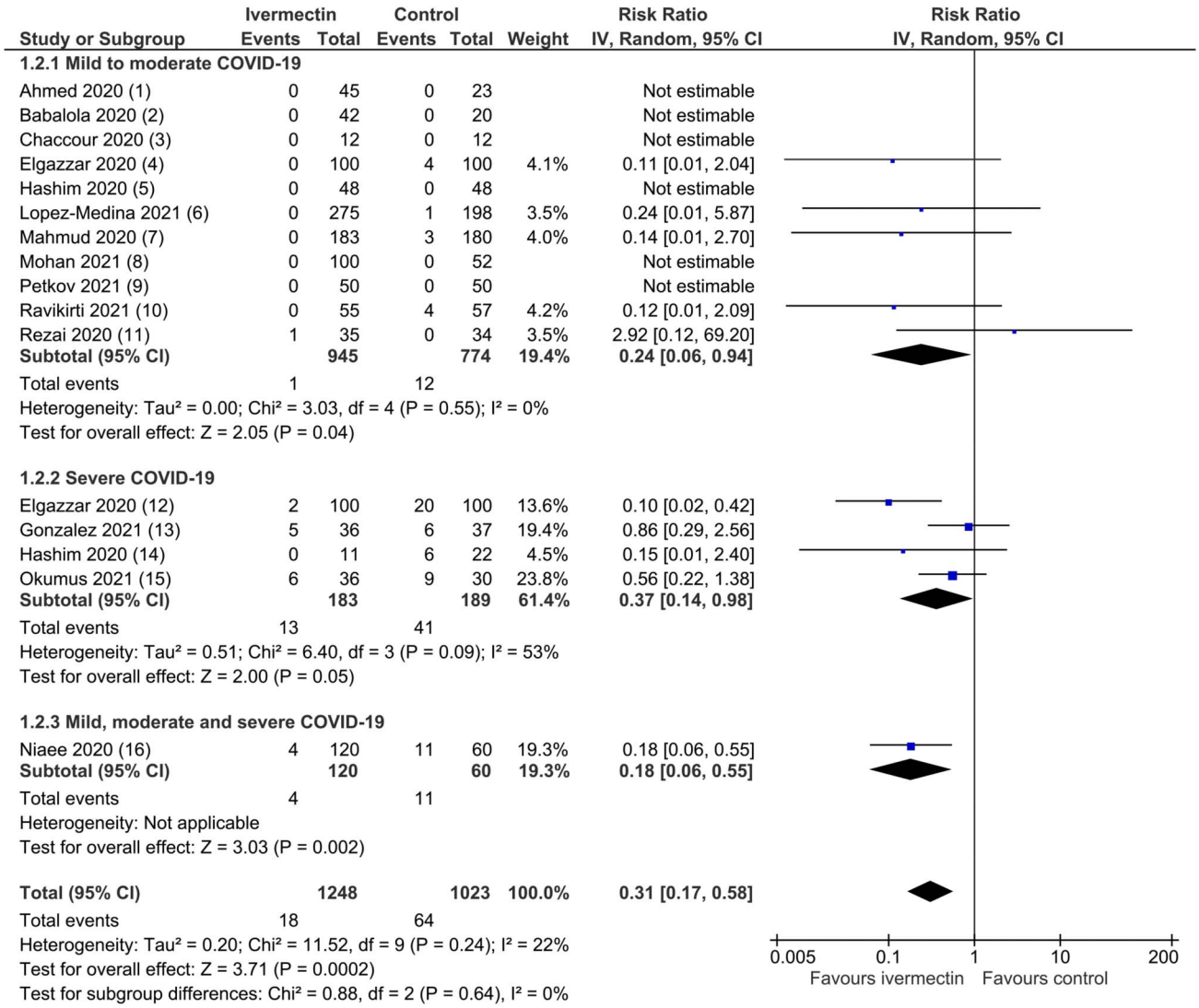
Sensitivity analysis excluding the trial of Fonseca[44] significantly reduced heterogeneity in the meta-analysis and thus the diversity estimate in the TSA using the DL model. This strengthened the suggestion in the primary core analysis that the required IS had been reached (Figure 9). Because the DL estimator could potentially underestimate the between-trials variance,[43] we performed further sensitivity analyses using 2 alternative random-effects model approaches. The results of the primary TSA analysis were robust to sensitivity analysis using the BT method with the same parameters, excluding the Fonseca[44] trial, which was a cause of substantial heterogeneity (Figure 10). The TSA



Footnotes

(1) IVM 12mg x 5 days (24 pts) or IVM 12 mg + doxy x 5 days (24 pts)
(2) IVM 6mg-12mg every 84 hrs for 2 wks; vs lopinavir/ritonavir
(3) IVM 0.4mg/kg single dose
(4) IVM up to 24 mg daily for 4 days vs HCQ
(5) IVM 0.2mg/kg x 2-3 days + Doxy 100 mg BID x 10 days
(6) IVM 0.3mg/kg solution for 5 days vs placebo solution
(7) IVM 6mg once + Doxy 100 mg x 5 days
(8) IVM 12mg or 24 mg single dose
(9) IVM 0.4mg/kg x 3 days
(10) IVM 12 mg x 2 days
(11) IVM 0.2mg/kg single dose
(12) IVM up to 24 mg daily for 4 days vs HCQ
(13) IVM 14 mg x 3 days vs HCQ x 5 days or CQ x 5 days
(14) IVM single dose 12mg or 18mg depending on weight
(15) IVM 0.2mg/kg x 2-3 days + Doxy 100 mg BID x 10 days
(16) IVM 0.2mg/kg x 5 days (both arms received HCQ, favipiravir, azithromycin)
(17) IVM 0.2mg/kg to 400 µgm/kg (1 to 3 doses) vs HCQ

FIGURE 3. Death due to any cause.



Footnotes

(1) IVM 12mg x 5 days (24 pts) or IVM 12 mg + doxy x 5 days (24 pts)
(2) IVM 6mg-12mg every 84 hrs for 2 wks; vs lopinavir/ritonavir
(3) IVM 0.4mg/kg single dose
(4) IVM up to 24 mg daily for 4 days vs HCQ
(5) IVM 0.2mg/kg x 2-3 days + Doxy 100 mg BID x 10 days
(6) IVm 0.3mg/kg for 5 days
(7) IVM 6mg once + Doxy 100 mg x 5 days
(8) IVM 12mg or 24 mg single dose
(9) IVM 0.4mg/kg x 3 days
(10) IVM 12 mg x 2 days
(11) IVM 0.2mg/kg single dose
(12) IVM up to 24 mg daily for 4 days vs HCQ
(13) IVM single dose 12mg or 18mg depending on weight
(14) IVM 0.2mg/kg x 2-3 days + Doxy 100 mg BID x 10 days
(15) IVM 0.2mg/kg x 5 days (both arms received HCQ, favipiravir, azithromycin)
(16) IVM 0.2mg/kg to 400 µgm/kg (1 to 3 doses) vs HCQ

FIGURE 4. Death due to any cause, excluding an outlier study responsible for the heterogeneity.

