PUBLIC HEALTH AND OTHER LEGISLATION (FURTHER EXTENSION OF EXPIRING PROVISIONS) AMENDMENT BILL 2021

FORM F SUBMISSION

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Public Health and Other Legislation (Further Extension of Expiring Provisions) Amendment Bill 2021

Submission

I am a long time resident of Queensland. It is my view the Bill should not be supported and herewith oppose the Amendment Bill 2021.

Primary reason for this view is the mounting evidence of cheap, safe and effective medication being available for both treatment of COVID19 infection and COVID19 prophylaxis[i].

This medication, Ivermectin, has been in use for more than 40 years and 3.7 billion doses have been administered. This medication is on the list of essential medication of the WHO and is out of Patent. In 2015 the Nobel Prize was awarded to the discoverers of Ivermectin for its development[ii].

On June the 17th 2021, The American Journal of Therapeutics published a Cochrane standard peer reviewed meta-analysis of Ivermectin for Prevention and Treatment of COVID19 Infection (research paper provided in pdf).

Conclusions of Cochrane standard peer reviewed meta-analysis have never been overturned[iii].

Key findings[iv]:

- **Ivermectin prophylaxis reduced COVID19 infection by an average of 86%.**
- **Treatment with Ivermectin reduced the risk of death by an average of 62% compared to no Ivermectin treatment (meta-analysis of 15 trials, assessing 2438 participants).**

A further summary of research data on Ivermectin, 60 studies to date, (of over 18.900 patients) is given on the website https://ivmmeta.com/ . Similar positive outcomes for the use of Ivermectin for Treatment and Prophylaxis are presented. A copy of the data of this website is included for your perusal.

The UK and USA have adopted medication for COVID19 treatment on the basis of 1 study with lower percentages of positive outcomes (see Supporting documents 3., “Table 1: Evidence base used for other COVID Treatments”). The overwhelming number of Ivermectin studies with positive outcomes for treatment and prevention should make this drug a key component of Queensland’s Health Response.

Widespread adoption of Ivermectin as part of the pandemic response should render the need for a further extension beyond the current Queensland’s declared public health emergency until the 27th of September 2021 unnecessary.

Yours Faithfully,

[redacted]

[redacted] [redacted]

Supporting Documents:

1. American Journal of therapeutics, June 17th 2021: “Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systemic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines.”

Authors: Bryant, Andrew MSc; Lawrie, Theresa A. MBBCh, PhD; Dowswell, Therese PhD; Fordham, Edmund J. PhD; Mitchell, Scott MBChB, MRCS; Hill, Sarah R. PhD; Tham, Tony C. MD, FRCP

2. https://ivmmeta.com/ PDF document of contents of website
3. Table 1. Evidence base used for other COVID-19 approvals

References:

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[i] https://bird-group.org/bird-group-get-ivermectin-approved/ and https://covid19criticalcare.com/

[ii] https://covid19criticalcare.com/ivermectin-in-covid-19/ and https://open.spotify.com/episode/7uVXKgE6eLJKMXkETwcw0D?si=PQvcbb-ERem23FjYshkwGQ&dl_branch=1&nd=1

[iii] https://podcasts.apple.com/us/podcast/how-to-save-the-world-in-three-easy-steps/id1471581521?i=1000525032595 : between 1:26:30 and 2:03:00 by Steve Kirsch CEO COVID-19 Early Treatment Fund: https://www.treatearly.org/team/steve-kirsch

[iv]

https://journals.lww.com/americantherapeutics/abstract/9000/ivermectin_for_prevention_and_treatment_of.98040.aspx

American Journal of Therapeutics 0, e1–e27 ()

OPEN

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

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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,"

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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.
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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

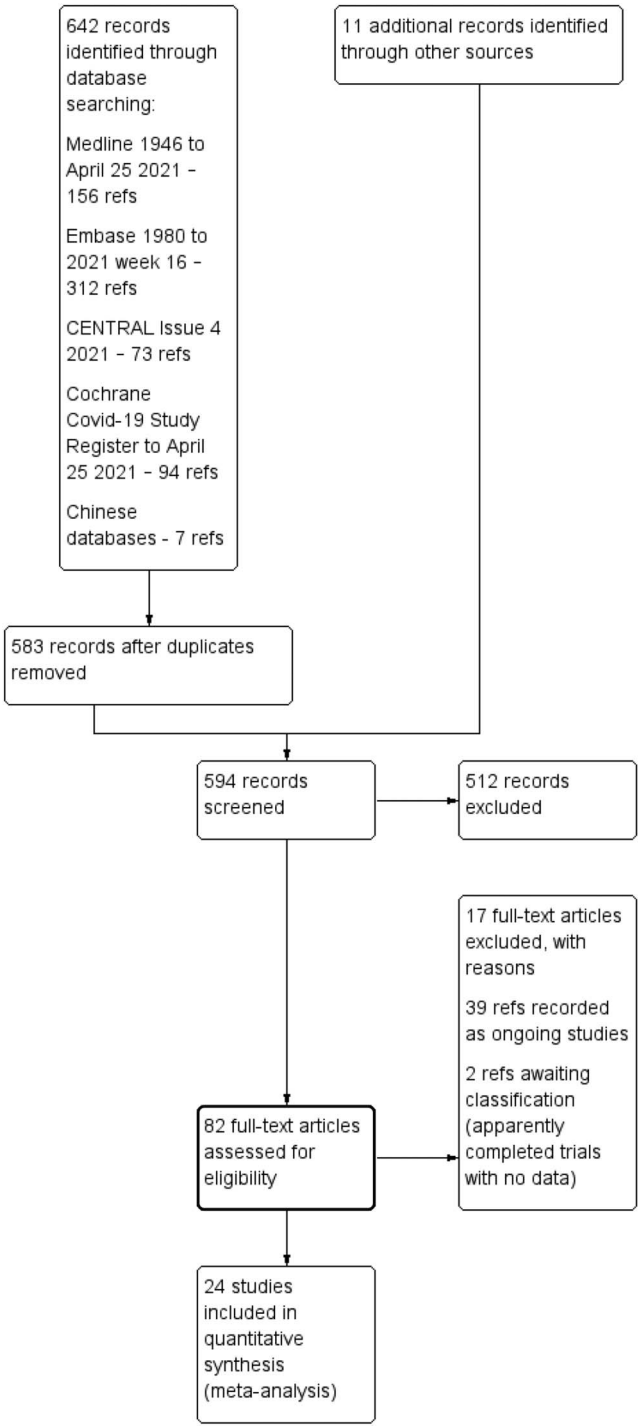


FIGURE 1. Study flow diagram from search on 25 April 2021.

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]

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.

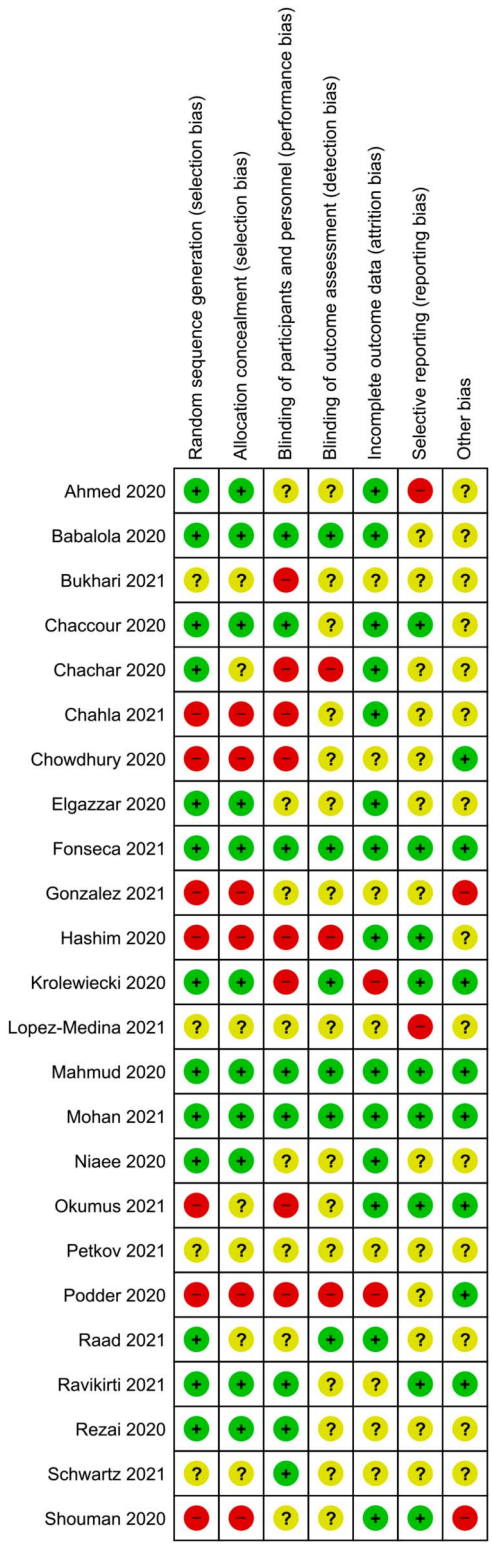


FIGURE 2. Risk-of-bias summary: review authors' judgments about each risk of bias item for each included study.

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.

	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)
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.

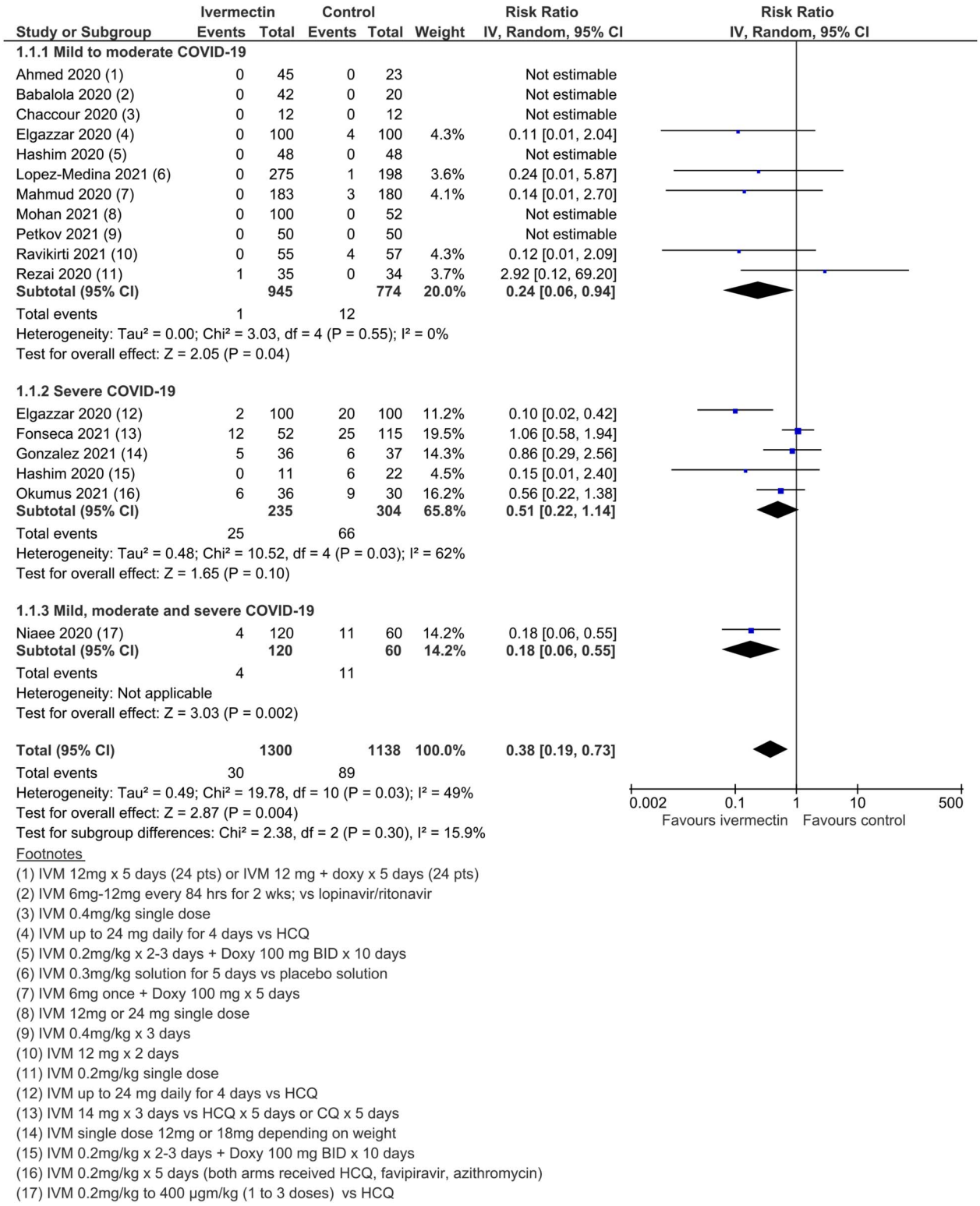
Method	Measure	Model	Effect size (95% CI)	Details
Peto	OR	FE	0.35 (0.24 to 0.53)	Handles single-zero trials
M-H	OR	FE	0.37 (0.24 to 0.56)	Handles single-zero trials
M-H	OR	RE	0.33 (0.16 to 0.68)	Handles single-zero trials
M-H	RR	FE	0.42 (0.29 to 0.60)	Handles single-zero trials
M-H	RR	RE	0.37 (0.19 to 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

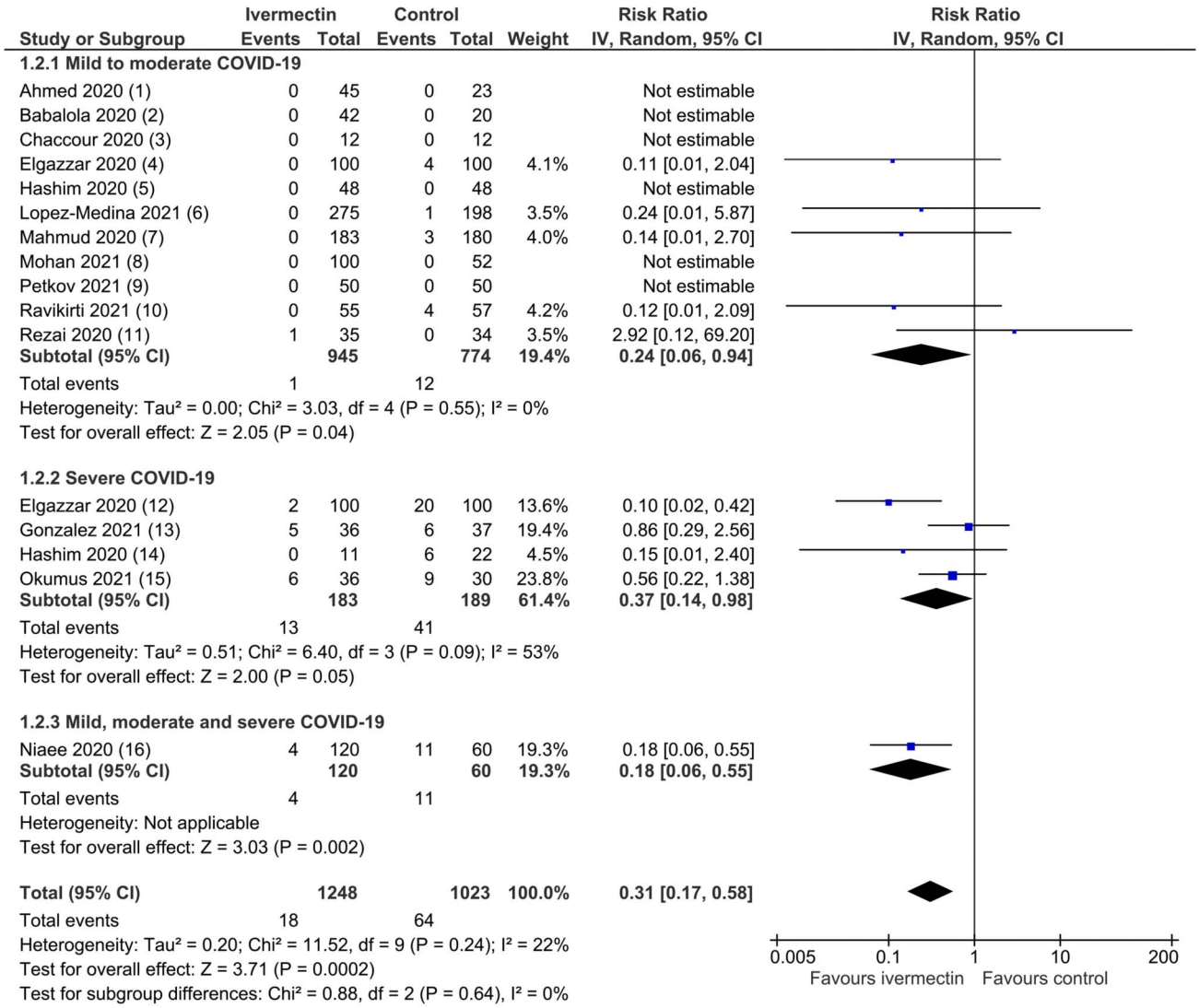
Sensitivity analysis excluding the trial of Fonseca[44] significantly reduced heterogeneity in the meta-analysis and thus the diversity estimate in the TSA using the DL model. This strengthened the suggestion in the primary core analysis that the required IS had been reached (Figure 9). Because the DL 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)
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(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.

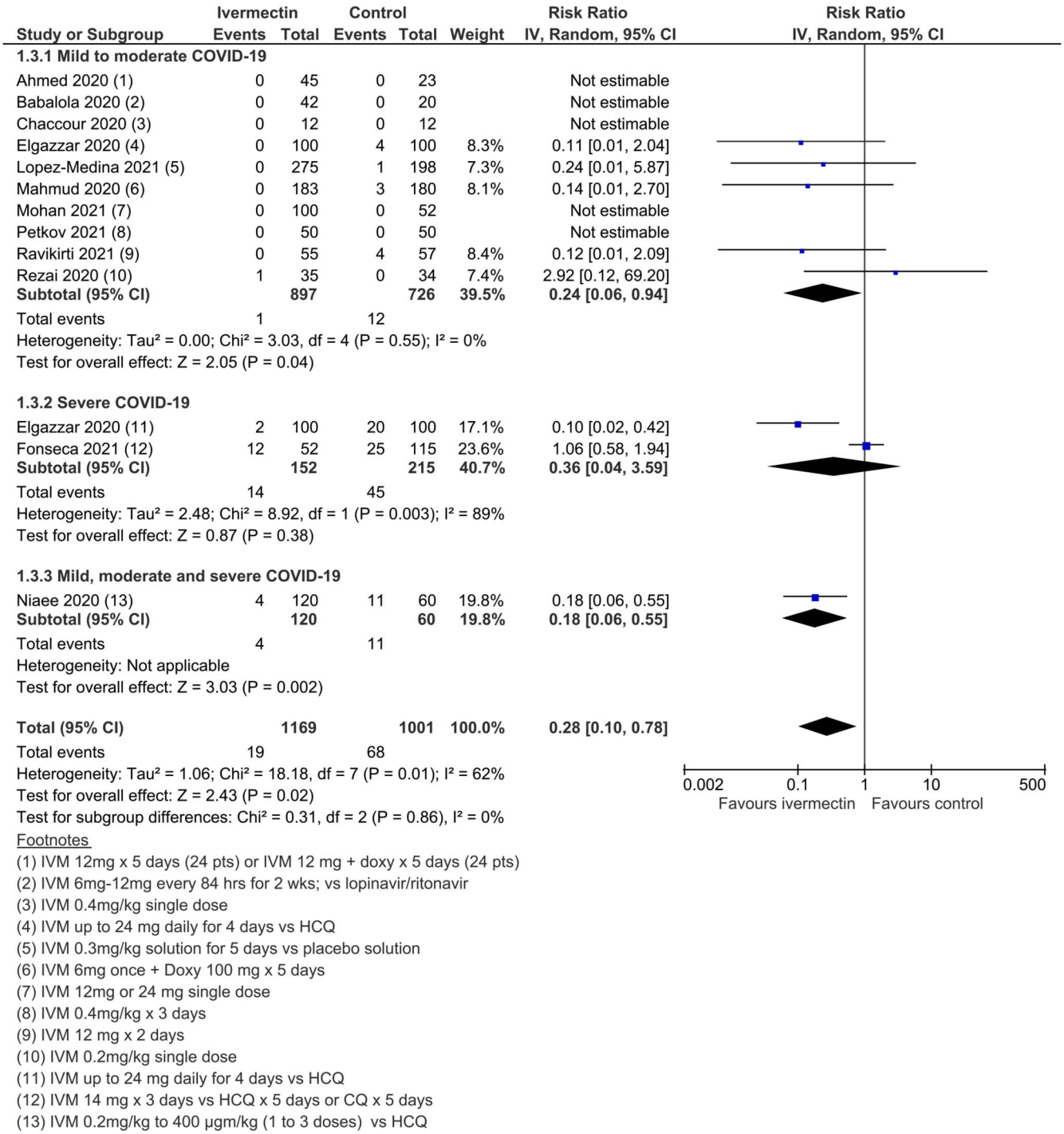


FIGURE 5. Death due to any cause, excluding high risk-of-bias studies.