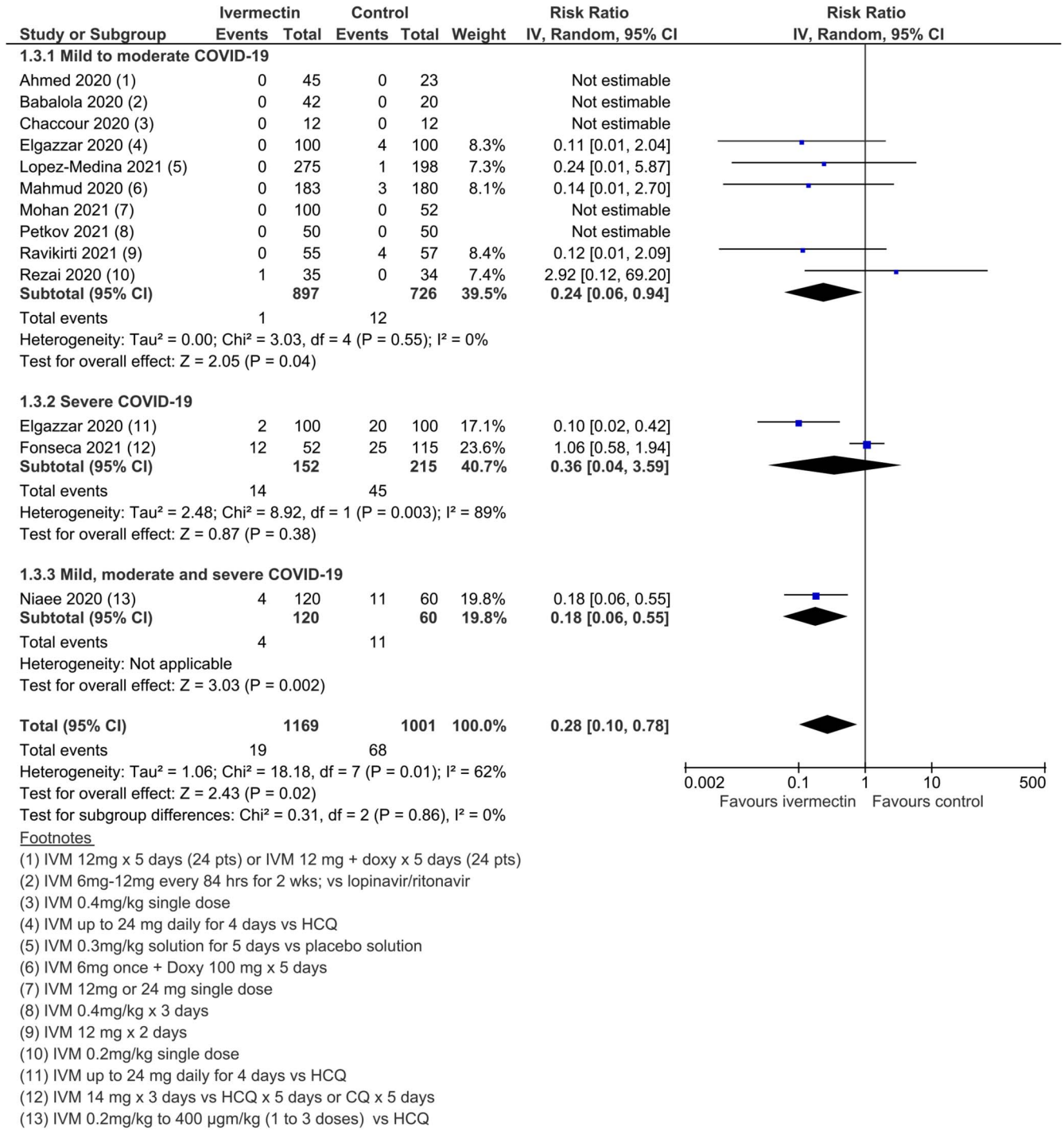


FIGURE 5. Death due to any cause, excluding high risk-of-bias studies.

comprehensively confirms the result of the conventional meta-analysis. The required IS was 1064.

The required IS was not reached in the TSA using the SJ method, largely because diversity from the model was high (Figure 11). The SJ estimator may overestimate the between-trials variance in meta-analyses with mild heterogeneity, thus producing artificially wide confidence intervals.[43] When the diversity estimate was reduced to the same as in the DL model, the required IS was reached in the SJ model (data not shown). There was no evidence of futility using the SJ method in any scenario.

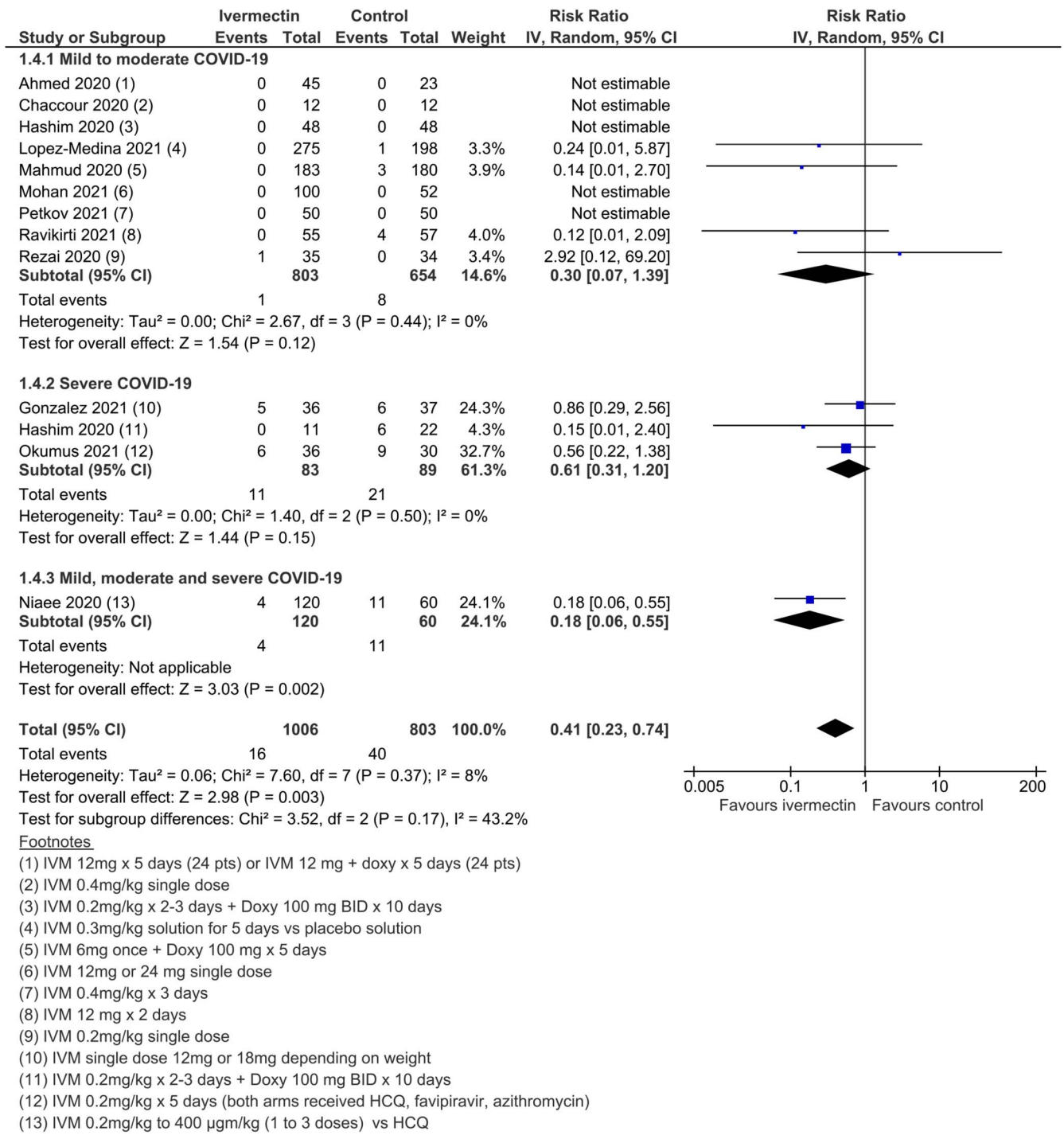


FIGURE 6. Death due to any cause, excluding studies with active controls.