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.

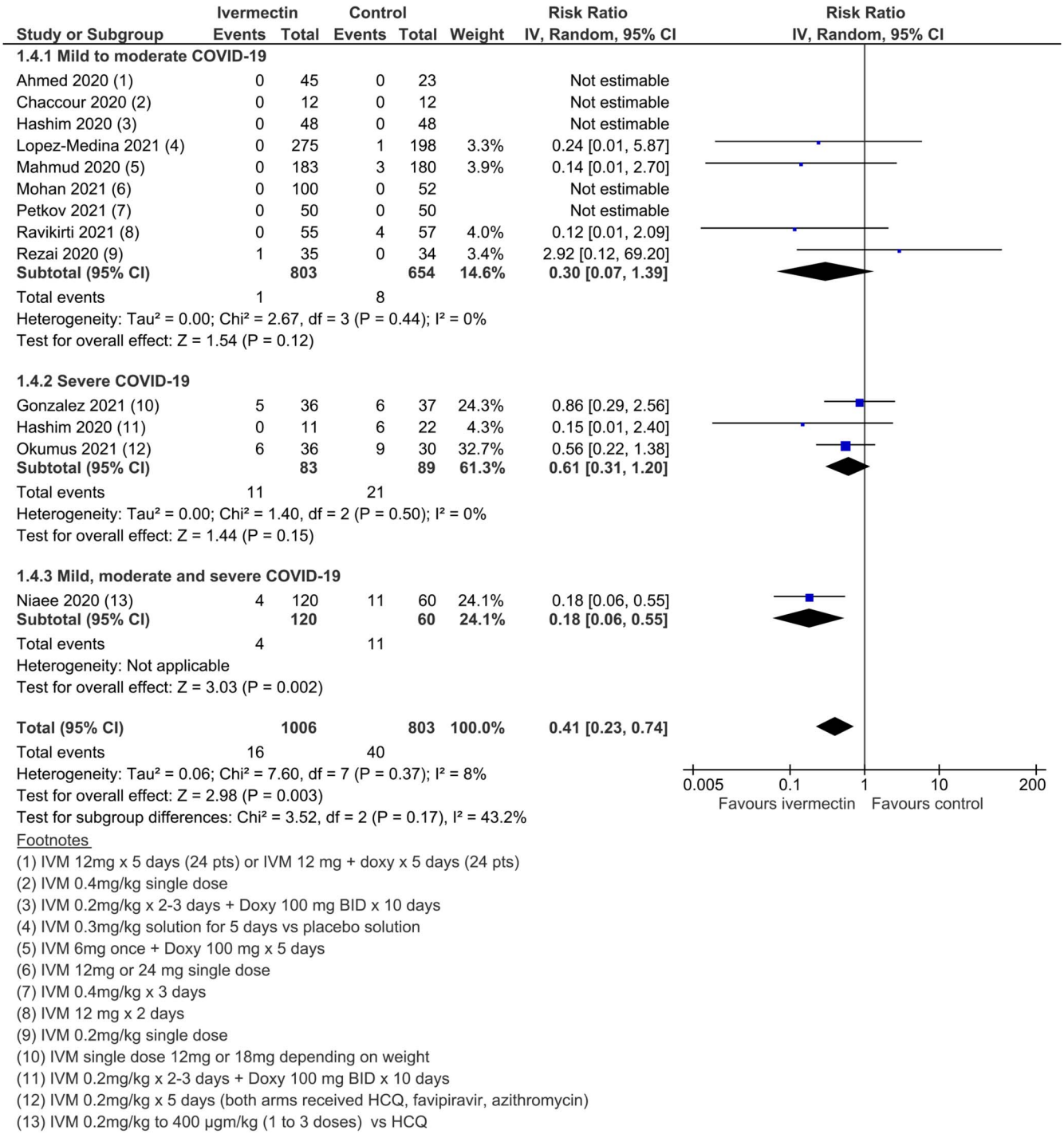


FIGURE 6. Death due to any cause, excluding studies with active controls.

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.

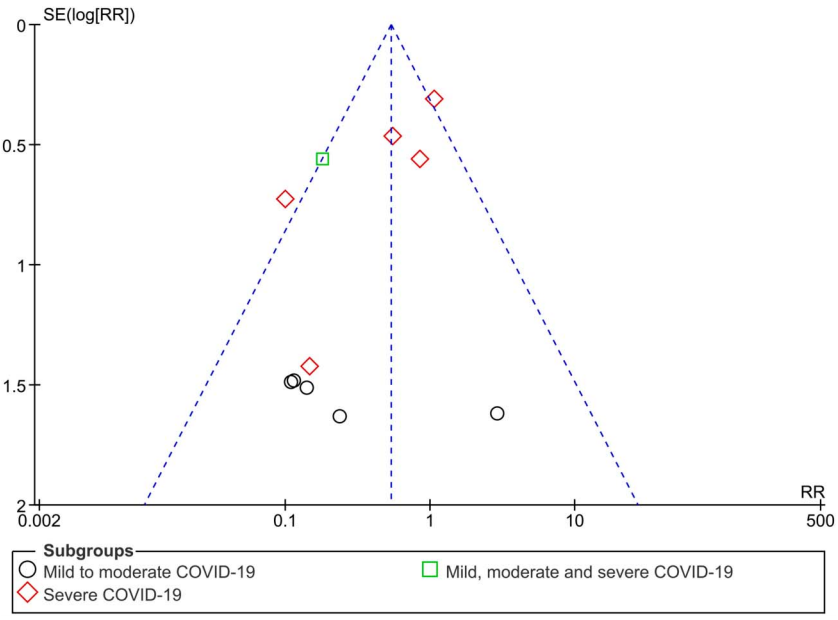


FIGURE 7. Funnel plot of ivermectin versus control for COVID-19 treatment for all-cause death (subgrouped by severity).

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.

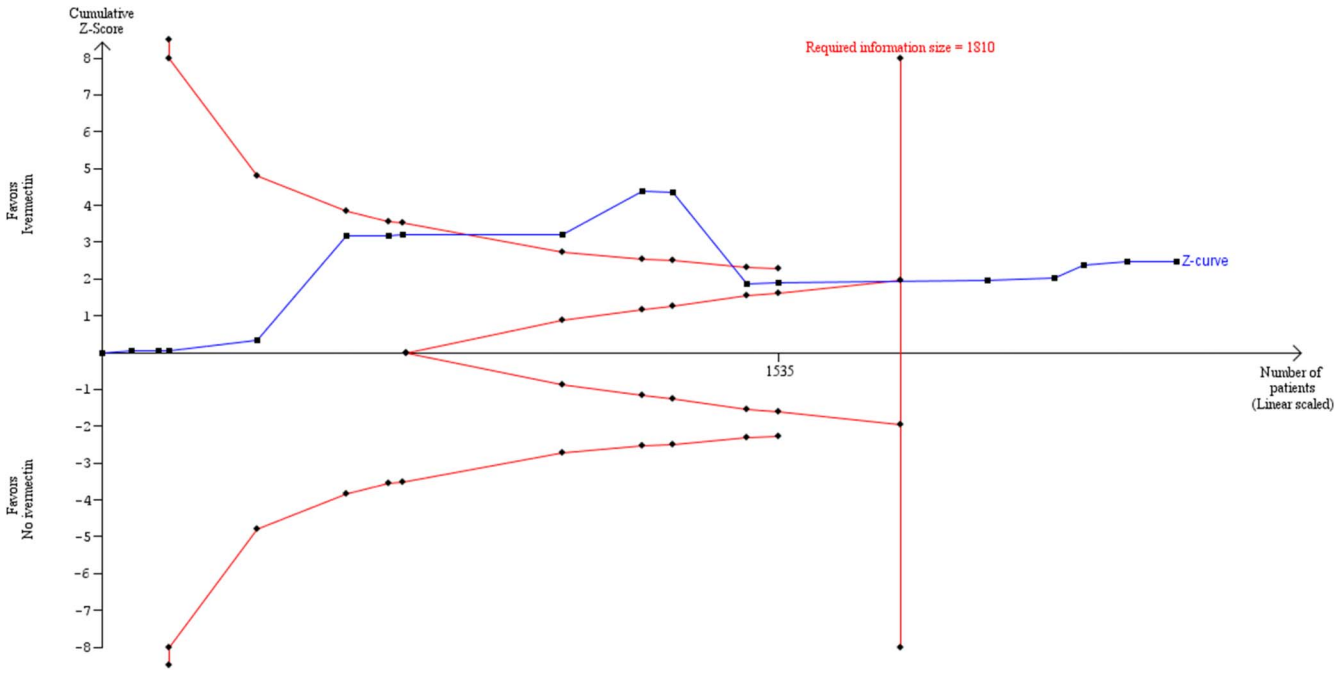


FIGURE 8. Trial sequential analysis using DL random-effects method with parameter estimates of $\alpha = 0.05$, $\beta = 0.1$, control rate = 7.8%, RRR = 62%, and diversity = 49.5%.

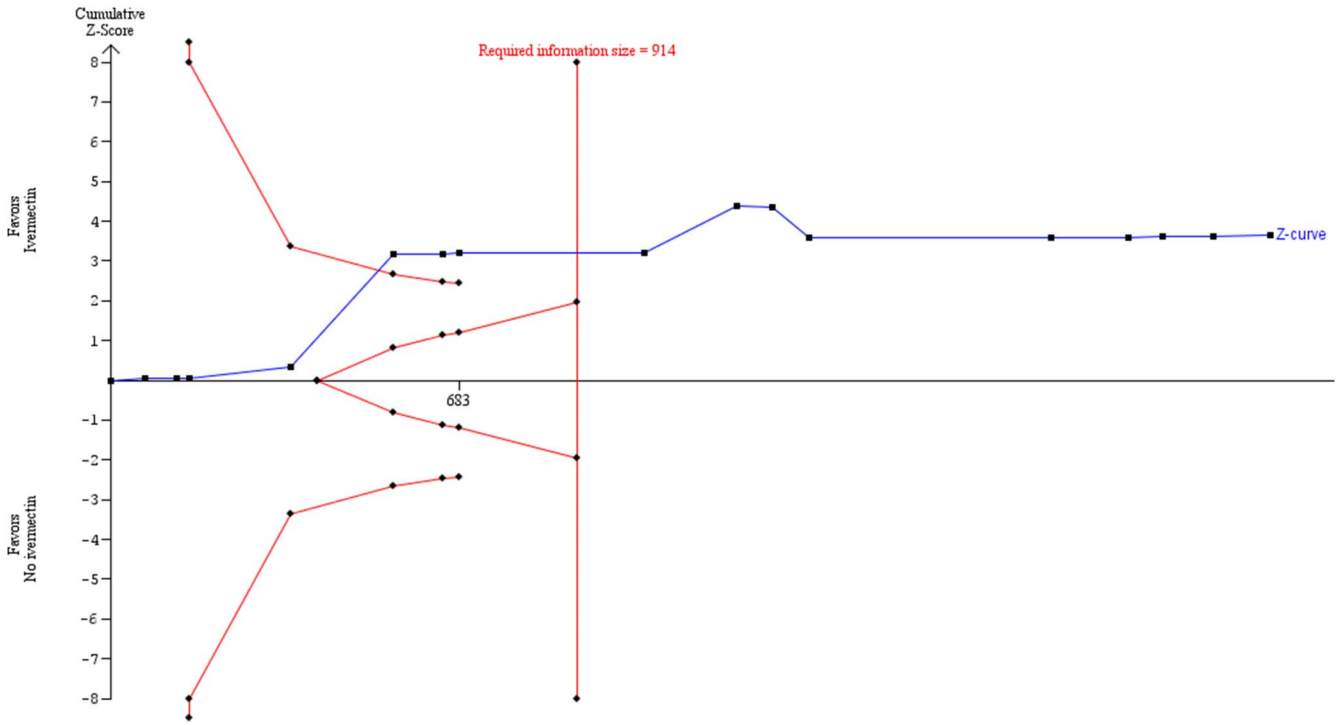


FIGURE 9. Sensitivity analysis excluding an outlier study responsible for the heterogeneity, showing trial sequential analysis using DL random-effects method with parameter estimates of $\alpha = 0.05$, $\beta = 0.1$, control rate = 7.8%, = 62%, and diversity = 0%.

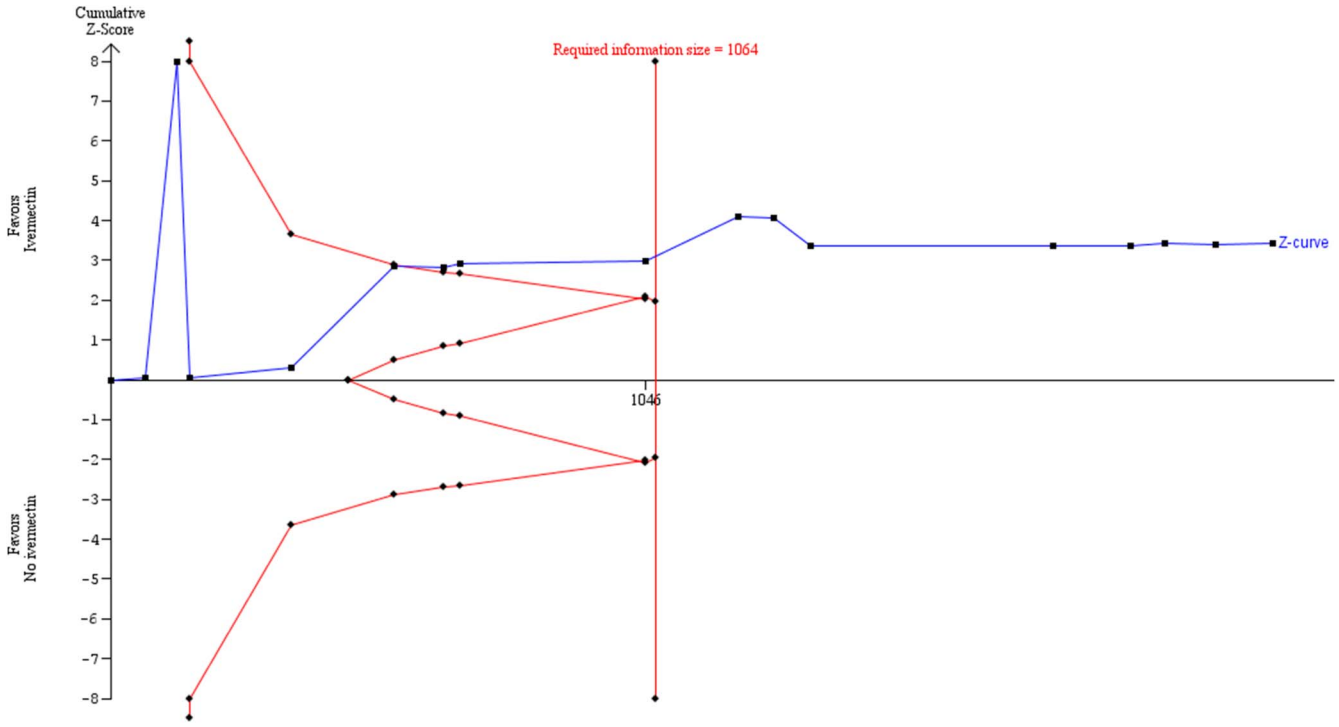


FIGURE 10. Sensitivity analysis excluding an outlier study responsible for the heterogeneity, showing trial sequential analysis using Biggerstaff–Tweedie random-effects method with parameter estimates of $\alpha = 0.05$, $\beta = 0.1$, control rate = 7.8%, RRR = 62%, and diversity = 14.2%.

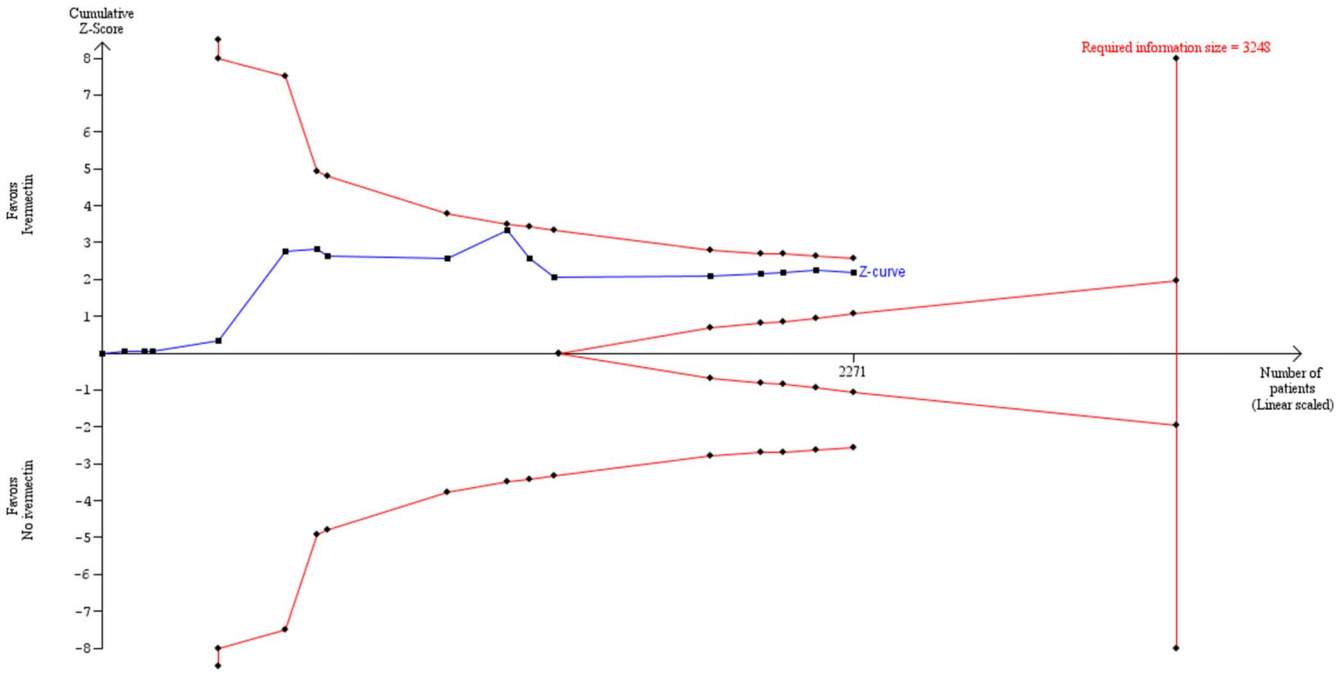


FIGURE 11. Sensitivity analysis excluding an outlier study responsible for the heterogeneity, showing trial sequential analysis using Sidik–Jonkman random-effects method with parameter estimates of $\alpha = 0.05$, $\beta = 0.1$, control rate = 7.8%, RRR = 62%, and diversity = 71.9%.