Certainty of the evidence for all-cause mortality

Overall, death from any cause, taking into account all composite analyses, was judged to provide moderate-certainty evidence (SoF Table 2 and Figures 4–11). A funnel plot corresponding to the primary outcome of death from any cause did not seem to suggest any evidence of publication bias (Figure 7). Furthermore, the ease with which trial reports can be uploaded as preprints should reduce this risk.

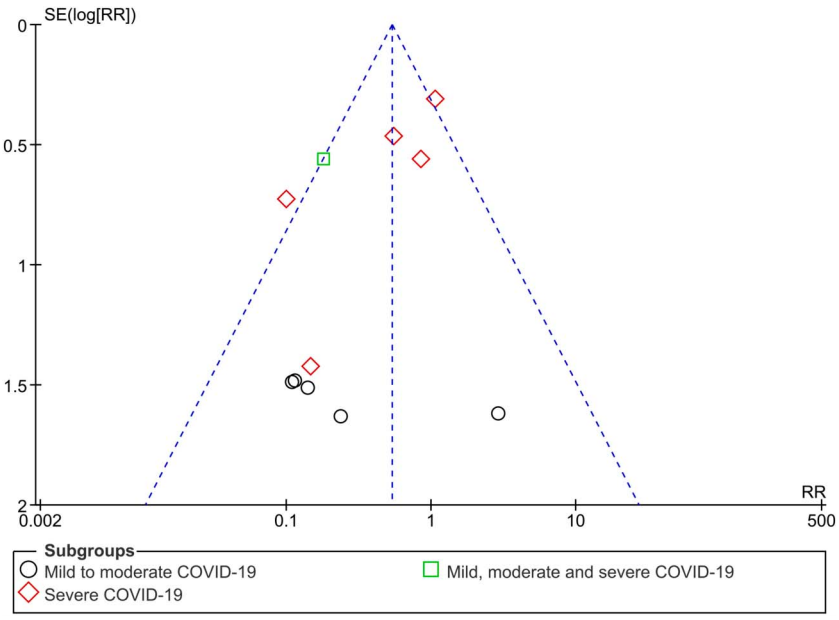


FIGURE 7. Funnel plot of ivermectin versus control for COVID-19 treatment for all-cause death (subgrouped by severity).

Secondary outcomes

Secondary outcomes provided low to very low certainty evidence (SoF Table 2). Low-certainty findings suggested that there may be no benefit with ivermectin for "need for mechanical ventilation," whereas effect estimates for "improvement" and "deterioration" favored ivermectin but were graded as low certainty due to study design limitations and inconsistency (Figures 12–14). All other secondary outcome findings were assessed as very low certainty.

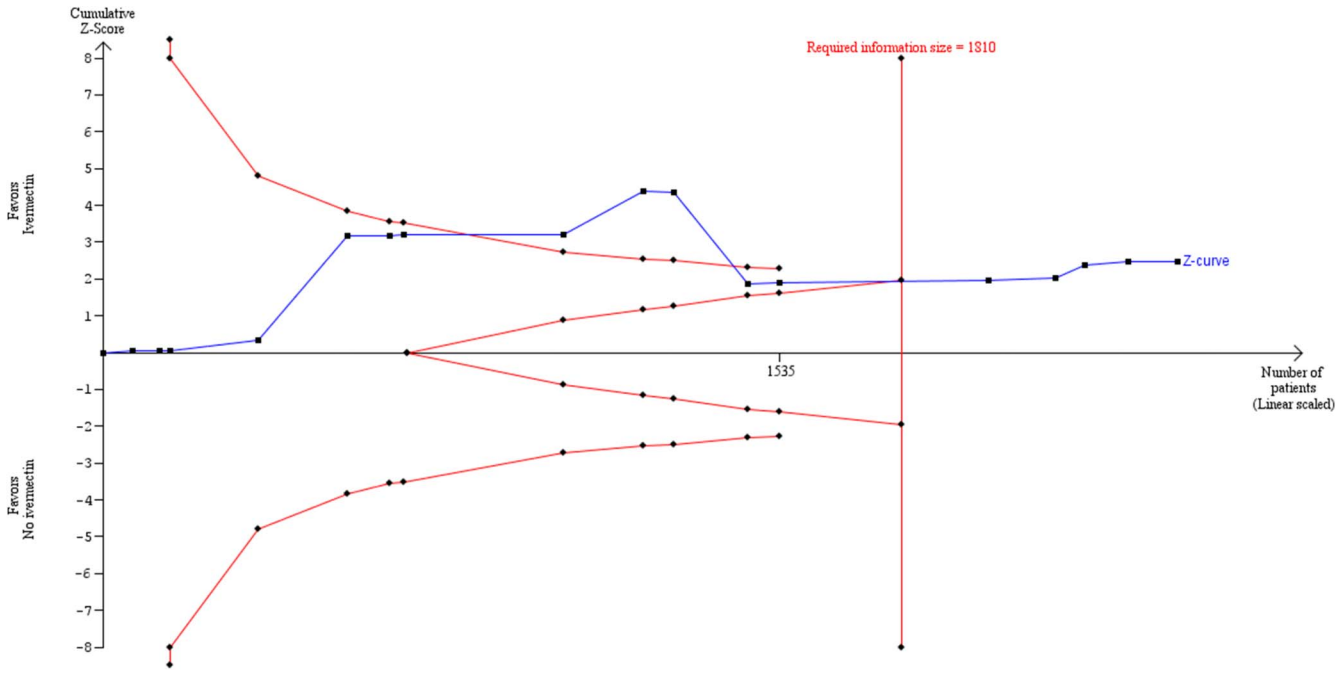


FIGURE 8. Trial sequential analysis using DL random-effects method with parameter estimates of $\alpha = 0.05$, $\beta = 0.1$, control rate = 7.8%, RRR = 62%, and diversity = 49.5%.

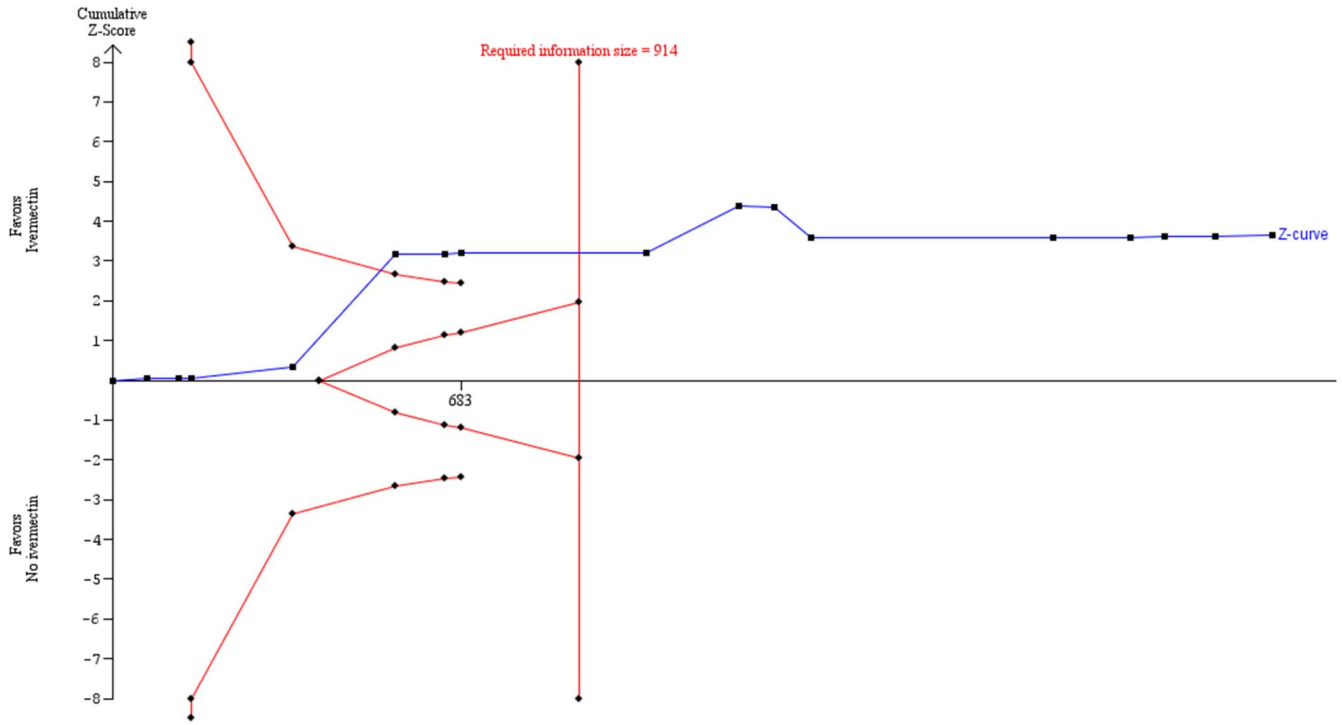


FIGURE 9. Sensitivity analysis excluding an outlier study responsible for the heterogeneity, showing trial sequential analysis using DL random-effects method with parameter estimates of $\alpha = 0.05$, $\beta = 0.1$, control rate = 7.8%, = 62%, and diversity = 0%.

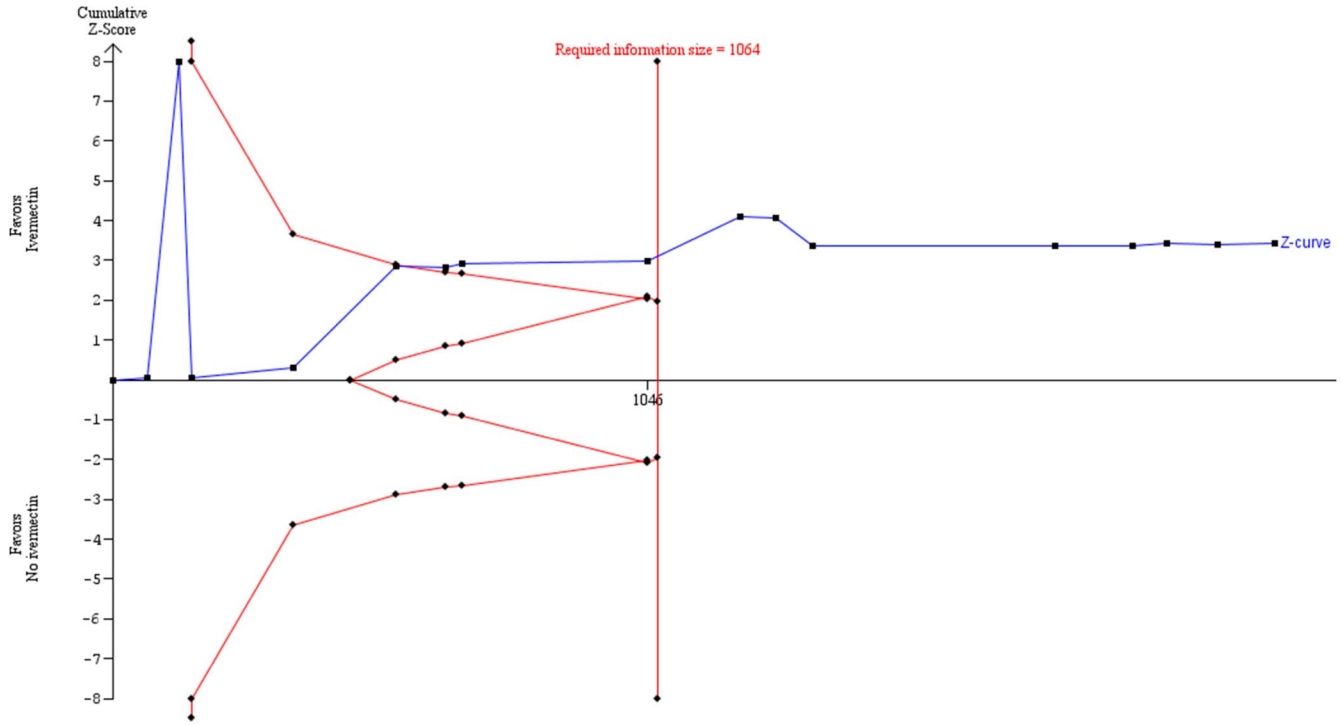


FIGURE 10. Sensitivity analysis excluding an outlier study responsible for the heterogeneity, showing trial sequential analysis using Biggerstaff–Tweedie random-effects method with parameter estimates of $\alpha = 0.05$, $\beta = 0.1$, control rate = 7.8%, RRR = 62%, and diversity = 14.2%.