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

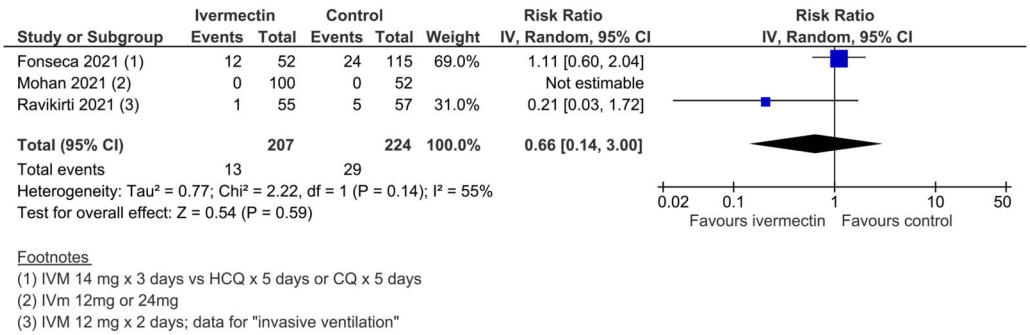
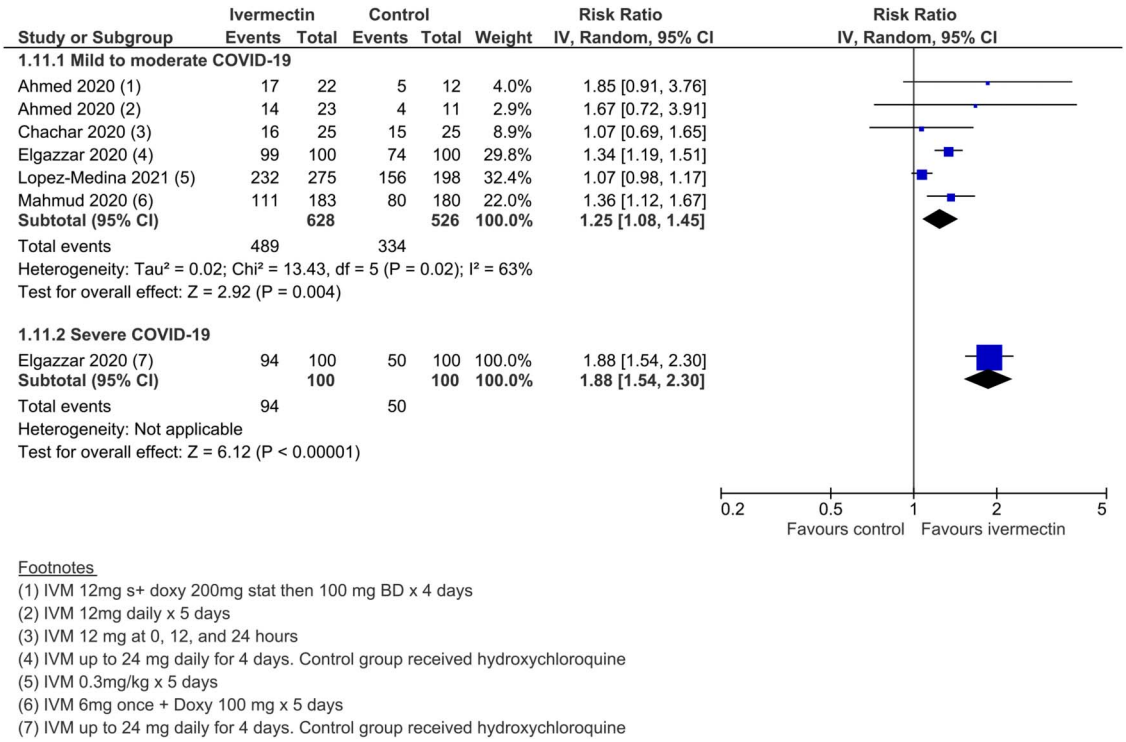


FIGURE 12. Need for mechanical ventilation.



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

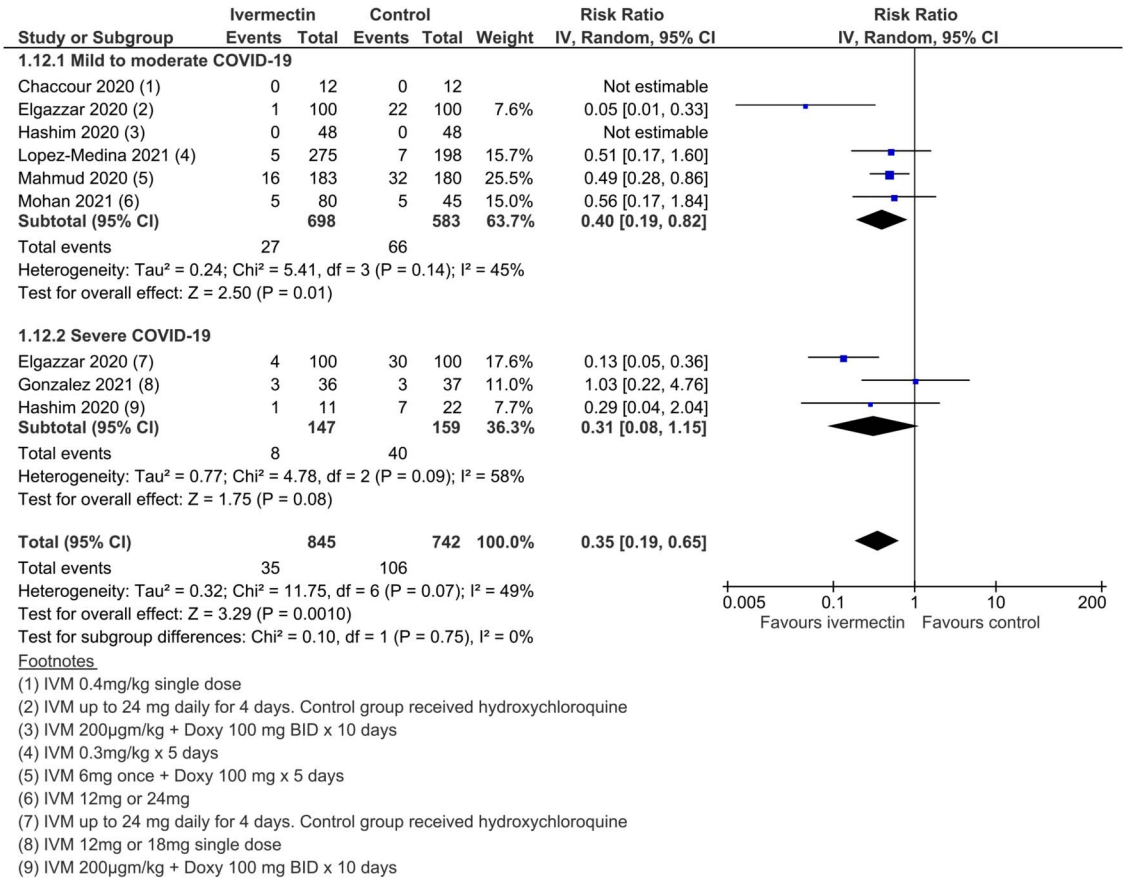


FIGURE 14. Deterioration.

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

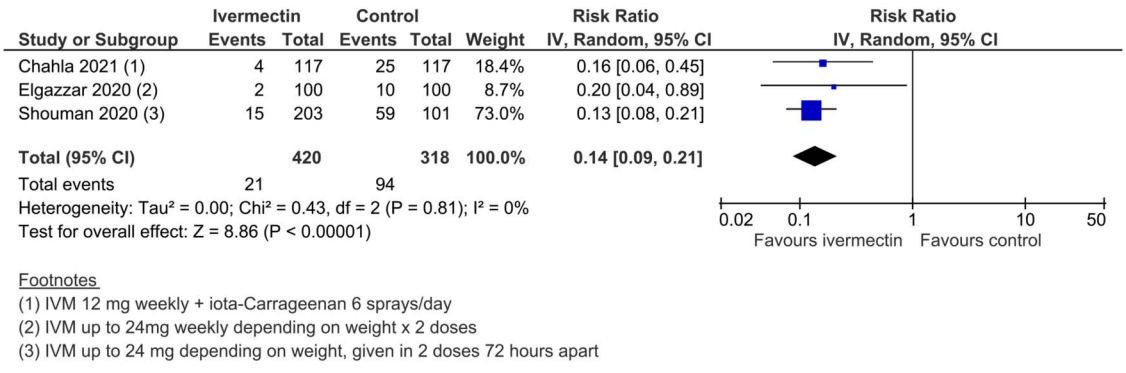


FIGURE 15. COVID-19 infection (prophylaxis studies).

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.

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Ivermectin for COVID-19: real-time meta analysis of 60 studies

Covid Analysis Nov 26 2020 (Version 94 Jul 2, 2021 — updated Niaee)

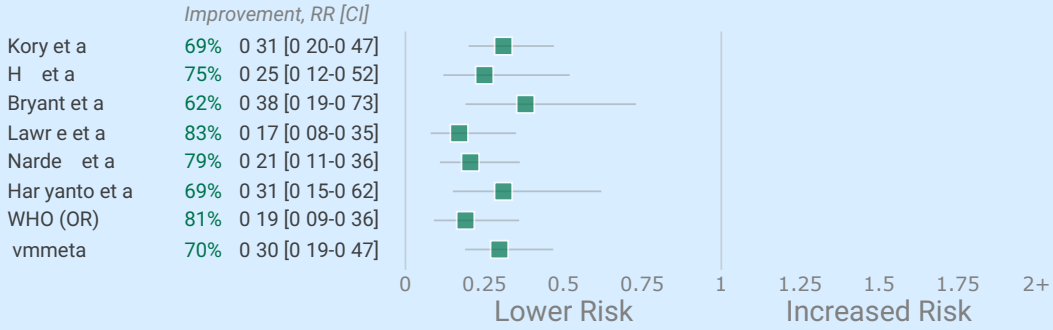
https://ivmmeta.com/

- Meta ana ys s us ng the most ser ous outcome reported shows 76% and 85% mprovement for ear y treatment and prophy ax s (RR 0.24 [0.14 0.41] and 0.15 [0.09 0.25]) w th s m ar resu ts after exc us on based sens t v ty ana ys s restr ct on to peer rev ewed stud es and restr ct on to Random zed Contro ed Tr a s.
- 81% and 96% ower morta ty s observed for ear y treatment and prophy ax s (RR 0.19 [0.07 0.54] and 0.04 [0.00 0.58]). Stat st ca y s gn ficant mprovements are seen for morta ty vent at on hosp ta zat on cases and v ra c earance. 28 stud es show stat st ca y s gn ficant mprovements n so at on.

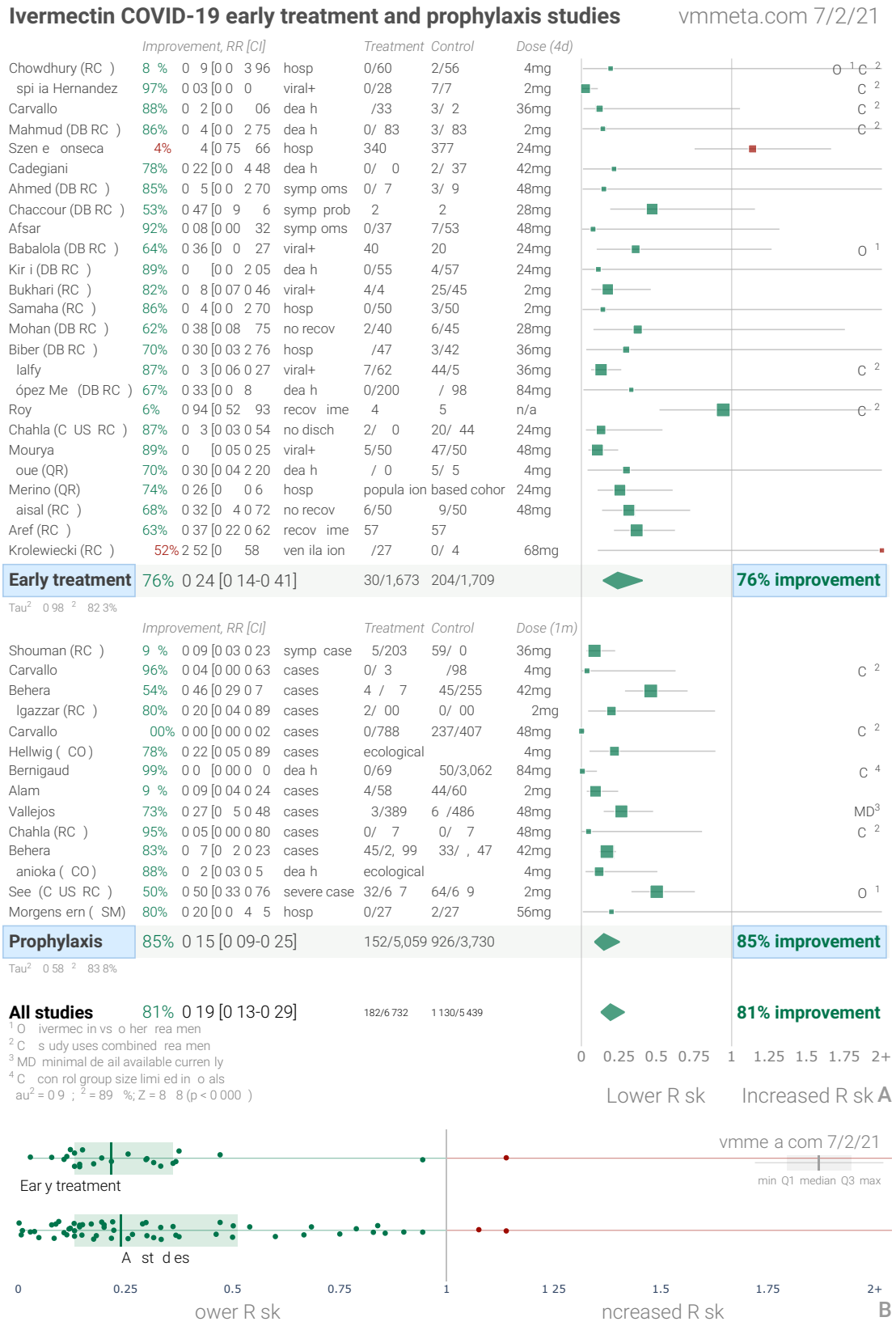
	Studies	*Prophylaxis*	*Early treatment*	*Late treatment*	*Patients*
A stud es	60	**85%** 75-91%]	**76%** 59-86%]	**46%** 29-59%]	18,931
W th exc us ons	51	**87%** 75-93%]	**78%** 69-84%]	**54%** 33-68%]	14,554
Peer-rev ewed	35	**88%** 70-95%]	**77%** 62-86%]	**42%** 19-58%]	7,611
Random zed Contro ed Tr a s	31	**83%** 39-95%]	**69%** 57-77%]	**40%** 11-60%]	5,316
Morta ty resu ts	22	**96%** 42-100%]	**81%** 46-93%]	**61%** 38-76%]	7,690

Percentage improvement with ivermectin treatment

- The probab ty that an neffect ve treatment generated resu ts as pos t ve as the 60 stud es to date s est mated to be 1 n 2 tr on (p = 0.00000000000045).
- Heterogene ty ar ses from many factors nc ud ng treatment de ay popu at on effect measured var ants and reg mens. The cons stency of pos t ve resu ts s remarkab e. Heterogene ty s ow n spec fic cases for examp e ear y treatment morta ty.
- Wh e many treatments have some eve of efficacy they do not rep ace vacc nes and other measures to avo d nfect on. On y 27% of vermect n stud es show zero events n the treatment arm.
- E m nat on of COVID 19 s a race aga nst v ra evo ut on. No treatment vacc ne or ntervent on s 100% ava ab e and effect ve for a current and future var ants. A pract ca effect ve and safe means shou d be used. Not do ng so ncreases the r sk of COVID 19 becom ng endem c; and ncreases morta ty morb d ty and co atera damage.
- Adm n strat on w th food often not spec fied may s gn ficant y ncrease p asma and t ssue concentrat on.
- The ev dence base s much arger and has much ower confl ct of nterest than typ ca y used to approve drugs.
- A data to reproduce th s paper and sources are n the append x. See *[Bryant, Hariyanto, Hill, Kory, Lawrie, Nardelli]* for other meta ana yses a w th s m ar resu ts confirm ng effect veness.



Evidence base used for other COVID-19 approvals			
Med cat on	Stud es	Pat ents	Improvement
Budeson de (UK)	1	1,779	17%
Remdes v r (USA)	1	1,063	31%
Cas r / mdev mab (USA)	1	799	66%
Ivermectin evidence	60	18,931	71% 62-77%]


Ivermectin COVID-19 early treatment and prophylaxis studies
vmmeta.com 7/2/21
Improvement, RR [CI]
Treatment Control
Dose (4d)
Chowdhury (RC) 8 % 0 9 [0 0 3 96 hosp 0/60 2/56 4mg
spi ia Hernandez 97% 0 03 [0 0 0 viral+ 0/28 7/7 2mg
Carvallo 88% 0 2 [0 0 06 dea h /33 3/ 2 36mg
Mahmud (DB RC) 86% 0 4 [0 0 2 75 dea h 0/ 83 3/ 83 2mg
Szen e onseca 4% 4 [0 75 66 hosp 340 377 24mg
Cadegiani 78% 0 22 [0 0 4 48 dea h 0/ 0 2/ 37 42mg
Ahmed (DB RC) 85% 0 5 [0 0 2 70 symp oms 0/ 7 3/ 9 48mg
Chaccour (DB RC) 53% 0 47 [0 9 6 symp prob 2 2 28mg
Afsar 92% 0 08 [0 00 32 symp oms 0/37 7/53 48mg
Babalola (DB RC) 64% 0 36 [0 0 27 viral+ 40 20 24mg
Kir i (DB RC) 89% 0 [0 0 2 05 dea h 0/55 4/57 24mg
Bukhari (RC) 82% 0 8 [0 07 0 46 viral+ 4/4 25/45 2mg
Samaha (RC) 86% 0 4 [0 0 2 70 hosp 0/50 3/50 2mg
Mohan (DB RC) 62% 0 38 [0 08 75 no recov 2/40 6/45 28mg
Biber (DB RC) 70% 0 30 [0 03 2 76 hosp /47 3/42 36mg
lalfy 87% 0 3 [0 06 0 27 viral+ 7/62 44/5 36mg
ópez Me (DB RC) 67% 0 33 [0 0 8 dea h 0/200 / 98 84mg
Roy 6% 0 94 [0 52 93 recov ime 4 5 n/a
Chahla (C US RC) 87% 0 3 [0 03 0 54 no disch 2/ 0 20/ 44 24mg
Mourya 89% 0 [0 05 0 25 viral+ 5/50 47/50 48mg
oue (QR) 70% 0 30 [0 04 2 20 dea h / 0 5/ 5 4mg
Merino (QR) 74% 0 26 [0 0 6 hosp popula ion based cohor 24mg
aisal (RC) 68% 0 32 [0 4 0 72 no recov 6/50 9/50 48mg
Aref (RC) 63% 0 37 [0 22 0 62 recov ime 57 57
Krolewiecki (RC) 52% 2 52 [0 58 ven ila ion /27 0/ 4 68mg
Early treatment 76% 0 24 [0 14-0 41] 30/1,673 204/1,709
76% improvement
Tau² 0 98 ² 82 3%
Improvement, RR [CI]
Treatment Control
Dose (1m)
Shouman (RC) 9 % 0 09 [0 03 0 23 symp case 5/203 59/ 0 36mg
Carvallo 96% 0 04 [0 00 0 63 cases 0/ 3 /98 4mg
Behera 54% 0 46 [0 29 0 7 cases 4 / 7 45/255 42mg
lgazzar (RC) 80% 0 20 [0 04 0 89 cases 2/ 00 0/ 00 2mg
Carvallo 00% 0 00 [0 00 0 02 cases 0/788 237/407 48mg
Hellwig (CO) 78% 0 22 [0 05 0 89 cases ecological 4mg
Bernigaud 99% 0 0 [0 00 0 0 dea h 0/69 50/3,062 84mg
Alam 9 % 0 09 [0 04 0 24 cases 4/58 44/60 2mg
Vallejos 73% 0 27 [0 5 0 48 cases 3/389 6 /486 48mg
Chahla (RC) 95% 0 05 [0 00 0 80 cases 0/ 7 0/ 7 48mg
Behera 83% 0 7 [0 2 0 23 cases 45/2, 99 33/ , 47 42mg
anioka (CO) 88% 0 2 [0 03 0 5 dea h ecological 4mg
See (C US RC) 50% 0 50 [0 33 0 76 severe case 32/6 7 64/6 9 2mg
Morgens ern (SM) 80% 0 20 [0 0 4 5 hosp 0/27 2/27 56mg
Prophylaxis 85% 0 15 [0 09-0 25] 152/5,059 926/3,730
85% improvement
Tau² 0 58 ² 83 8%
All studies 81% 0 19 [0 13-0 29] 182/6 732 1 130/5 439
81% improvement
1 O ivermec in vs o her rea men
2 C s udy uses combined rea men
3 MD minimal de ail available curren ly
4 C con rol group size limi ed in o als
au² = 0 9 ; ² = 89 %; Z = 8 8 (p < 0 000)
0 0.25 0.5 0.75 1 1.25 1.5 1.75 2+
Lower R sk Increased R sk A
vmme a com 7/2/21
min Q1 median Q3 max
Ear y treatment
A st d es
0 0.25 0.5 0.75 1 1 25 1.5 1.75 2+
ower R sk ncreased R sk B