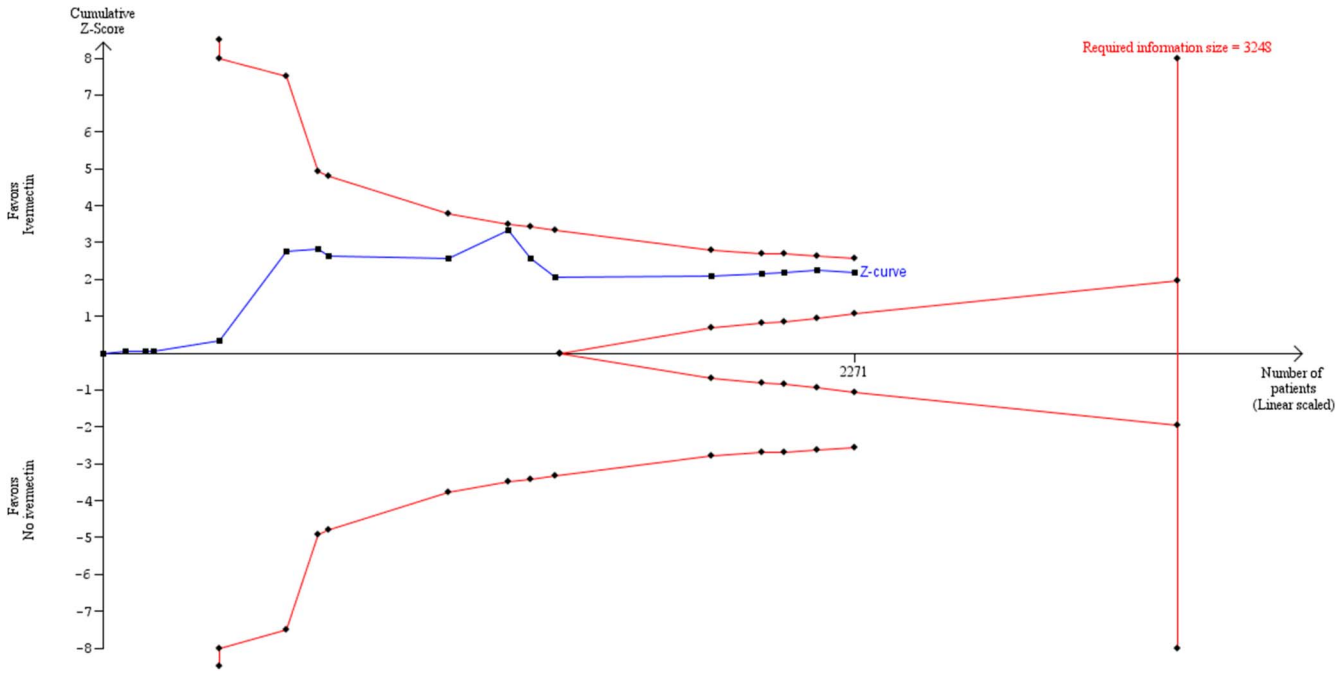


FIGURE 11. Sensitivity analysis excluding an outlier study responsible for the heterogeneity, showing trial sequential analysis using Sidik–Jonkman random-effects method with parameter estimates of $\alpha = 0.05$, $\beta = 0.1$, control rate = 7.8%, RRR = 62%, and diversity = 71.9%.

Meta-analysis of 11 trials, assessing 1533 participants, found that there was no significant difference between ivermectin and control in the risk of severe adverse events (aRR 1.65, 95% CI 0.44–6.09; $I^2 = 0\%$; *low certainty evidence*, downgraded for imprecision and study design limitations). Seven severe adverse events were reported in the ivermectin group and 2 in controls. The SAEs were as follows: 2 patients in the Mahmud trial[107] had esophagitis (this is a known side effect of doxycycline, which was coadministered with ivermectin in this trial); one patient in the study by Krolewiecki et al[106] had hyponatremia (this trial used high-dose ivermectin for 5 days); and 2 patients in a study from Turkey[115] had serious "delirium-like behavior, agitation, aggressive attitude, and altered state of consciousness," which the authors attributed to metabolic insufficiencies in MDR-1/ABCB1 or CYP3A4 genes, screening for which was a study feature. In the Lopez-Medina et al[85] trial, there were 2 SAEs in each arm (SoF Table 2).

Ivermectin prophylaxis versus no ivermectin prophylaxis

Three studies involving 738 participants evaluated ivermectin for COVID-19 prophylaxis among health care workers and COVID-19 contacts. Meta-analysis of these 3 trials, assessing 738 participants, found that ivermectin prophylaxis among health care workers and COVID-19 contacts probably reduces the risk of

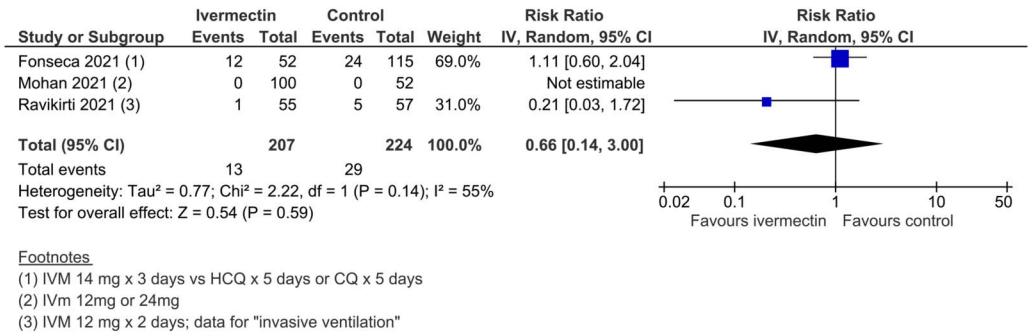
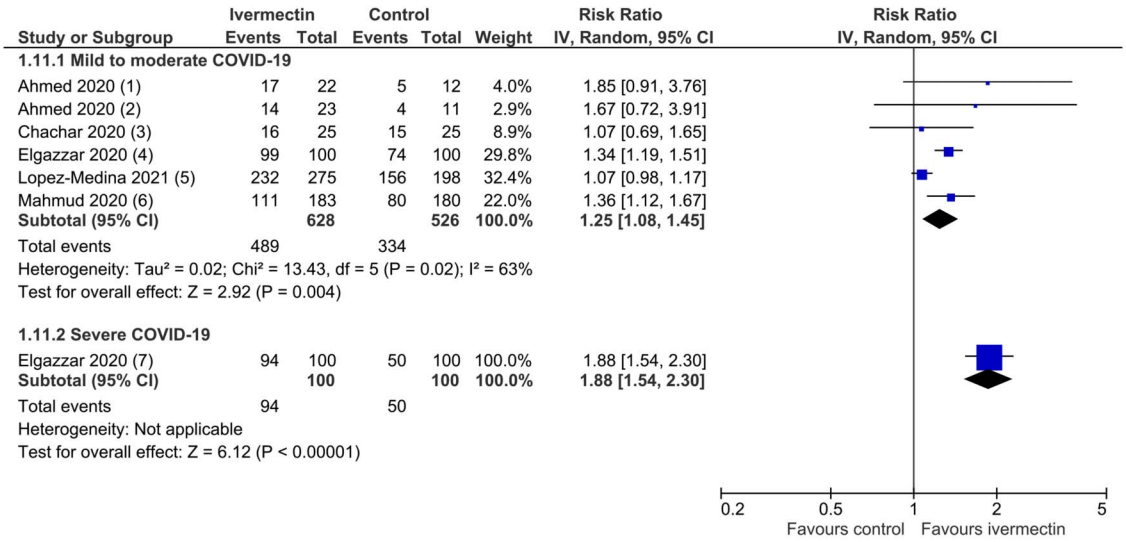


FIGURE 12. Need for mechanical ventilation.



Footnotes
(1) IVM 12mg s+ doxy 200mg stat then 100 mg BD x 4 days
(2) IVM 12mg daily x 5 days
(3) IVM 12 mg at 0, 12, and 24 hours
(4) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine
(5) IVM 0.3mg/kg x 5 days
(6) IVM 6mg once + Doxy 100 mg x 5 days
(7) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine

FIGURE 13. Improvement.

COVID-19 infection by an average of 86% (79%–91%) (3 trials, 738 participants; aRR 0.14, 95% CI 0.09–0.21; 5.0% vs. 29.6% contracted COVID-19, respectively; *low-certainty evidence*; downgraded due to study design limitations and few included trials) (Figure 15). In 2 trials involving 538 participants, no severe adverse events were recorded (SoF Table 4).

DISCUSSION

The findings indicate with moderate certainty that ivermectin treatment in COVID-19 provides a significant survival benefit. Our certainty of evidence judgment was consolidated by the results of trial sequential analyses, which show that the required IS has probably already been met. Low-certainty evidence on improvement and deterioration also support a likely clinical benefit of ivermectin. Low-certainty evidence suggests a significant effect in prophylaxis. Overall, the evidence also suggests that early use of ivermectin may reduce morbidity and mortality from COVID-19. This is based on (1) reductions in COVID-19 infections when ivermectin was used as prophylaxis, (2) the more favorable effect estimates for mild to moderate disease compared with severe disease for death due to any cause, and (3) on the evidence demonstrating reductions in deterioration.

The evidence on severe adverse events in this review was graded as low certainty, partly because there were too few events to reach statistical significance. Evidence from a recent systematic review of ivermectin use among people with parasitic infections suggests that ivermectin administered at the usual doses (0.2 or 0.4 mg/kg) is safe and could be safe at higher doses.[7,116] A recent World Health Organization document on ivermectin use for scabies found that adverse events with ivermectin were primarily minor and transient.[22]

We restricted the included studies to the highest level of evidence, that is, RCTs, as a policy. This was despite there being numerous observational but nonrandomized trials of ivermectin, which one could argue could also be considered in an emergency. We included preprint and unpublished data from completed but not yet published trials due to the urgency related to evidence synthesis in the context of a global pandemic.[117] Although there is the potential for selective reporting of outcomes and publication bias, we have factored in these considerations in interpreting results and forming conclusions. We adhered to PRISMA guidelines and the WHO statement on developing global norms for sharing data and results during public health emergencies.[117]

There are a number of limitations with this review. Several of the studies contributing data did not

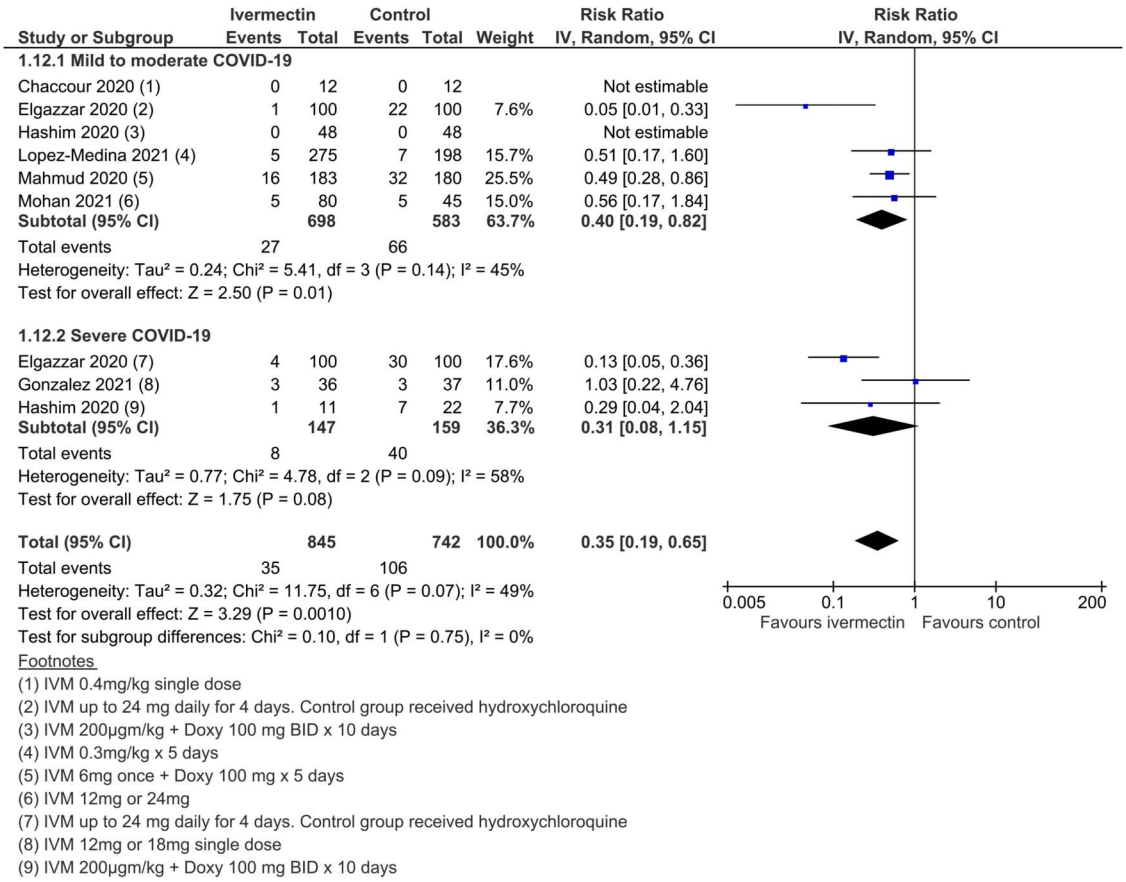


FIGURE 14. Deterioration.

provide full descriptions of methods, so assessing risk of bias was challenging. Where descriptions of study methods were sparse or unclear, we attempted to contact authors to clarify methods, but lack of information led us to downgrade findings in several instances. Overall interpretation of findings was hampered due to variability in the participants recruited, treatment regimen, and the care offered to those in control groups. We have tried to take this variation into account through subgroup and sensitivity analyses. Nevertheless, dosing and treatment regimens and the use of ivermectin with other components of "standard care" require further research. We did not include laboratory outcome measures, such as viral clearance. The latter and other biochemical outcomes have been reported in several studies and reviews and tend to favor ivermectin.[10,47,105,108] Several trials reported continuous data, such as length of hospital stay, as medians and interquartile ranges; therefore, we were unable to include these data in meta-analysis. Because we did not undertake in our protocol to perform narrative evidence synthesis, and because these data tended to favor ivermectin, the certainty of the effects of ivermectin on these continuous outcomes may be underestimated.

At least 5 other reviews of ivermectin use for COVID-19 have been published, including one coauthored with Nobel Laureate Professor Satoshi Ōmura, discoverer of ivermectin,[9,10,118,119,120] but only 3 have been peer-reviewed[9,118,120] and only 2 attempt full systematic review.[10,119] We applied AMSTAR 2,[121] a critical appraisal tool for systematic reviews of health care interventions, to the 2 nonpeered systematic reviews[10,119] and both were judged to be of low quality (Table 5). However, there was also a suggestion that ivermectin reduced the risk of death in treatment of COVID-19 in these reviews.

The recently updated WHO therapeutics guidelines[12] included 7 trials and 1419 people in the analysis of mortality. Reporting a risk reduction of 81% (odds ratio 0.19, 95% CI 0.09–0.36), the effect estimate favoring ivermectin was downgraded by 2 levels for imprecision, although the justification for this is unclear as the reported CI is precise (64%–91%).

In addition to the evidence from systematic reviews, the findings of several controlled observational studies

Table 4. Summary of findings table of ivermectin versus no ivermectin for COVID-19 prophylaxis in healthy population (people without COVID-19 infection).