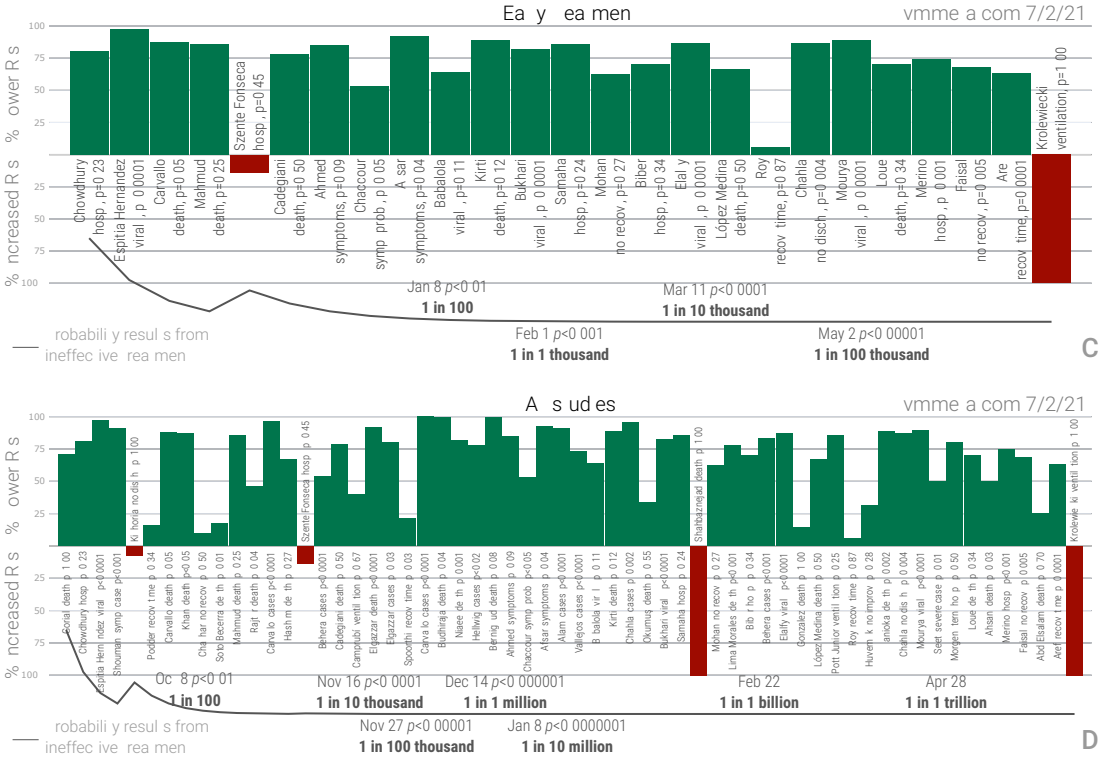


Figure 1. *A. Random effects meta analysis excluding late treatment. This plot shows pooled effects, analysis for individual outcomes is below, and more details on pooled effects can be found in the heterogeneity section. Effect extraction is pre specified, see the appendix for details. Simplified dosages are shown for comparison, these are the total dose in the first four days for treatment, and the monthly dose for prophylaxis, for a 70kg person. For full details see the appendix.* ***B.*** *Scatter plot showing the distribution of effects reported in early treatment studies and in all studies.* ***C and D.*** *Chronological history of all reported effects, with the probability that the observed frequency of positive results occurred due to random chance from an ineffective treatment.*

Introduction

We ana yze a s gn ficant stud es concern ng the use of vermect n for COVID 19. Search methods nc us on cr ter a effect extract on cr ter a (more ser ous outcomes have pr or ty) a nd v dua study data PRISMA answers and stat st ca methods are deta ed n Append x 1. We present random effects meta ana ys s resu ts for a stud es for stud es w th n each treatment stage for morta ty resu ts for COVID 19 case resu ts for v ra c earance resu ts for peer rev ewed stud es for Random zed Contro ed r a s (RC s) and after exc us ons.

We a so perform a s mp e ana ys s of the d str but on of study effects. If treatment was not effect ve the observed effects wou d be random y d str buted (or more ke y to be negat ve f treatment s harmfu). We can compute the probab ty that the observed percentage of pos t ve resu ts (or h gher) cou d occur due to chance w th an neffect ve treatment (the probab ty of >= *k* heads n *n* co n tosses or the one s ded s gn test / b nom a test). Ana ys s of pub cat on b as s mportant and adjustments may be needed f there s a b as toward pub sh ng pos t ve resu ts.

F gure 2 shows stages of poss b e treatment for COVID 19. **Prophylaxis** refers to regu ar y tak ng med cat on before becom ng s ck n order to prevent or m n m ze nfect on. **Early Treatment** refers to treatment mmed ate y or soon after symptoms appear wh e **Late Treatment** refers to more de ayed treatment.

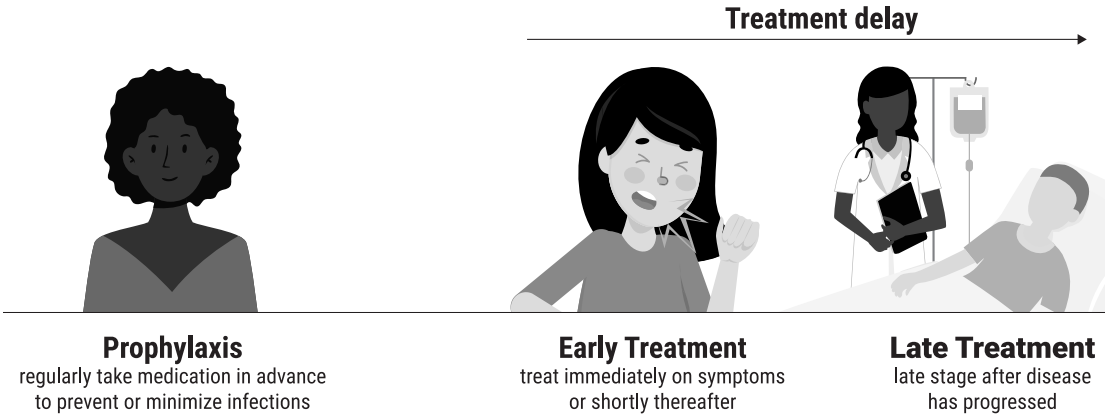


Figure 2. *Treatment stages.*

Results

F gure 3 4 and 5 show resu ts by treatment stage. F gure 6 7 8 9 10 11 and 12 show forest p ots for a random effects meta ana ys s of a stud es w th poo ed effects and for stud es report ng morta ty resu ts ICU adm ss on mechan ca vent at on hosp ta zat on COVID 19 cases and v ra c earance resu ts on y. F gure 13 shows resu ts for peer rev ewed tr a s on y. ab e 1 summar zes the resu ts.

T ea men me	Numbe of s ud es epo ng pos ve effec s	To a numbe of s ud es	Pe cen age of s ud es epo ng pos ve effec s	P obab y of an equa o g ea e pe cen age of pos ve esu s f om an neffec ve ea men	Random effec s me a-ana ys s esu s
Ea y ea men	23	25	**92 0%**	**0 0000097** 1 n 103 housand	**76%** mp ovemen RR 0 24 [0 14-0 41] p < 0 0001
a e ea men	19	21	**90 5%**	**0 00011** 1 n 9 housand	46% mp ovemen RR 0 54 [0 41-0 71] p < 0 0001
P ophy ax s	14	14	**100%**	**0 000061** 1 n 16 housand	**85%** mp ovemen RR 0 15 [0 09-0 25] p < 0 0001
A s ud es	56	60	**93 3%**	**0 00000000000045** 1 n 2 on	**71%** mp ovemen RR 0 29 [0 23-0 38] p < 0 0001

Table 1. *Results by treatment stage.*

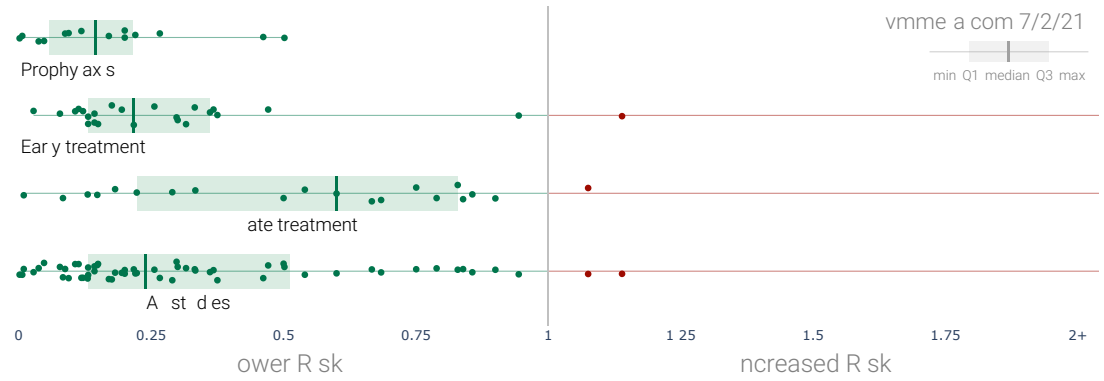


Figure 3. *Results by treatment stage.*

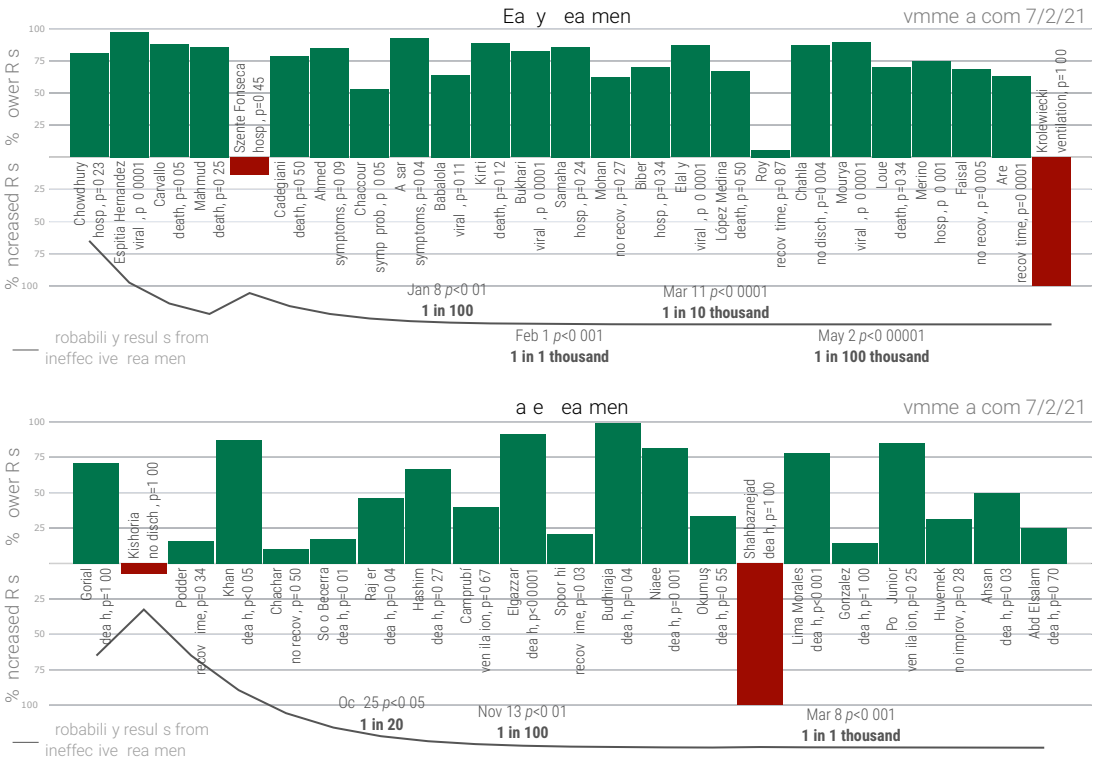


Figure 4. *Chronological history of early and late treatment results, with the probability that the observed frequency of positive results occurred due to random chance from an ineffective treatment.*

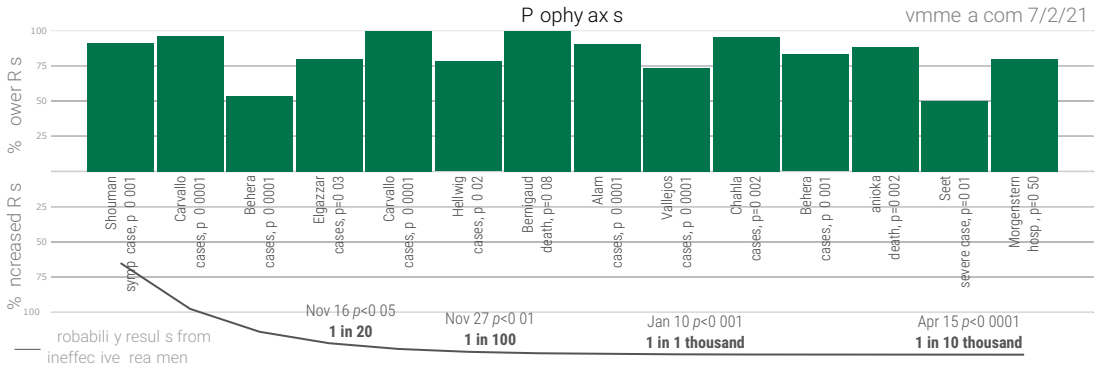


Figure 5. *Chronological history of prophylaxis results.*

All 60 ivermectin COVID-19 studies

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	Improvement, RR [CI]		Treatment	Control	Dose (4d)
Chowdhury (RC)	8 %	0 9 [0 0 3 96 hosp	0/60	2/56	4mg
spi ia Hernandez	97%	0 03 [0 0 0 viral+	0/28	7/7	2mg
Carvallo	88%	0 2 [0 0 06 dea h	/33	3/ 2	36mg
Mahmud (DB RC)	86%	0 4 [0 0 2 75 dea h	0/ 83	3/ 83	2mg
Szen e onseca	4%	4 [0 75 66 hosp	340	377	24mg
Cadegiani	78%	0 22 [0 0 4 48 dea h	0/ 0	2/ 37	42mg
Ahmed (DB RC)	85%	0 5 [0 0 2 70 symp oms	0/ 7	3/ 9	48mg
Chaccour (DB RC)	53%	0 47 [0 9 6 symp prob	2	2	28mg
Afsar	92%	0 08 [0 00 32 symp oms	0/37	7/53	48mg
Babalola (DB RC)	64%	0 36 [0 0 27 viral+	40	20	24mg
Kir i (DB RC)	89%	0 [0 0 2 05 dea h	0/55	4/57	24mg
Bukhari (RC)	82%	0 8 [0 07 0 46 viral+	4/4	25/45	2mg
Samaha (RC)	86%	0 4 [0 0 2 70 hosp	0/50	3/50	2mg
Mohan (DB RC)	62%	0 38 [0 08 75 no recov	2/40	6/45	28mg
Biber (DB RC)	70%	0 30 [0 03 2 76 hosp	/47	3/42	36mg
lalfy	87%	0 3 [0 06 0 27 viral+	7/62	44/5	36mg
ópez Me (DB RC)	67%	0 33 [0 0 8 dea h	0/200	/ 98	84mg
Roy	6%	0 94 [0 52 93 recov ime	4	5	n/a
Chahla (C US RC)	87%	0 3 [0 03 0 54 no disch	2/ 0	20/ 44	24mg
Mourya	89%	0 [0 05 0 25 viral+	5/50	47/50	48mg
oue (QR)	70%	0 30 [0 04 2 20 dea h	/ 0	5/ 5	4mg
Merino (QR)	74%	0 26 [0 0 6 hosp	popula ion	based cohor	24mg
aisal (RC)	68%	0 32 [0 4 0 72 no recov	6/50	9/50	48mg
Aref (RC)	63%	0 37 [0 22 0 62 recov ime	57	57	
Krolewiecki (RC)	52%	2 52 [0 58 ven ila ion	/27	0/ 4	68mg
Early treatment	76%	0 24 [0 14-0 41]	30/1,673	204/1,709	**76% improvement**

Tau² 0 98 ² 82 3%

	Improvement, RR [CI]		Treatment	Control	Dose (4d)
Gorial	7 %	0 29 [0 0 5 76 dea h	0/ 6	2/7	4mg
Kishoria (RC)	8%	08 [0 57 2 02 no disch	/ 9	7/ 3	2mg
odder (RC)	6%	0 84 [0 55 2 recov ime	32	30	4mg
Khan	87%	0 3 [0 02 0 dea h	/ 5	9/ 33	2mg
Chachar (RC)	0%	0 90 [0 44 83 no recov	9/25	0/25	36mg
So o Becerra	7%	0 83 [0 7 0 97 dea h	92/203	,438/2,630	4mg
Raj er (SM)	46%	0 54 [0 27 0 99 dea h	3/98	24/98	4mg
Hashim (SB RC)	67%	0 33 [0 07 60 dea h	2/70	6/70	28mg
Camprubí	40%	0 60 [0 8 2 0 ven ila ion	3/ 3	5/ 3	4mg
lgazzar (RC)	92%	0 08 [0 02 0 35 dea h	2/200	24/200	2mg
Spoor hi	2 %	0 79 [0 62 0 recov ime	50	50	n/a
Budhiraja	99%	0 0 [0 00 0 5 dea h	0/34	03/942	n/a
Niaee (DB RC)	82%	0 8 [0 06 0 55 dea h	4/ 20	/60	28mg
Okumuş (DB RC)	33%	0 67 [0 27 64 dea h	6/30	9/30	56mg
Shahbazn (DB RC)	97%	2 97 [0 3 70 5 dea h	/35	0/34	4mg
ima Morales	78%	0 22 [0 2 0 4 dea h	5/48	52/287	2mg
Gonzalez (DB RC)	4%	0 86 [0 29 2 56 dea h	5/36	6/37	2mg
o Junior (RC)	85%	0 5 [0 0 93 ven ila ion	/27	/4	4mg
Huvemek (DB RC)	32%	0 68 [0 38 23 no improv	3/50	9/50	84mg
Ahsan	50%	0 50 [0 28 0 90 dea h	7/ 0	7/55	2 mg
Abd lsalam (RC)	25%	0 75 [0 7 3 06 dea h	3/82	4/82	36mg
Late treatment	46%	0 54 [0 41-0 71]	198/1 846	1 747/4 914	**46% improvement**