	Illustrative comparative risks* (95% CI)				
	Assumed risk	Corresponding risk			
Outcomes	No ivermectin	Ivermectin	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
COVID-19 infection	296 per 1000	245 fewer infections per 1000 (234–269)	RR = 0.14 (0.09–0.21)	738 (3)	Low†
Admission to hospital	Not reported				
Death from any cause	Not reported				
Serious adverse events	No events occurred in 538 participants (2 studies), therefore the effect could not be estimated.				

GRADE working group grades of evidence; High quality: Further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: We are very uncertain about the estimate.
*The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
†Downgraded −2 for study design limitations.
NNT, number needed to treat.

are consistent with existing evidence and suggest improved outcomes with ivermectin treatment.[55,57,59] Similarly, with respect to ivermectin prophylaxis of frontline workers and those at risk, controlled observational studies from Bangladesh and Argentina (the latter which involved 1195 health care workers) have shown apparent reductions in COVID-19 transmission with ivermectin prophylaxis, including in some reports total protection (zero infections) where infection rates in the control group exceeded 50%.[122,123] A very large trial of ivermectin prophylaxis in health care workers in India[124] covered 3532 participants and reported risk ratios not significantly different from this meta-analysis (prophylaxis outcome).

Clarifying ivermectin safety in pregnancy is a key question in patient acceptability for pregnant women contracting COVID-19. A recent meta-analysis[5] found little evidence of increased risk of abnormal pregnancies but similarly weak evidence of absence of risk. For (pre-exposure) prophylaxis in pregnancy, where vaccines may be contraindicated, the alternative of hydroxychloroquine has been advocated.[125,126] In addition to safety and relative efficacy, different risk–benefit judgments may be presented for prophylaxis

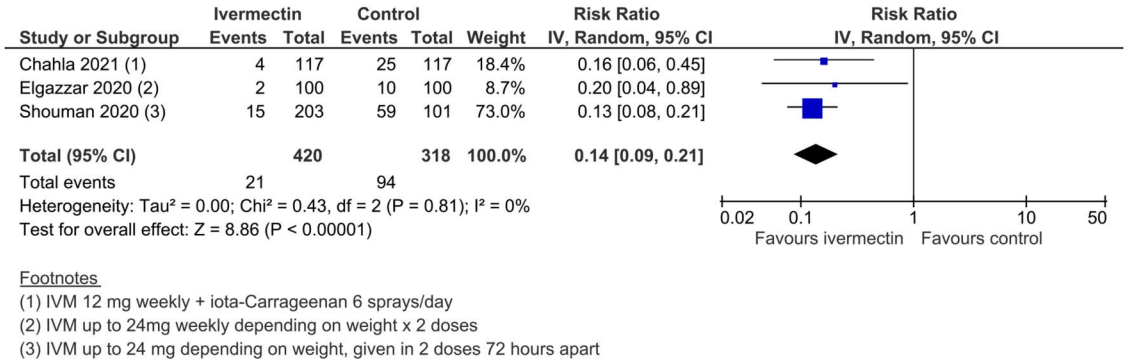


FIGURE 15. COVID-19 infection (prophylaxis studies).

Table 5. Methodological quality of other systematic reviews (AMSTAR 2).

Systematic review	Components of PICO described	A priori study design	Explain selection of study designs	Comprehensive literature search	Duplicate study selection	Duplicate data extraction	List of excluded studies justified	Characteristics of included studies provided
Hill et al, 2021[10]	+	−	+	+	?	?	−*	?†
Castañeda-Sabogal et al 2021[119]	+‖	?	−	?#	+	+	−*	+

Systematic review	Risk of bias adequately assessed and documented	Sources of funding reported	Appropriate methods to combine findings	Appropriate risk-of-bias sensitivity analyses conducted	Risk-of-bias assessment used in conclusions	Satisfactory explanation of observed heterogeneity	Likelihood of publication bias assessed	Conflict of interest stated
Hill et al, 2021[10]	−‡	−	−§	−*	−¶	−*	NA	−
Castañeda-Sabogal et al 2021[119]	−**	−	−††	−‡‡	−*	+	NA	+

Assessed using AMSTAR 2[121]; +, adequately assessed; −, inadequately assessed; ?, unclear assessment; NA, not applicable (less than 10 included studies in meta-analysis).

*Not documented or inadequately reported.

†Participant population, description of comparator interventions, and time frame for follow-up were not described or inadequately reported.

‡No summary of risk-of-bias assessment was given in the main text in the review, other than stating trials were of poor, fair, or high quality. There were some further details about bias in the discussion, but these were largely generic and did not follow the recommended Cochrane tool used to assess risk of bias in RCTs.

§A meta-analysis for all-cause death was presented but authors did not specify why meta-analyses were not conducted for other outcomes, which included at least 2 trials reporting the same comparison and outcome, other than in some parts of the discussion. For example, if viral clearance was reported in most trials, there would have been scope to have performed subgroup analyses and/or split the time point for each comparison to account for the varying duration of follow-up across trials. Instead, they gave a vote count-type narrative of the results, which did not follow synthesis without meta-analysis (SWiM) in systematic review reporting guidelines.[144]

¶There was some further details about bias in the discussion, but this was largely generic and did not follow the recommended Cochrane tool used to assess risk of bias in RCTs. Similarly, in terms of certainty/quality of the evidence, the authors used terms in a summary table that included "good," "fair," and "limited," without offering any explanation or justification.

‖Outcomes were reported but lacked definitions.

#A significant number of pertinent RCTs have not been included in the review. Given the adequate due diligence of review process, the comprehensive nature of the search strategy is questionable.

**No description of risk-of-bias assessment in any domain apart from missing outcome data but attrition rates not documented to justify judgment.

††Authors did not report data from RCTs that we obtained from various sources and some conclusions were not reflective of the observed data. It was reported that in an analysis of 4 preprint retrospective studies at high risk of bias, ivermectin was not associated with reduced mortality (logRR 0.89, 95% CI 0.09–1.70, $P = 0.04$). Although the caveat of studies being at high risk of bias and statistical heterogeneity should be added to any interpretation, it is incorrect to interpret these results as not demonstrating a potential association based on the observed result. Furthermore, the high risk of bias judgment is not adequately justified.

‡‡A sensitivity analysis was performed excluding those studies without adjustment for confounding but no details are provided. Given that there was some evidence of a potential association with ivermectin treatment and survival in 4 retrospective studies (although downplayed as no association due to concerns about attrition), it is highly implausible that any sensitivity analysis would not remove any suggestion of association.

(pre- and post-exposure), and for treatment, with pregnancy a high-risk status for COVID-19.

RCTs in this review did not specifically examine use of ivermectin in the elderly, although this is a known high-risk group for severe COVID-19. In the setting of care homes, it is also notorious for rapid contagion. A standard indication for ivermectin in the elderly is scabies. We identified 2 recent reports suggesting that ivermectin may be efficacious as prevention and treatment of COVID-19 in this age group.[50,127] A letter on positive experience in 7 elder care facilities in Virginia covering 309 patients was sent to NIH[127] and has recently been submitted for publication.