Tau² 0 17 ² 64 2%

	Improvement, RR [CI]		Treatment	Control	Dose (1m)
Shouman (RC)	9 %	0 09 [0 03 0 23 symp case	5/203	59/ 0	36mg
Carvallo	96%	0 04 [0 00 0 63 cases	0/ 3	/98	4mg
Behera	54%	0 46 [0 29 0 7 cases	4 / 7	45/255	42mg
lgazzar (RC)	80%	0 20 [0 04 0 89 cases	2/ 00	0/ 00	2mg
Carvallo	00%	0 00 [0 00 0 02 cases	0/788	237/407	48mg
Hellwig (CO)	78%	0 22 [0 05 0 89 cases	ecological		4mg
Bernigaud	99%	0 0 [0 00 0 0 dea h	0/69	50/3,062	84mg
Alam	9 %	0 09 [0 04 0 24 cases	4/58	44/60	2mg
Vallejos	73%	0 27 [0 5 0 48 cases	3/389	6 /486	48mg
Chahla (RC)	95%	0 05 [0 00 0 80 cases	0/ 7	0/ 7	48mg
Behera	83%	0 7 [0 2 0 23 cases	45/2, 99	33/ , 47	42mg
anioka (CO)	88%	0 2 [0 03 0 5 dea h	ecological		4mg
See (C US RC)	50%	0 50 [0 33 0 76 severe case	32/6 7	64/6 9	2mg
Morgens ern (SM)	80%	0 20 [0 0 4 5 hosp	0/27	2/27	56mg
Prophylaxis	85%	0 15 [0 09-0 25]	152/5,059	926/3,730	**85% improvement**

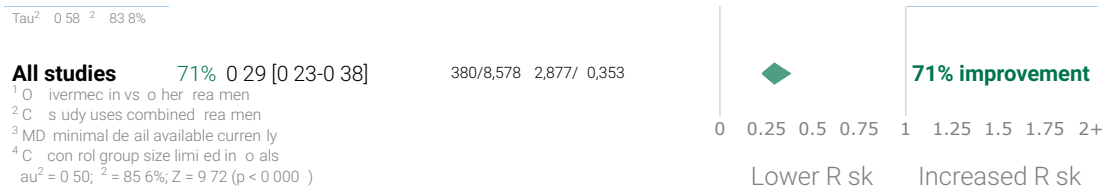


Figure 6. *Random effects meta analysis for all studies.*

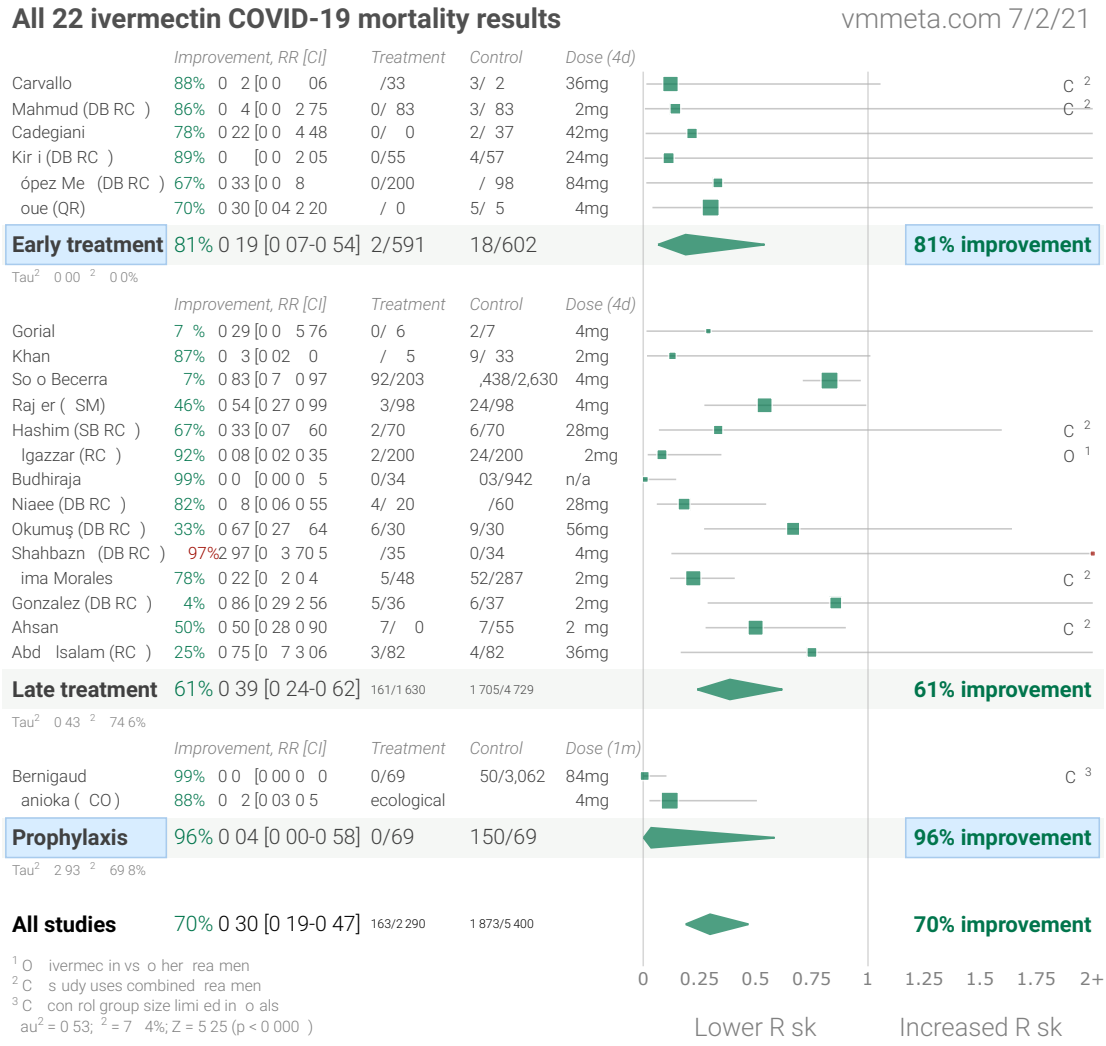


Figure 7. *Random effects meta analysis for mortality results only. The control group size for [**Bernigaud**] is limited when calculating the total number of patients, see the appendix for details.*

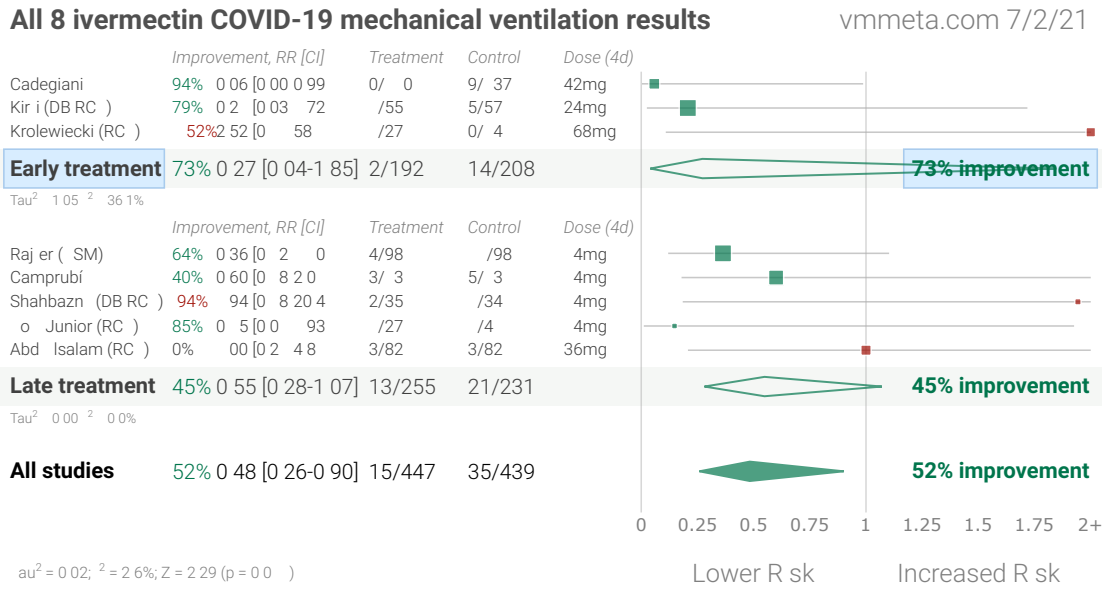


Figure 8. *Random effects meta analysis for mechanical ventilation results only.*

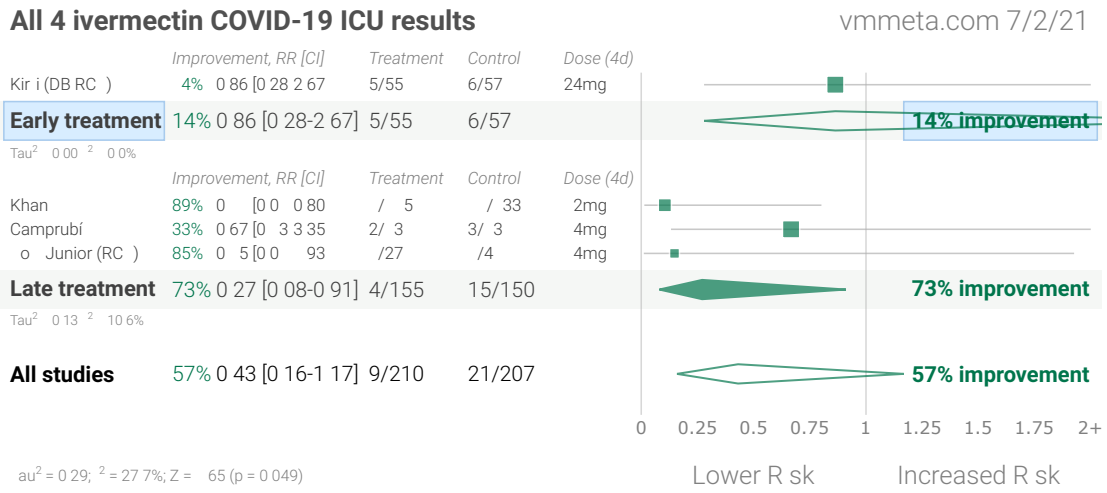


Figure 9. *Random effects meta analysis for ICU admission results only.*

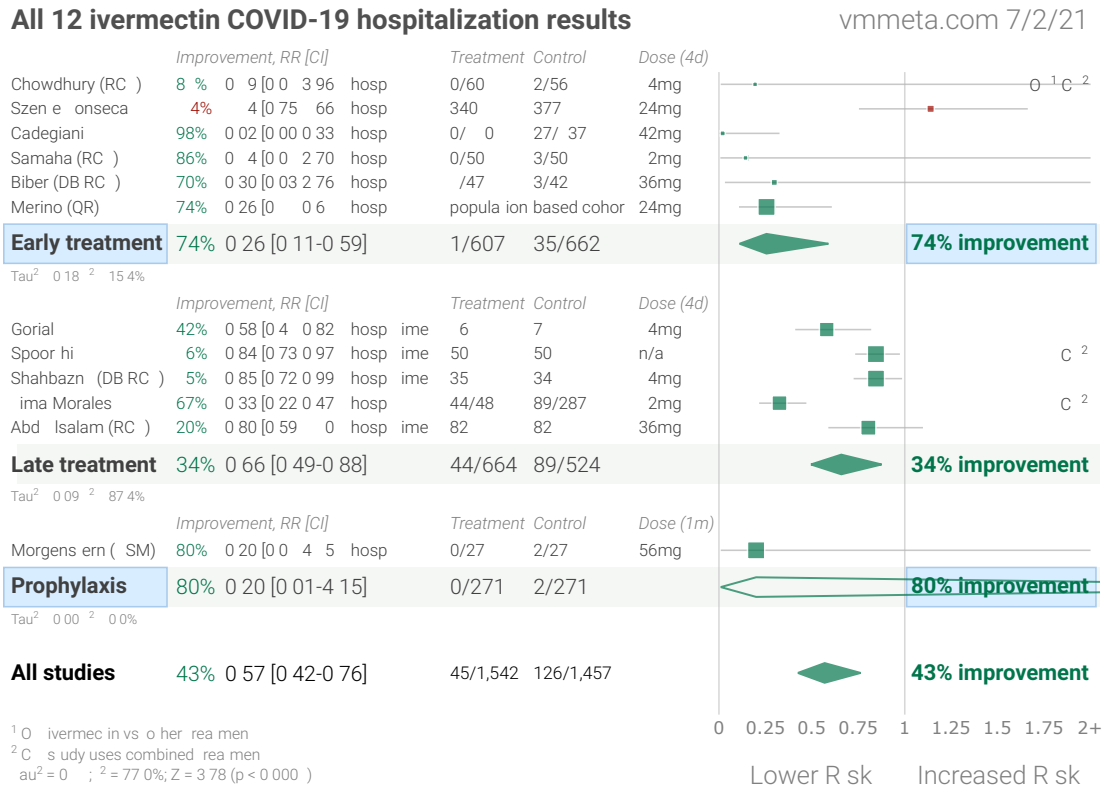
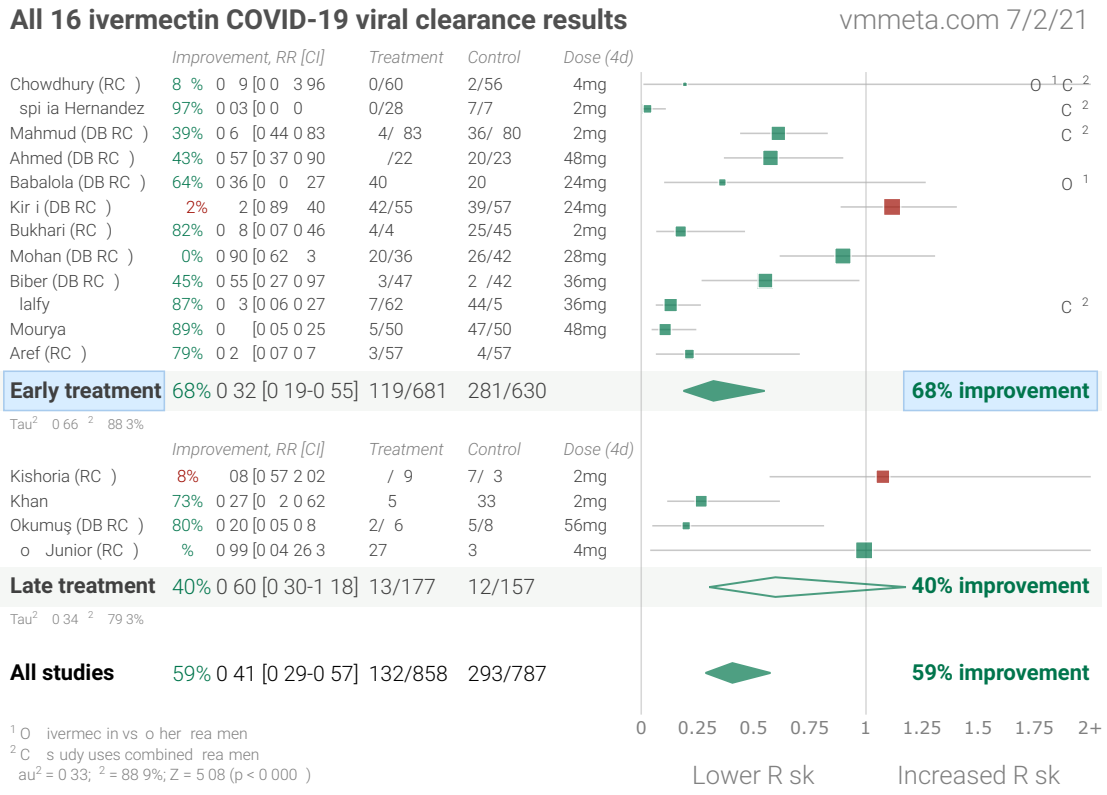


Figure 10. *Random effects meta analysis for hospitalization results only.*

Figure 11. *Random effects meta analysis for COVID 19 case results only.*



[1] O ivermec in vs o her rea men
[2] C s udy uses combined rea men
au² = 0 33; ² = 88 9%; Z = 5 08 (p < 0 000)

Figure 12. *Random effects meta analysis for viral clearance results only.*

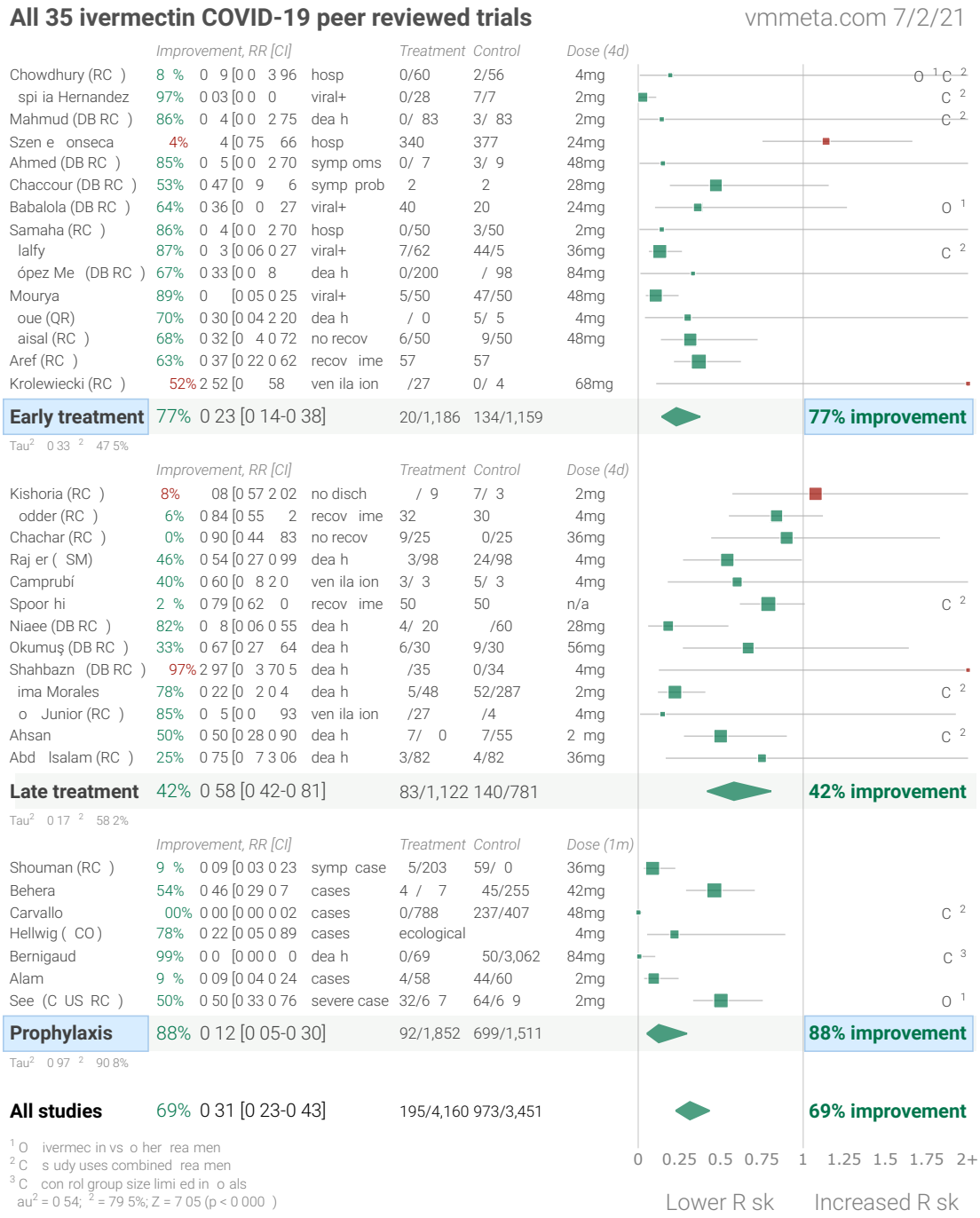


Figure 13. *Random effects meta analysis for peer reviewed trials only.*

Randomized Controlled Trials (RCTs)

Resu ts restr cted to Random zed Contro ed r a s (RC s) are shown n F gure 14 15 16 and 17 and ab e 2. RC resu ts are s m ar to non RC resu ts. Ev dence shows that non RC tr a s can a so prov de re ab e resu ts. *[Concato]* find that we des gned observat ona stud es do not systemat ca y overest mate the magn tude of the effects of treatment compared to RC s. *[Anglemyer]* summar zed rev ews compar ng RC s to observat ona stud es and found tt e

ev dence for s gn ficant d fferences n effect est mates. *[**Lee**]* shows that on y 14% of the gu de nes of the Infect ous D seases Soc ety of Amer ca were based on RC s. Eva uat on of stud es re es on an understand ng of the study and potent a b ases. L m tat ons n an RC can outwe gh the benefits for examp e excess ve dosages excess ve treatment de ays or Internet survey b as cou d have a greater effect on resu ts. Eth ca ssues may a so prevent runn ng RC s for known effect ve treatments. For more on ssues w th RC s see *[**Deaton**, **Nichol**]*.

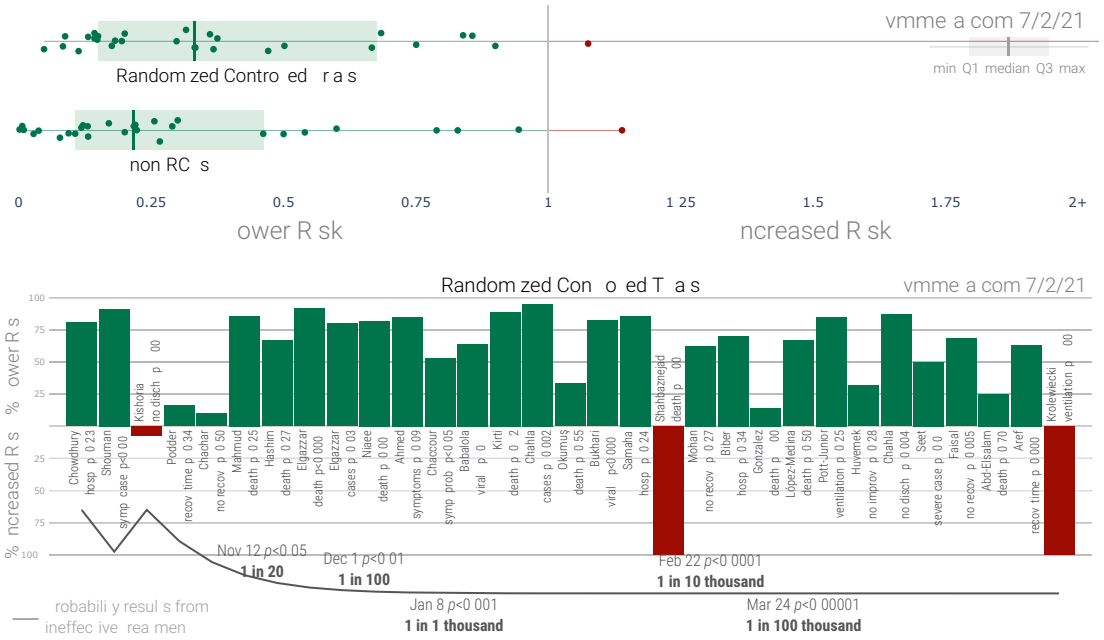


Figure 14. *Randomized Controlled Trials. The distribution of results for RCTs is similar to the distribution for all other studies.*

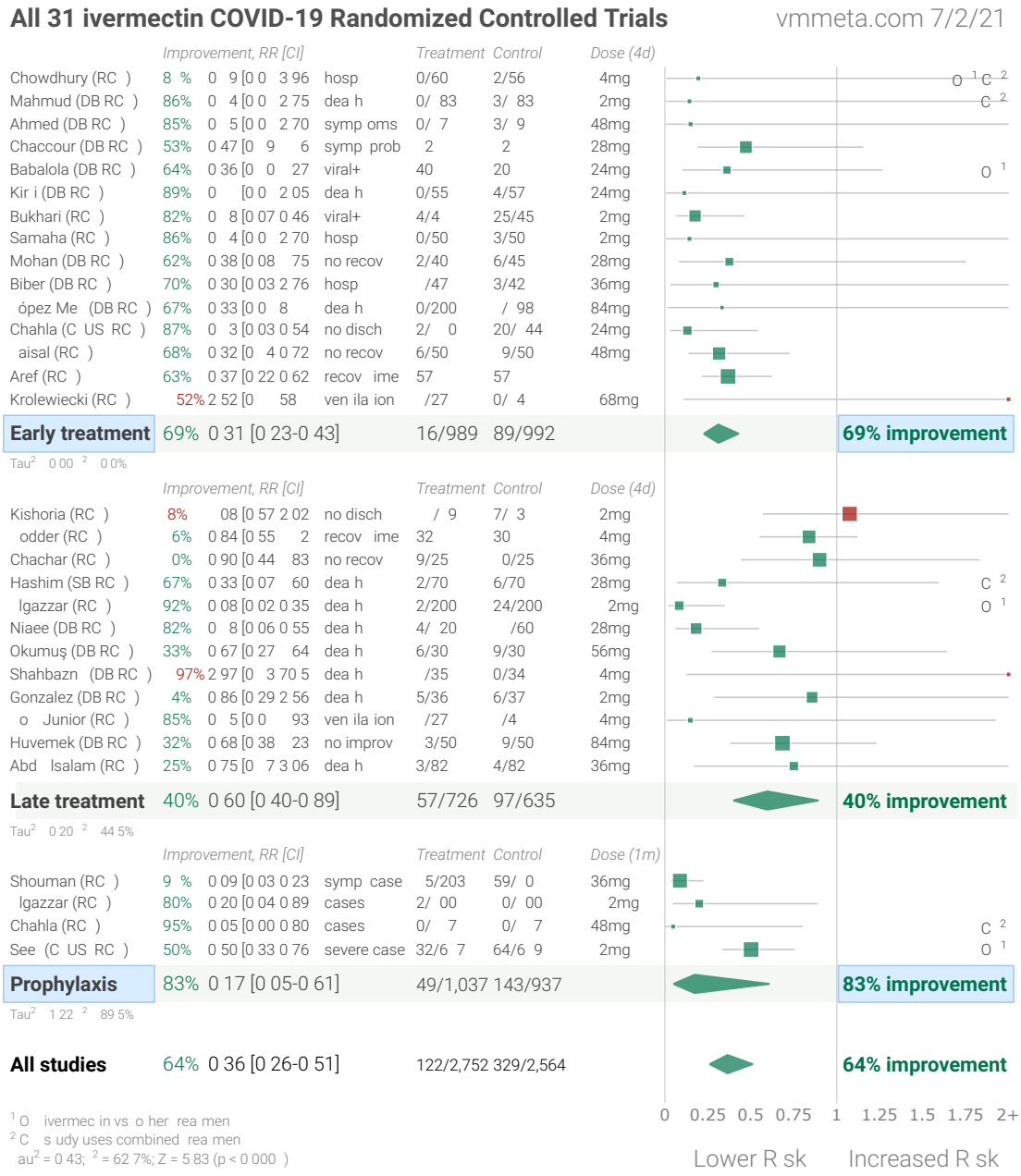


Figure 15. *Random effects meta analysis for Randomized Controlled Trials only.*

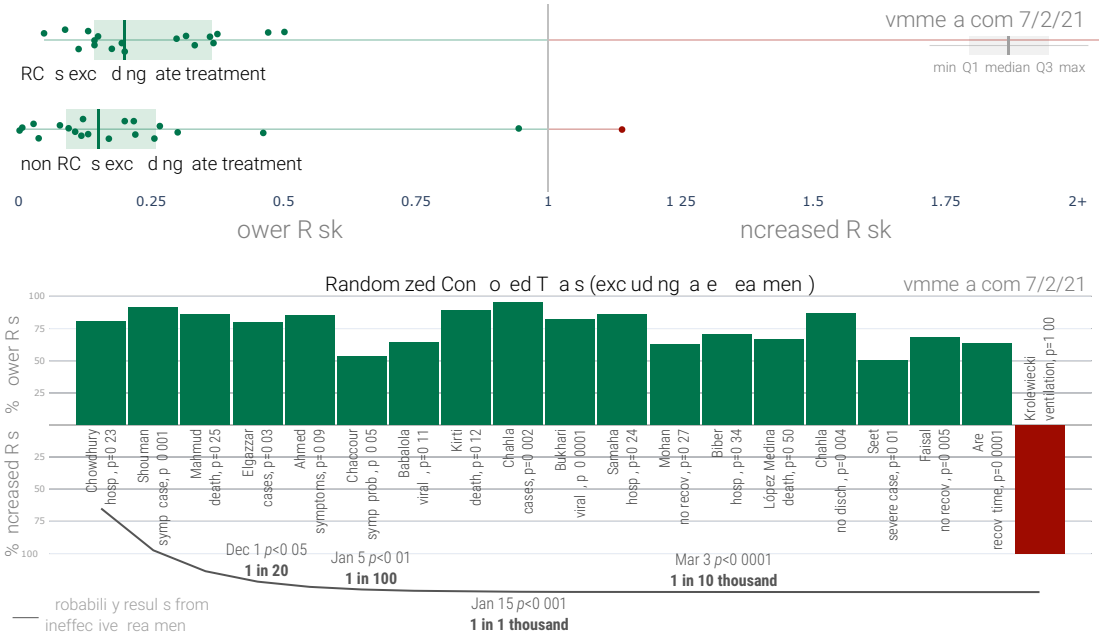


Figure 17. *RCTs excluding late treatment.*

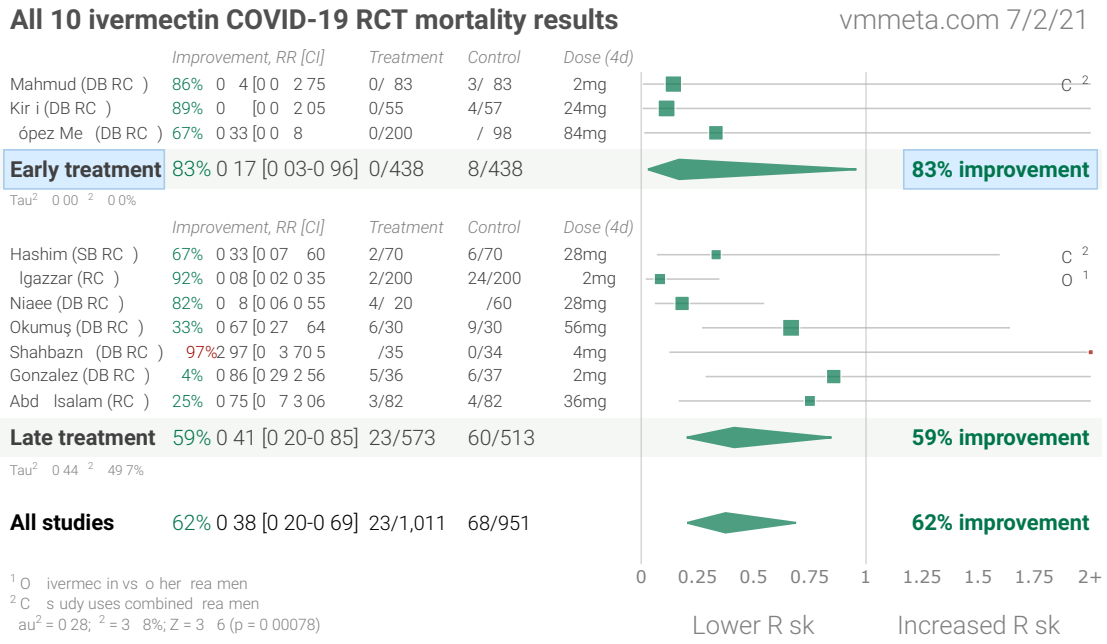


Figure 16. *Random effects meta analysis for Randomized Controlled Trial mortality results only.*

T ea men me	Numbe of s ud es epo ng pos ve effec s	To a numbe of s ud es	Pe cen age of s ud es epo ng pos ve effec s	P obab y of an equa o g ea e pe cen age of pos ve esu s f om an neffec ve ea men	Random effec s me a-ana ys s esu s
Random zed Con o ed T a s	28	31	**90 3%**	**0 0000023** 1 n 430 housand	**64%** mp ovemen RR 0 36 [0 26-0 51] p < 0 0001
Random zed Con o ed T a s (exc ud ng a e ea men)	18	19	**94 7%**	**0 000038** 1 n 26 housand	**75%** mp ovemen RR 0 25 [0 17-0 38] p < 0 0001

Table 2. *Summary of RCT results.*

Exclusions

o avo d b as n the se ect on of stud es we nc ude a stud es n the ma n ana ys s. Here we show the resu ts after exc ud ng stud es w th cr t ca ssues ke y to a ter resu ts non standard stud es and stud es where very m n ma deta s current y ava ab e. Our b as eva uat on s based on fu ana ys s of each study and dent fy ng when there s a s gn ficant chance that m tat ons w substant a y change the outcome of the study. We be eve th s can be more va uab e than check st based approaches such as Cochrane GRADE wh ch may underemphas ze ser ous ssues not captured n the check sts and overemphas ze ssues un ke y to a ter outcomes n spec fic cases (for examp e ack of b nd ng for an object ve morta ty outcome or certa n spec fics of random zat on w th a very arge effect s ze). However these approaches can be very h gh qua ty when we done espec a y when the authors carefu y rev ew each study n deta *[Bryant]*.

[Soto Becerra] s a database ana ys s cover ng anyone w th ICD 10 COVID 19 codes wh ch nc udes asymptomat c PCR+ pat ents. herefore many pat ents n the contro group are ke y asymptomat c w th regards to SARS CoV 2 but n the hosp ta for another reason. For those that had symptomat c COVID 19 there s a so ke y s gn ficant confound ng by nd cat on. KM curves show that the treatment groups were n more ser ous cond t on w th more than the tota excess morta ty at 30 days occurr ng on day 1. A treatments are worse than the contro group at 30 days wh e at the atest fo owup a treatments show ower morta ty than contro . he mach ne earn ng system used a so appears over parameter zed and ke y to resu t n s gn ficant overfitt ng and naccurate resu ts. here s a so no rea contro group n th s study pat ents rece v ng the treatments after 48 hours were put n the contro group. Authors a so state that outcomes w th n 24 hours were exc uded however the KM curves show s gn ficant morta ty at day 1 (on y for the treatment groups). Severa protoco v o at ons have a so been reported n th s study *[Yim]*. Note that th s study prov des both 30 day morta ty and we ghted KM curves up to day 43 for vermect n we use the day 43 resu ts as per our protoco .

[López Medina] has many ssues. he pr mary outcome was changed m d tr a from c n ca deter orat on to comp ete reso ut on of symptoms nc ud ng not hosp ta zed and no m tat on of act v t es as a negat ve outcome. Cr t ca y temporary s de effects of a successfu treatment may be cons dered as a negat ve outcome wh ch cou d resu t n fa se y conc ud ng that the treatment s not effect ve. Such an outcome s a so not very mean ngfu n terms of assess ng how treatment affects the nc dence of ser ous outcomes. W th the ow r sk pat ent popu at on n th s study there s a so tt e room for mprovement 58% recovered w th n the first 2 days to not hosp ta zed and no

m tat on of act v t es or better. here was on y one death (n the contro arm). h s study a so gave vermect n to the contro arm for 38 pat ents and t s unknown f the fu extent of the error was dent fied or f there were add t ona und scovered errors. he s de effect data reported n th s tr a ra ses major concerns w th more s de effects reported n the p acebo arm suggest ng that more p acebo pat ents may have rece ved treatment. Ivermect n was w de y used n the popu at on and ava ab e O C at the t me of the study. he study protoco a ows other treatments but does not report on usage. he name of the study drug was concea ed by refer ng to t as D11AX22 . he presentat on of th s study a so appears to be s gn ficant y b ased. Wh e a outcomes show a benefit for vermect n the abstract fa s to ment on that much arger benefits are seen for ser ous outcomes nc ud ng the or g na pr mary outcome and that the reason for not reach ng stat st ca s gnficance s the ow number of events n a ow r sk popu at on where most recover qu ck y w thout treatment.

*[**Vallejos**]* reports prophy ax s resu ts however on y very m n ma deta s are current y ava ab e n a news report. We nc ude these resu ts for add t ona confirmat on of the efficacy observed n other tr a s however th s study s exc uded here. *[**Hellwig**]* ana yze Afr can countr es and COVID 19 cases n October 2020 as a funct on of whether w despread prophy act c use of vermect n s used for paras t c nfect ons. *[**Tanioka**]* perform a s m ar ana ys s for COVID 19 morta ty n January 2021. hese stud es are exc uded because they are not c n ca tr a s. *[**Galan**]* perform an RC compar ng vermect n and other treatments w th very ate stage severe cond t on hosp ta zed pat ents not show ng s gn ficant d fferences between the treatments. Authors were unab e to add a contro arm due to eth ca ssues. he c osest contro compar son we cou d find s *[**Baqui**]* wh ch shows 43% hosp ta morta ty n the northern reg on of Braz where the study was performed from wh ch we can est mate the morta ty w th vermect n n th s study as 47% ower RR 0.53. Further the study s restr cted to more severe cases hence the expected morta ty and therefore the benefit of treatment may be h gher. *[**Kishoria**]* restr ct nc us on to pat ents that d d not respond to standard treatment prov de no deta s on the t me of the d scharge status and there are very arge unadjusted d fferences n the groups w th over tw ce as many pat ents n the vermect n group w th age >40 and a pat ents over 60 n the vermect n group.

Summar z ng the stud es exc uded are as fo ows and the resu t ng forest p ot s shown n F gure 18.

*[**Ahsan**]* unadjusted resu ts w th no group deta s.

*[**Carvallo**]* contro group formed from cases n the same hosp ta not n the study deta s of contro group pat ents not prov ded.

*[**Hellwig**]* not a typ ca tr a ana ys s of Afr can countr es that used or d d not use vermect n prophy ax s for paras t c nfect ons.

*[**Kishoria**]* excess ve unadjusted d fferences between groups.

*[**López Medina**]* strong ev dence of pat ents n the contro group se f med cat ng vermect n w de y used n the popu at on at that t me and the study drug dent ty was concea ed by us ng the name D11AX22.

*[**Roy**]* no ser ous outcomes reported and fast recovery n treatment and contro groups there s tt e room for a treatment to mprove resu ts.

*[**Soto Becerra**]* substant a unadjusted confound ng by nd cat on ke y nc udes PCR+ pat ents that may be asymptomat c for COVID 19 but n hosp ta for other reasons.

*[**Tanioka**]* not a typ ca tr a ana ys s of Afr can countr es that used or d d not use vermect n prophy ax s for paras t c nfect ons.

*[**Vallejos**]* deta too m n ma .