There is also evidence emerging from countries where ivermectin has been implemented. For example, Peru had a very high death toll from COVID-19 early on in the pandemic.[128] Based on observational evidence, the Peruvian government approved ivermectin for use against COVID-19 in May 2020.[128] After implementation, death rates in 8 states were reduced between 64% and 91% over a two-month period.[128] Another analysis of Peruvian data from 24 states with early ivermectin deployment has reported a drop in excess deaths of 59% at 30+ days and of 75% at 45+ days.[129] However, factors such as change in behavior, social distancing, and face-mask use could have played a role in this reduction.

Other considerations related to the use of ivermectin treatment in the COVID-19 pandemic include people's values and preferences, equity implications, acceptability, and feasibility.[130] None of the identified reviews specifically discussed these criteria in relation to ivermectin. However, in health care decision making, evidence on effectiveness is seldom taken in isolation without considering these factors. Ultimately, if ivermectin is to be more widespread in its implementation, then some considerations are needed related to these decision-making criteria specified in the GRADE-DECIDE framework.[130]

There are numerous emerging ongoing clinical trials assessing ivermectin for COVID-19. The trade-off with policy and potential implementation based on evidence synthesis reviews and/or RCTs will vary considerably from country to country. Certain South American countries, Indian states, and, more recently, Slovakia and other countries in Europe have implemented its use for COVID-19.[129,131,132,133,134] A recent survey of global trends[118] documents usage worldwide. Despite ivermectin being a low-cost medication in many countries globally, the apparent shortage of economic evaluations indicates that economic evidence on ivermectin for treatment and prophylaxis of SARS-CoV-2 is currently lacking. This may impact more on LMICs that are potentially waiting for guidance from organizations like the WHO.

Given the evidence of efficacy, safety, low cost, and current death rates, ivermectin is likely to have an impact on health and economic outcomes of the pandemic across many countries. Ivermectin is not a new and experimental drug with an unknown safety profile. It is a WHO "Essential Medicine" already used in several different indications, in colossal cumulative volumes. Corticosteroids have become an accepted standard of care in COVID-19, based on a single RCT of dexamethasone.[1] If a single RCT is sufficient for the adoption of dexamethasone, then a fortiori the evidence of 2 dozen RCTs supports the adoption of ivermectin.

Ivermectin is likely to be an equitable, acceptable, and feasible global intervention against COVID-19. Health professionals should strongly consider its use, in both treatment and prophylaxis.

ACKNOWLEDGMENTS

This work was inspired by the prior literature review of Dr Pierre Kory.

The authors thank Information Specialist, Jo Platt, of the Cochrane Gynaecological, Neuro-oncology, and Orphan Cancer (CGNOC) group for designing the search strategy and running the search, as well as Anna Noel Storr for reviewing the strategy. The authors also thank Isabella Rushforth for her voluntary assistance with the preparation of the reference lists.

The authors thank Gill Gyte for detailed comments, feedback, and involvement in this review, and Michael Grayling and David Tovey for useful peer review comments before submission. The authors also thank the external peer reviewers for their helpful comments and Peter Manu for the opportunity to publish our findings.

REFERENCES

1. Horby P, Lim WS, Emberson J, et al. Dexamethasone in hospitalized patients with covid-19. *NEJM.* 2021;384: 693–704.
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.
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.
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.
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.

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.
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.
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.
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.
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.
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.
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.
13. Heidary H, Gharebaghi R. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. *J Antibiot.* 2020;73:593–602.
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.
15. Jans DA, Wagstaff KM. Ivermectin as a broad-spectrum host-directed anti-viral: the real deal? *Cells.* 2020;9:2100.
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.
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.
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.
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.
20. Lehrer A, Rheinstein PH. Ivermectin docks to the SARS-CoV-2 spike receptor binding domain attached to ACE2. *vivo*. 2020;34:3023–3026.
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.
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.
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.
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
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.
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.
27. Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions Version 6. 0 Cochrane*. 2019.
28. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327:557–560.
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.
30. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clin Trials.* 1986;7:177–188.
31. *RevMan. Review Manager 5*. The Cochrane Collaboration; 2020.
32. *R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing V, Austria*. R Foundation for Statistical Computing. Vienna, Austria; 2021.
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.
34. Rücker G, Schwarzer G, Krahn U, et al. *Network Meta-Analysis Using Frequentist Methods*; 2017.
35. Efthimiou O. Practical guide to the meta-analysis of rare events. *Evid Based Ment Health.* 2018;21:72–76.
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.
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.
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.
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.
40. Cai T, Parast L, Ryan L. Meta-analysis for rare events. *Stat Med.* 2010;29:2078–2089.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
58. Hellwig MD, Maia A. A covid-19 Prophylaxis? Lower incidence associated withprophylactic administration of Ivermectin. *Int J Antimicrob Agent.* 2021;57:106248.
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.
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.
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.
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.
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.
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.
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.
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.

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.
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.
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.
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.
71. Bisoffi Z. *COVidIVERmectin: Ivermectin for Treatment of Covid-19 (COVER)*. 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04438850. Accessed January 2021.
72. ProgenaBiom. *Trial of Combination Therapy to Treat Covid-19 Infection*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04482686. Accessed January 2021.
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.
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.
75. Elalfy H. *New Antiviral Drugs for Treatment of Covid-19*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04392427. Accessed January 2021.
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.
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.
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.
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.
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.
81. Temple University. *Outpatient Use of Ivermectin in Covid-19*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04530474. Accessed January 2021.
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.
83. Kamal E. *Ivermectin in Treatment of Covid 19 Patients*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04425707. Accessed January 2021.
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.
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.
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-PE-RU)*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04635943. Accessed January 2021.
87. Okasha K. *Ivermectin and Nitazoxanide Combination Therapy for Covid-19*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04360356. Accessed January 2021.
88. Okasha K. *Ivermectin Nasal Spray for Covid19 Patients*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04510233. Accessed January 2021.
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.
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.
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.
92. Ochoa-Jaramillo F. *Ivermectin in Adults with Severe Covid-19*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04602507. Accessed January 2021.
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.
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.

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.
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.
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.
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.
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.
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.
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.
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.
103. Asghar A. *Efficacy of Ivermectin in COVID-19*; 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04392713. Accessed January 2021.
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.
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.
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.
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).
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
125. Fesler ML, Stricker RB. Pre-exposure prophylaxis for covid-19 in pregnant women. *Int J Gen Med.* 2021;14: 279–284.
126. Stricker RB, Fesler ML. Flattening the risk: pre-exposure prophylaxis for COVID-19. *Infect Drug Resist.* 2020;13: 3689–3694.
127. Chesler DL. *Letter to Dr Bray at the National Institutes of Health*. 2021. Available at: https://tinyurl.com/dnemehxn. Accessed March 16, 2021.
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.
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.
130. GRADE-DECIDE. *The DECIDE Project*. 2016. Available at: http://www.decide-collaboration.eu/. Accessed January 2021.
131. Roguski J. *Ivermectin*; 2020. Available at: https://www.thecompleteguidetohealth.com/Ivermectin.html#. Accessed January 2021.
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.
133. Despacho de Comunicaciones y Estrategia Presidencial. *Coronavirus COVID-19 in Honduras*; 2021. Available at: https://covid19honduras.org/. Accessed January 2021.
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.
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.
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.
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.
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.
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.
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.
141. Schwartz E. Viral load and culture viability in mild COVID-19 patients treated with Ivermectin. *New England J Med.* 2021.Submitted.
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.
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.
144. Campbell M, McKenzie JE, Sowden A, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ*. 2020;16:l6890.