All 51 ivermectin COVID-19 studies with exclusions

vmmeta.com 7/2/21

	Improvement, RR [CI]		Treatment	Control	Dose (4d)
Chowdhury (RC)	8 %	0 9 [0 0 3 96 hosp	0/60	2/56	4mg
spi ia Hernandez	97%	0 03 [0 0 0 viral+	0/28	7/7	2mg
Mahmud (DB RC)	86%	0 4 [0 0 2 75 dea h	0/ 83	3/ 83	2mg
Szen e onseca	4%	4 [0 75 66 hosp	340	377	24mg
Cadegiani	78%	0 22 [0 0 4 48 dea h	0/ 0	2/ 37	42mg
Ahmed (DB RC)	85%	0 5 [0 0 2 70 symp oms	0/ 7	3/ 9	48mg
Chaccour (DB RC)	53%	0 47 [0 9 6 symp prob	2	2	28mg
Afsar	92%	0 08 [0 00 32 symp oms	0/37	7/53	48mg
Babalola (DB RC)	64%	0 36 [0 0 27 viral+	40	20	24mg
Kir i (DB RC)	89%	0 [0 0 2 05 dea h	0/55	4/57	24mg
Bukhari (RC)	82%	0 8 [0 07 0 46 viral+	4/4	25/45	2mg
Samaha (RC)	86%	0 4 [0 0 2 70 hosp	0/50	3/50	2mg
Mohan (DB RC)	62%	0 38 [0 08 75 no recov	2/40	6/45	28mg
Biber (DB RC)	70%	0 30 [0 03 2 76 hosp	/47	3/42	36mg
lalfy	87%	0 3 [0 06 0 27 viral+	7/62	44/5	36mg
Chahla (C US RC)	87%	0 3 [0 03 0 54 no disch	2/ 0	20/ 44	24mg
Mourya	89%	0 [0 05 0 25 viral+	5/50	47/50	48mg
oue (QR)	70%	0 30 [0 04 2 20 dea h	/ 0	5/ 5	4mg
Merino (QR)	74%	0 26 [0 0 6 hosp	popula ion	based cohor	24mg
aisal (RC)	68%	0 32 [0 4 0 72 no recov	6/50	9/50	48mg
Aref (RC)	63%	0 37 [0 22 0 62 recov ime	57	57	
Krolewiecki (RC)	52%	2 52 [0 58 ven ila ion	/27	0/ 4	68mg
Early treatment	78%	0 22 [0 16-0 31]	29/1,426	200/1,484	
Tau² 0 15 ² 27 2%					
	Improvement, RR [CI]		*Treatment*	*Control*	*Dose (4d)*
Gorial	7 %	0 29 [0 0 5 76 dea h	0/ 6	2/7	4mg
odder (RC)	6%	0 84 [0 55 2 recov ime	32	30	4mg
Khan	87%	0 3 [0 02 0 dea h	/ 5	9/ 33	2mg
Chachar (RC)	0%	0 90 [0 44 83 no recov	9/25	0/25	36mg
Raj er (SM)	46%	0 54 [0 27 0 99 dea h	3/98	24/98	4mg
Hashim (SB RC)	67%	0 33 [0 07 60 dea h	2/70	6/70	28mg
Camprubí	40%	0 60 [0 8 2 0 ven ila ion	3/ 3	5/ 3	4mg
lgazzar (RC)	92%	0 08 [0 02 0 35 dea h	2/200	24/200	2mg
Spoor hi	2 %	0 79 [0 62 0 recov ime	50	50	n/a
Budhiraja	99%	0 0 [0 00 0 5 dea h	0/34	03/942	n/a
Niaee (DB RC)	82%	0 8 [0 06 0 55 dea h	4/ 20	/60	28mg
Okumuş (DB RC)	33%	0 67 [0 27 64 dea h	6/30	9/30	56mg
Shahbazn (DB RC)	97%	2 97 [0 3 70 5 dea h	/35	0/34	4mg
ima Morales	78%	0 22 [0 2 0 4 dea h	5/48	52/287	2mg
Gonzalez (DB RC)	4%	0 86 [0 29 2 56 dea h	5/36	6/37	2mg
o Junior (RC)	85%	0 5 [0 0 93 ven ila ion	/27	/4	4mg
Huvemek (DB RC)	32%	0 68 [0 38 23 no improv	3/50	9/50	84mg
Abd lsalam (RC)	25%	0 75 [0 7 3 06 dea h	3/82	4/82	36mg
Late treatment	54%	0 46 [0 32-0 67]	78/1,514	285/2,216	
Tau² 0 29 ² 62 5%					
	Improvement, RR [CI]		*Treatment*	*Control*	*Dose (1m)*
Shouman (RC)	9 %	0 09 [0 03 0 23 symp case	5/203	59/ 0	36mg
Carvallo	96%	0 04 [0 00 0 63 cases	0/ 3	/98	4mg
Behera	54%	0 46 [0 29 0 7 cases	4 / 7	45/255	42mg
lgazzar (RC)	80%	0 20 [0 04 0 89 cases	2/ 00	0/ 00	2mg
Carvallo	00%	0 00 [0 00 0 02 cases	0/788	237/407	48mg
Bernigaud	99%	0 0 [0 00 0 0 dea h	0/69	50/3,062	84mg
Alam	9 %	0 09 [0 04 0 24 cases	4/58	44/60	2mg
Chahla (RC)	95%	0 05 [0 00 0 80 cases	0/ 7	0/ 7	48mg
Behera	83%	0 7 [0 2 0 23 cases	45/2, 99	33/ , 47	42mg
See (C US RC)	50%	0 50 [0 33 0 76 severe case	32/6 7	64/6 9	2mg
Morgens ern (SM)	80%	0 20 [0 0 4 5 hosp	0/27	2/27	56mg
Prophylaxis	87%	0 13 [0 07-0 25]	139/4,670	865/3,244	
Tau² 0 70 ² 87 4%					
All studies	74%	0 26 [0 20-0 35]	246/7 610	1 350/6 944	

[1] O ivermec in vs o her rea men
[2] C s udy uses combined rea men
[3] C con rol group size limi ed in o als
au² = 0 54; ² = 76 3%; Z = 9 32 (p < 0 000)

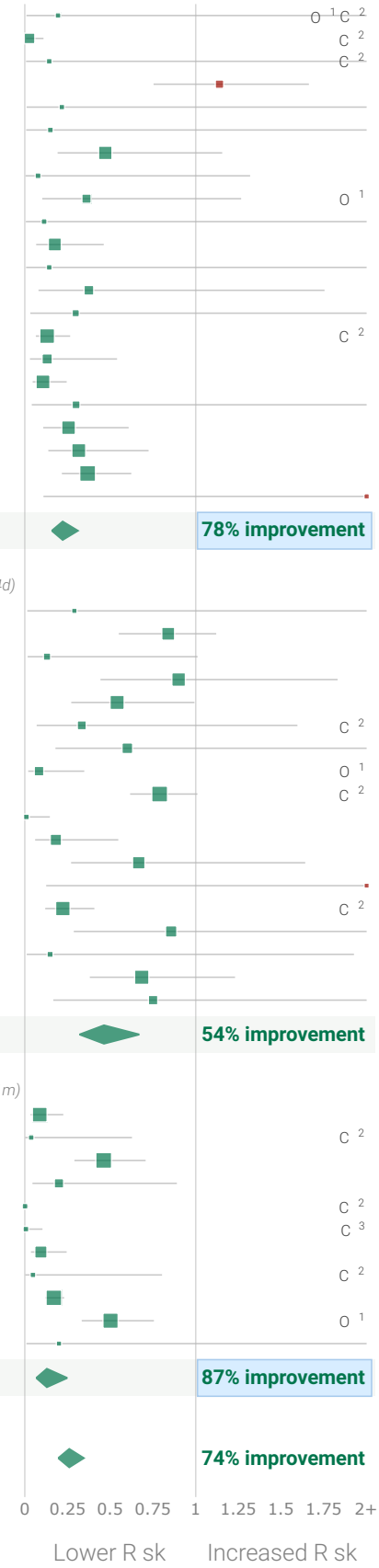


Figure 18. *Random effects meta analysis excluding studies with significant issues.*

Heterogeneity

Heterogene ty n COVID 19 stud es ar ses from many factors nc ud ng:

Treatment delay. he t me between nfect on or the onset of symptoms and treatment may cr t ca y affect how we a treatment works. For examp e an ant v ra may be very effect ve when used ear y but may not be effect ve n ate stage d sease and may even be harmfu . F gure 19 shows an examp e where efficacy dec nes as a funct on of treatment de ay. Other med cat ons m ght be benefic a for ate stage comp cat ons wh e ear y use may not be effect ve or may even be harmfu . Ose tam v r for examp e s genera y on y cons dered effect ve for nfluenza when used w th n 0 36 or 0 48 hours *[McLean, Treanor]*.

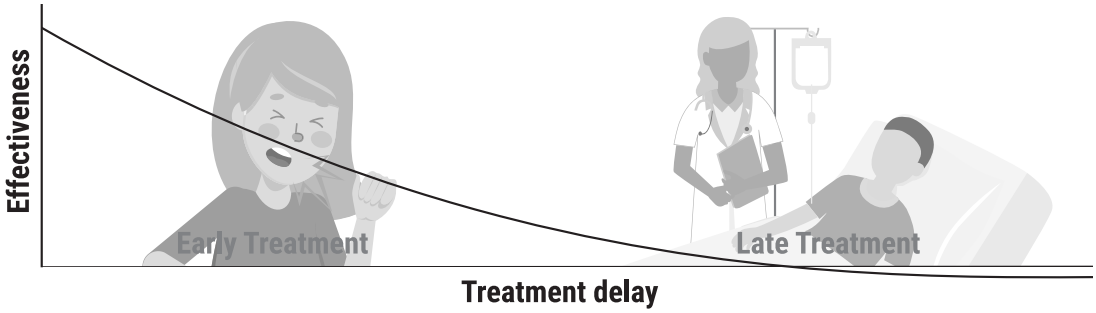


Figure 19. *Effectiveness may depend critically on treatment delay.*

Patient demographics. Deta s of the pat ent popu at on nc ud ng age and comorb d t es may cr t ca y affect how we a treatment works. For examp e many COVID 19 stud es w th re at ve y young ow comorb d ty pat ents show a pat ents recover ng qu ck y w th or w thout treatment. In such cases there s tt e room for an effect ve treatment to mprove resu ts (as n *[López Medina]*).

Effect measured. Efficacy may d ffer s gn ficant y depend ng on the effect measured for examp e a treatment may be very effect ve at reduc ng morta ty but ess effect ve at m n m z ng cases or hosp ta zat on. Or a treatment may have no effect on v ra c earance wh e st be ng effect ve at reduc ng morta ty.

Variants. here are thousands of d fferent var ants of SARS CoV 2 and efficacy may depend cr t ca y on the d str but on of var ants encountered by the pat ents n a study.

Regimen. Effect veness may depend strong y on the dosage and treatment reg men. H gher dosages have been found to be more successfu for vermect n *[Hill]*. Method of adm n strat on may a so be cr t ca . *[Guzzo]* show that the p asma concentrat on of vermect n s much h gher when adm n stered w th food (F gure 20: geometr c mean AUC 2.6 t mes h gher). Many vermect n stud es spec fy fast ng or they do not spec fy adm n strat on. Fast ng adm n strat on s expected to reduce effect veness for COVID 19 due to ower p asma and t ssue concentrat ons. Note that th s s d fferent to anthe m nt c use n the gastro ntest na tract where fast ng s recommended.

Treatments. he use of other treatments may s gn ficant y affect outcomes nc ud ng anyth ng from supp ements other med cat ons or other k nds of treatment such as prone pos t on ng.

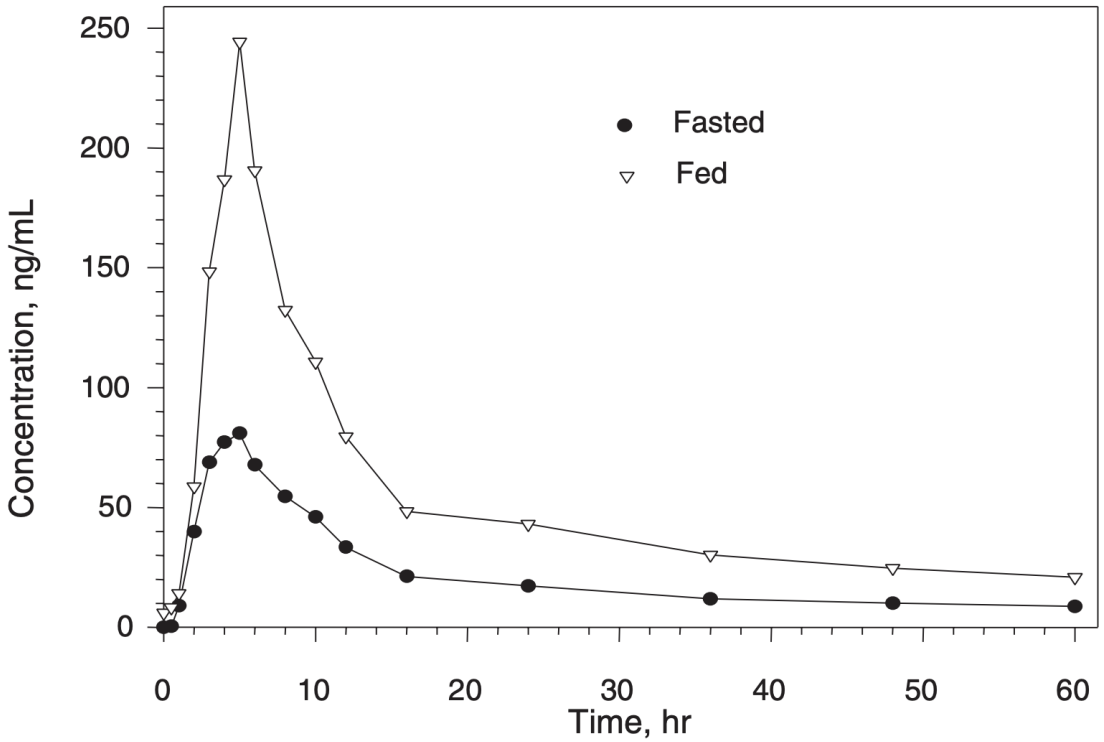


Figure 20. *Mean plasma concentration (ng/ml) profiles of ivermectin following single oral doses of 30mg (fed and fasted administration), from [**Guzzo**].*

he d str but on of stud es w a ter the outcome of a meta ana ys s. Cons der a s mp fied examp e where everyth ng s equa except for the treatment de ay and effect veness decreases to zero or be ow w th ncreas ng de ay. If there are many stud es us ng very ate treatment the outcome may be negat ve even though the treatment may be very effect ve when used ear er.

In genera by comb n ng heterogeneous stud es as a meta ana yses do we run the r sk of obscur ng an effect by nc ud ng stud es where the treatment s ess effect ve not effect ve or harmfu .

When nc ud ng stud es where a treatment s ess effect ve we expect the est mated effect s ze to be ower than that for the opt ma case. We do not *a priori* expect that poo ng a stud es w create a pos t ve resu t for an effect ve treatment. Look ng at a stud es s va uab e for prov d ng an overv ew of a research and mportant to avo d cherry p ck ng but the resu t ng est mate does not app y to spec fic cases such as ear y treatment n h gh r sk popu at ons.

Ivermect n stud es vary w de y n a the factors above wh ch makes the cons stent y pos t ve resu ts even more remarkab e. A fa ure to detect an assoc at on after comb n ng heterogeneous stud es does not mean the treatment s not effect ve (t may on y work n certa n cases) however the reverse s not true — an dent fied assoc at on s va d a though the magn tude of the effect may be arger for more opt ma cases and ower for ess opt ma cases. As above the probab ty that an neffect ve treatment generated resu ts as pos t ve as the 60 stud es to date s est mated to be 1 n 2 tr on (p = 0.00000000000045). h s resu t benefits from the fact that vermect n shows some

degree of efficacy for COVID 19 n a w de var ety of cases. It a so ke y benefits from the fact that re at ve y few vermect n tr a s to date have been des gned n a way that favors poor resu ts. However more tr a s des gned n th s way are expected for examp e the OGE HER tr a s test ng vermect n n ocat ons known to have a h gh degree of se f med cat on and us ng ow doses compared to current c n ca recommendat ons as updated for current var ants. As w th a compan on tr a th s tr a may a so nc ude very ow r sk pat ents nc ude re at ve y ate treatment wh e dent fy ng as an ear y treatment tr a and use an act ve p acebo (v tam n C). Wh e we present resu ts for a stud es n th s paper the nd v dua outcome and treatment t me ana yses are more re evant for spec fic use cases.

Discussion

Pub sh ng s often b ased towards pos t ve resu ts wh ch we wou d need to adjust for when ana yz ng the percentage of pos t ve resu ts. For vermect n there s current y not enough data to eva uate pub cat on b as w th h gh confidence. One method to eva uate b as s to compare prospect ve vs. retrospect ve stud es. Prospect ve stud es are ke y to be pub shed regard ess of the resu t wh e retrospect ve stud es are more ke y to exh b t b as. For examp e researchers may perform pre m nary ana ys s w th m n ma effort and the resu ts may nfluence the r dec s on to cont nue. Retrospect ve stud es a so prov de more opportun t es for the spec fics of data extract on and adjustments to nfluence resu ts. F gure 21 shows a scatter p ot of resu ts for prospect ve and retrospect ve stud es. he med an effect s ze for prospect ve stud es s 78% mprovement compared to 74% for retrospect ve stud es show ng no s gn ficant d fference. *[**Bryant**]* a so perform a funne p ot ana ys s wh ch they found d d not suggest ev dence of pub cat on b as.

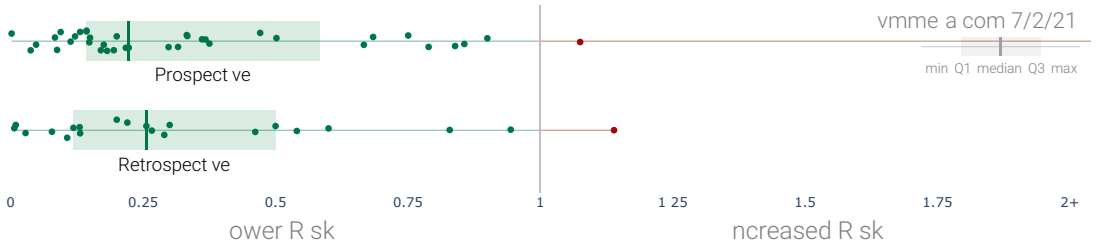


Figure 21. *Prospective vs. retrospective studies.*

News coverage of vermect n stud es s extreme y b ased. On y one study to date has rece ved s gn ficant press coverage n western med a *[**López Medina**]* wh ch s ne ther the argest or the east b ased study and s one of the two stud es w th the most cr t ca ssues as d scussed ear er.

4 of the 60 stud es compare aga nst other treatments rather than p acebo. Current y vermect n shows better resu ts than these other treatments however vermect n may show greater mprovement when compared to p acebo. 13 of 60 stud es comb ne treatments for examp e vermect n + doxycyc ne. he resu ts of vermect n a one may d ffer. 4 of 31 RC s use comb ned treatment three w th doxycyc ne and one w th ota carrageenan. 1 of 60 stud es current y have m n ma pub shed deta s ava ab e.

yp ca meta ana yses nvo ve subject ve se ect on cr ter a effect extract on ru es and study b as eva uat on wh ch can be used to b as resu ts towards a spec fic outcome. In order to avo d b as we nc ude a stud es and use a pre spec fied method to extract resu ts from a stud es (we a so

present resu ts after exc us ons). he resu ts to date are overwhe m ng y pos t ve very cons stent and very nsens t ve to potent a se ect on cr ter a effect extract on ru es and/or b as eva uat on.

Add t ona meta ana yses confirm ng the effect veness of vermect n can be found n *[**Bryant**, **Hill**, **Kory**, **Lawrie**]*. F gure 22 shows a compar son of morta ty resu ts across meta ana yses. *[**Kory**]* a so rev ew ep dem o og ca data and prov de suggested treatment reg mens.

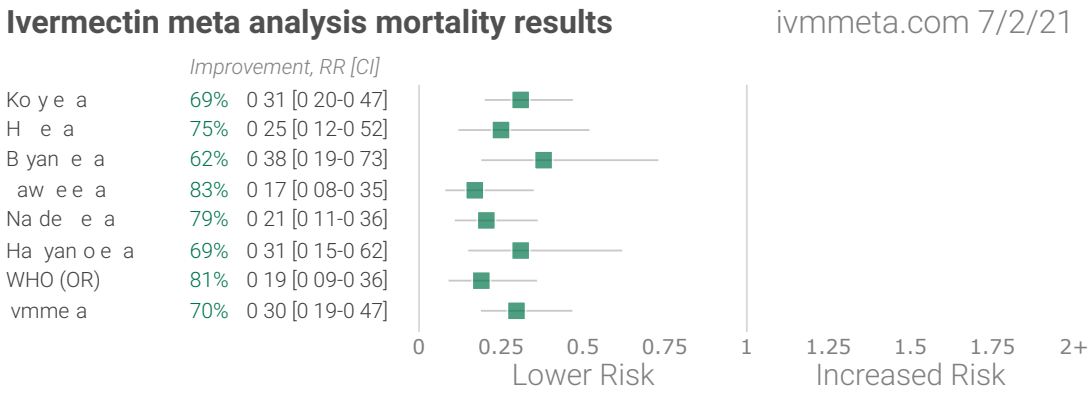


Figure 22. *Comparison of mortality results from different meta analyses. OR converted to RR for [**Kory**, **Nardelli**]. OR displayed for [**WHO**]. WHO provides two results, one based on 5 studies and one based on 7, with no explanation for the difference. The result based on 7 studies is shown here, for which the details required to calculate the RR are not provided.*

he ev dence support ng vermect n for COVID 19 far exceeds the typ ca amount of ev dence used for the approva of treatments. *[**Lee**]* shows that on y 14% of the gu de nes of the Infect ous D seases Soc ety of Amer ca were based on RC s. ab e 3 and ab e 4 compare the amount of ev dence for vermect n compared to that used for other COVID 19 approva s and that used by WHO for the approva of vermect n for scab es and strongy o d as s. ab e 5 compares US CDC recommendat ons for buprofen and vermect n.

Indication	*Studies*	*Patients*	*Status*
S ongy o d as s *[**Kory (B)**]*	5	591	App oved
Scab es *[**Kory (B)**]*	10	852	App oved
COV D-19	60	18,931	Pend ng
COV D-19 RCTs	31	5,316	

Table 3. *WHO ivermectin approval status.*

Medication	*Studies*	*Patients*	*Improvement*	*Status*
Budeson de (UK)	1	1,779	17%	App oved
Remdes v (USA)	1	1,063	31%	App oved
Cas / mdev mab (USA)	1	799	66%	App oved
Ivermectin evidence	60	18,931	71% [62-77%]	Pend ng

Table 4. *Evidence base used for other COVID 19 approvals compared with the ivermectin evidence base.*

	Ibuprofen	*Ivermectin (for scabies)*	*Ivermectin (for COVID-19)*
ves saved	0	0	>500,000
Dea hs pe yea	~450	<1	<1
CDC ecommended	Yes	Yes	No
Based on	0 RCTs	10 RCTs 852 pa en s	31 RCTs 5,316 pa en s

Table 5. *Comparison of CDC recommendations [**Kory (B)**].*

WHO Analysis

WHO updated the r treatment recommendat ons on 3/30/2021 *[**WHO**]*. For vermect n they reported a morta ty odds rat o of 0.19 [0.09 0.36] based on 7 stud es w th 1 419 pat ents. hey do not spec fy wh ch tr a s they nc uded. he report s ncons stent w th a forest p ot that on y shows 4 stud es w th morta ty resu ts.

Desp te th s extreme y pos t ve resu t they recommended on y us ng vermect n n c n ca tr a s. he ana ys s conta ns many flaws *[**Kory (C)**]*:

- Of the 60 stud es (31 RC s) they on y nc uded 16.
- hey exc uded a 14 prophy ax s stud es (4 RC s).
- here was no protoco for data exc us on.
- r a s nc uded n the or g na UNI AID search protoco *[**Hill**]* were exc uded.
- hey exc uded a ep dem o og ca ev dence a though WHO has cons dered such ev dence n the past.
- hey comb ne ear y treatment and ate treatment stud es and do not prov de heterogene ty nformat on. As above ear y treatment s more successfu so poo ng ate treatment stud es w obscure the effect veness of ear y treatment. hey chose not to do subgroup ana ys s by d sease

sever ty across tr a s a though treatment de ay s c ear y a cr t ca factor n COVID 19 treatment the ana ys s s eas y done (as above) and t s we known that the stud es for vermect n and many other treatments c ear y show greater effect veness for ear y treatment.

- WHO downgraded the qua ty of tr a s compared to the UNI AID systemat c rev ew team *[Hill]* and a separate nternat ona expert gu de ne group that has ong worked w th the WHO *[Bryant]*.

- hey d sregarded the r own gu de nes that st pu ate qua ty assessments shou d be upgraded when there s ev dence of a arge magn tude effect (wh ch there s) and when there s ev dence of a dose response re at onsh p (wh ch there s). hey c a m there s no dose response re at onsh p wh e the UNI AID systemat c rev ew team found a c ear re at onsh p *[Hill]*.

- he r r sk of b as assessments do not match the actua r sk of b as n stud es. For examp e they c ass fy *[López Medina]* as ow r sk of b as however th s study has many ssues mak ng the resu ts unre ab e *[Covid Analysis]* even prompt ng an open etter from over 170 phys c ans conc ud ng that the study s fata y flawed *[Open Letter]*. *[Gonzalez]* s a so c ass fied as ow r sk of b as but s a study w th very ate stage severe cond t on h gh comorb d ty pat ents. here s a c ear treatment de ay response re at onsh p and very ate stage treatment s not expected to be as effect ve as ear y treatment. Converse y much h gher qua ty stud es were c ass fied as h gh r sk of b as.

- A though WHO s ana ys s s ca ed a v ng gu de ne t s rare y updated and very out of date. As of May 14 2021 four of the m ss ng RC s are known to WHO and abe ed RC s pend ng data extract on *[COVID NMA]*. We added these 4 4 2 and one month ear er.

- A s ng e person served as Methods Cha r member of the Gu dance Support Co aboraton Comm ttee and member of the L v ng Systemat c Rev ew/NMA team.

- Pub c statements from peop e nvo ved n the ana ys s suggest substant a b as. For examp e a co cha r reported y sa d that the data ava ab e was sparse and ke y based on chance *[Reuters]*. As above the data s comprehens ve and we est mate the probab ty that an neffect ve treatment generated resu ts as pos t ve as observed to be 1 n 2 tr on (p = 0.00000000000045). he c n ca team ead refers to the r ana ys s of vermect n as fight ng th s overuse of unproven therap es ... w thout ev dence of efficacy *[Reuters]* desp te the extens ve ev dence of efficacy from the 60 stud es by 549 sc ent sts w th 18 931 pat ents. Peop e nvo ved may be more favorab e to ate stage treatment of COVID 19 for examp e the co cha r recommended treat ng severe COVID 19 w th remdes v r *[Rochwerg]*.

In summary a though WHO s ana ys s pred cts that over 2 m on fewer peop e wou d be dead f vermect n was used from ear y n the pandem c they recommend aga nst use outs de tr a s. h s appears to be based pr mar y on exc ud ng the major ty of the ev dence and by ass gn ng b as est mates that do not match the actua r sk of b as n stud es.

Use ear y n the pandem c was proposed by K tasato Un vers ty nc ud ng the co d scoverer of vermect n Dr. Satosh Ōmura. hey requested Merck conduct c n ca tr a s of vermect n for COVID 19 n Japan because Merck has pr or ty to subm t an app cat on for an expans on of vermect n's nd cat ons. Merck dec ned *[Yagisawa]*.

Merck Analysis

Merck has recommended aga nst vermect n *[**Merck**]*. hey stated that there s *"no scientific basis for a potential therapeutic effect against COVID 19 from pre clinical studies"*. h s s contrad cted by many papers and stud es nc ud ng *[**Arévalo**, **Bello**, **Choudhury**, **de Melo**, **DiNicolantonio**, **DiNicolantonio (B)**, **Errecalde**, **Eweas**, **Francés Monerris**, **Heidary**, **Jans**, **Jeffreys**, **Kalfas**, **Kory**, **Lehrer**, **Li**, **Mody**, **Mountain Valley MD**, **Qureshi**, **Saha**, **Surnar**, **Udofia**, **Wehbe**, **Yesilbag**, **Zaidi**, **Zatloukal**]*.

hey state that there s *"no meaningful evidence for clinical activity or clinical efficacy in patients with COVID 19 disease"*. h s s contrad cted by numerous stud es nc ud ng *[**Afsar**, **Alam**, **Aref**, **Babalola**, **Behera**, **Behera (B)**, **Bernigaud**, **Budhiraja**, **Bukhari**, **Cadegiani**, **Carvallo (B)**, **Carvallo (C)**, **Chaccour**, **Chahla**, **Chahla (B)**, **Chowdhury**, **Elalfy**, **Elgazzar**, **Elgazzar (B)**, **Espitia Hernandez**, **Faisal**, **Hashim**, **Huvemek**, **Khan**, **Kirti**, **Lima Morales**, **Loue**, **Mahmud**, **Merino**, **Mohan**, **Morgenstern**, **Mourya**, **Niaee**, **Okumuş**, **Samaha**, **Seet**]*.

hey a so c a m that there s *"a concerning lack of safety data in the majority of studies"*. Safety ana ys s s found n *[**Descotes**, **Errecalde**, **Guzzo**, **Kory**, **Madrid**]* and safety data can be found n most stud es nc ud ng *[**Abd Elsalam**, **Afsar**, **Ahmed**, **Aref**, **Babalola**, **Behera (B)**, **Bhattacharya**, **Biber**, **Bukhari**, **Camprubí**, **Carvallo**, **Chaccour**, **Chahla (B)**, **Chowdhury**, **Elalfy**, **Elgazzar**, **Espitia Hernandez**, **Gorial**, **Huvemek**, **Khan**, **Kishoria**, **Krolewiecki**, **Lima Morales**, **Loue**, **López Medina**, **Mahmud**, **Mohan**, **Morgenstern**, **Mourya**, **Niaee**, **Okumuş**, **Pott Junior**, **Seet**, **Shahbaznejad**, **Shouman**, **Spoorthi**, **Szente Fonseca**]*.

Merck has a number of confl cts of nterest:

- Merck has comm tted to g ve vermect n away for free *"as much as needed, for as long as needed"* n the Mect zan® Donat on Program *[**Merck (B)**]* to he p e m nate r ver b ndness.
- Merck has the r own new COVID 19 treatments MK 7110 (former y CD24Fc) *[**Adams**]* and Mo nup rav r (MK 4482) *[**Wikipedia**]*. Merck has a ~$1.2B agreement to supp y mo nup rav r to the US government f t rece ves EUA or approva *[**Khan (B)**]*.
- Ivermect n s off patent there are many manufacturers and Merck s un ke y to be ab e to compete w th ow cost manufacturers.
- Promot ng the use of ow cost off patent med cat ons compared to new products may be undes rab e to some shareho ders.
- Japan requested Merck conduct c n ca tr a s ear y n the pandem c and they dec ned. Merck may be re uctant to adm t th s m stake *[**Yagisawa**]*.

Conclusion

Ivermect n s an effect ve treatment for COVID 19. he probab ty that an neffect ve treatment generated resu ts as pos t ve as the 60 stud es to date s est mated to be 1 n 2 tr on (p = 0.00000000000045). As expected for an effect ve treatment ear y treatment s more successfu w th an est mated reduct on of 76% n the effect measured us ng random effects meta ana ys s (RR 0.24 [0.14 0.41]). 81% and 96% ower morta ty s observed for ear y treatment and prophy ax s (RR 0.19 [0.07 0.54] and 0.04 [0.00 0.58]). Stat st ca y s gn ficant mprovements are seen for morta ty

vent at on hosp ta zat on cases and v ra c earance. he cons stency of pos t ve resu ts across a w de var ety of heterogeneous stud es s remarkab e w th 93% of the 60 stud es report ng pos t ve effects (28 stat st ca y s gn ficant n so at on).

Revisions

h s paper s data dr ven a graphs and numbers are dynam ca y generated. We w update the paper as new stud es are re eased or w th any correct ons. P ease subm t updates and correct ons at https:// vmmeta.com/.

12/2: We added *[Ahmed]*.

12/7: We added *[Chaccour]*.

12/11: We added *[Soto Becerra]*.

12/16: We added *[Afsar]*.

12/17: We added *[Alam]*.

12/26: We added *[Carvallo (B), Vallejos]*.

12/27: We added the tota number of authors and pat ents.

12/29: We added meta ana ys s exc ud ng ate treatment.

12/31: We added add t ona deta s about the stud es n the append x.

1/2: We added dosage nformat on and we added the number of pat ents to the forest p ots.

1/5: We added d rect nks to the study deta s n the forest p ots.

1/6: We added *[Babalola]*.

1/7: We added d rect nks to the study deta s n the chrono og ca p ots.

1/9: We added *[Kirti]*. Due to the much arger s ze of the contro group n *[Bernigaud]* we m ted the s ze of the contro group to be the same as the treatment group for ca cu at on of the tota number of pat ents.

1/10: We put a prophy ax s stud es n a s ng e group.

1/11: We added *[Chahla (B)]*.

1/12: We added *[Okumuş]*.

1/15: We added the effect measured for each study n the forest p ots.

1/16: We moved the ana ys s w th exc us ons to the ma n text and added add t ona commentary.

1/17: We added *[Bukhari]*.

1/19: We added *[**Samaha**, **Shahbaznejad**]*. *[**Chaccour**]* was updated to the journa vers on of the paper.

1/25: We updated *[**Vallejos**]* w th the recent y re eased resu ts.

1/26: We updated *[**Shouman**]* w th the journa vers on of the art c e.

2/2: We added *[**Mohan**]*.

2/5: We updated *[**Bukhari**]* to the prepr nt.

2/10: We added *[**Lima Morales**]*.

2/11: We added more deta s on the ana ys s of prospect ve vs. retrospect ve stud es.

2/12: We added *[**Biber**]*.

2/14: We added ana ys s restr cted to COVID 19 case outcomes and we added add t ona resu ts n the abstract.

2/15: We added *[**Behera (B)**]*.

2/16: We updated *[**Behera**]* to the journa vers on of the paper.

2/17: We added *[**Elalfy**]* and we added ana ys s restr cted to v ra c earance outcomes and morta ty resu ts restr cted to RC s.

2/18: We updated *[**Babalola**]* to the journa vers on of the paper.

2/23: We added *[**Gonzalez**]*.

2/24: We added a compar son of the ev dence base and WHO approva status for the use of vermect n w th scab es and COVID 19. We updated *[**Okumuş**]* w th the Research Square prepr nt.

2/27: We added ana ys s restr cted to peer rev ewed stud es.

3/2: We updated *[**Vallejos**]* w th the atest resu ts *[**Vallejos (B)**]*.

3/3: We updated the graphs to nd cate the t me per od for the dosage co umn now show ng the dosage over one month for prophy ax s and over four days for other stud es.

3/4: We added *[**López Medina**]* and we added more nformat on n the abstract.

3/5: We added d scuss on of poo ed effects (we show both poo ed effects and nd v dua outcome resu ts).

3/6: We added *[**Chowdhury**]* and we dent fy stud es that compare w th another treatment.

3/10: We added *[**Pott Junior**]*.

3/12: We added *[**Bryant**, **Roy**]*.

3/17: We added *[**Nardelli**]*.

3/25: We added *[**Huvemek**]*.

3/26: We added *[**Tanioka**]*.

3/28: We h gh ghted and added d scuss on for stud es that use comb ned treatments.

3/30: We added *[**Chahla**]*.

3/31: We updated *[**Chahla (B)**]* to the prepr nt.

4/4: We added event counts to the forest p ots.

4/5: We added *[**Mourya**]*.

4/7: We dent fied stud es where m n ma deta s current y ava ab e n the forest p ots.

4/9: We corrected a dup cate entry for *[**Bukhari**]*.

4/10: We added *[**Kishoria**]*.

4/14: We added *[**Seet**]*.

4/16: We added *[**Morgenstern**]*.

4/18: We updated *[**Morgenstern**]* to the prepr nt.

4/25: We updated *[**Biber**]* to the atest resu ts reported at the Internat ona Ivermect n for Cov d Conference.

4/26: We added notes on heterogene ty.

4/27: We added ana ys s restr cted to hosp ta zat on resu ts and a compar son w th the ev dence base used n the approva of other COVID 19 treatments.

4/28: We added the WHO meta ana ys s resu ts for compar son.

4/30: We added ana ys s of the WHO meta ana ys s and updated *[**Kory**]* to the journa vers on.

5/4: We added *[**Loue**]*.

5/5: We prev ous y m ted the s ze of the contro group n *[**Bernigaud**]* to be the same as the treatment group for ca cu at on of the tota number of pat ents. h s s now a so reflected and noted n the forest p ots.

5/5: We updated *[**Okumuş**]* to the journa paper.

5/6: We updated d scuss on based on peer rev ew nc ud ng d scuss on of heterogene ty exc us on based sens t v ty ana ys s and search cr ter a.

5/6: We added mechan ca vent at on and ICU adm ss on ana ys s.

5/6: We added a compar son of CDC recommendat ons.

5/6: We updated *[**Chahla**]* to the Research Square prepr nt.

5/7: We updated *[Shahbaznejad]* to the journa vers on wh ch nc udes add t ona outcomes not reported ear er.

5/8: We added *[Merino]*.

5/10: We added add t ona nformat on n the abstract.

5/10: We added *[Faisal]*.

5/13: We updated *[Mahmud]* to the journa vers on.

5/15: We updated the d scuss on of the WHO ana ys s.

5/17: We added *[Szente Fonseca]*.

5/18: We added ana ys s of Merck s recommendat on.

5/26: *[Samaha]* was updated to the journa vers on.

5/31: *[Biber]* was updated to the prepr nt.

6/2: We added *[Abd Elsalam]*.

6/5: We added *[Ahsan]*.

6/7: We added *[Hariyanto]*.

6/15: We added *[Aref]*.

6/18: We added *[Krolewiecki]*.

6/19: *[Gonzalez]* was ncorrect y nc uded n the peer rev ewed ana ys s.

6/19: We updated *[Bryant]* to the journa vers on.

6/21: We added more nformat on to the abstract.

7/2: We updated *[Niaee]* to the journa vers on.

Appendix 1. Methods and Study Results

We performed ongo ng searches of PubMed medRx v C n ca r a s.gov he Cochrane L brary Goog e Scho ar Co abov d Research Square Sc enceD rect Oxford Un vers ty Press the reference sts of other stud es and meta ana yses and subm ss ons to the s te c19 vermect n.com wh ch regu ar y rece ves subm ss ons of stud es upon pub cat on. Search terms were vermect n and COVID 19 or SARS CoV 2 or s mp y vermect n. Automated searches are performed every hour w th not ficat ons of new matches. he broad search terms resu t n a arge vo ume of new stud es on a da y bas s wh ch are rev ewed for nc us on. A stud es regard ng the use of vermect n for COVID 19 that report a compar son w th a contro group are nc uded n the ma n ana ys s. Sens t v ty ana ys s s performed exc ud ng stud es w th cr t ca ssues ep dem o og ca stud es and stud es w th m n ma ava ab e nformat on. h s s a v ng ana ys s and s updated regu ar y.

We extracted effect s zes and assoc ated data from a stud es. If stud es report mu t p e k nds of effects then the most ser ous outcome s used n ca cu at ons for that study. For examp e f effects for morta ty and cases are both reported the effect for morta ty s used th s may be d fferent to the effect that a study focused on. If symptomat c resu ts are reported at mu t p e t mes we used the atest t me for examp e f morta ty resu ts are prov ded at 14 days and 28 days the resu ts at 28 days are used. Morta ty a one s preferred over comb ned outcomes. Outcomes w th zero events n both arms were not used (th s does not resu t n the exc us on of any stud es — the next most ser ous outcome s used). C n ca outcome s cons dered more mportant than PCR test ng status. When bas ca y a pat ents recover n both treatment and contro groups preference for v ra c earance and recovery s g ven to resu ts m d recovery where ava ab e (after most or a pat ents have recovered there s no room for an effect ve treatment to do better). When resu ts prov de an odds rat o we computed the re at ve r sk when poss b e or converted to a re at ve r sk accord ng to *[Zhang]*. Reported confidence nterva s and *p* va ues were used when ava ab e us ng adjusted va ues when prov ded. If mu t p e types of adjustments are reported nc ud ng propens ty score match ng (PSM) the PSM resu ts are used. When needed convers on between reported *p* va ues and confidence nterva s fo owed *[Altman, Altman (B)]* and F sher s exact test was used to ca cu ate *p* va ues for event data. If cont nu ty correct on for zero va ues s requ red we use the rec proca of the oppos te arm w th the sum of the correct on factors equa to 1 *[Sweeting]*. Resu ts are a expressed w th RR < 1.0 suggest ng effect veness. Most resu ts are the re at ve r sk of someth ng negat ve. If stud es report re at ve t mes resu ts are expressed as the rat o of the t me for the vermect n group versus the t me for the contro group. Ca cu at ons are done n Python (3.9.2) w th sc py (1.6.2) pythonmeta (1.23) numpy (1.20.2) statsmode s (0.12.2) and p ot y (4.14.3).

he forest p ots are computed us ng PythonMeta *[Deng]* w th the DerS mon an and La rd random effects mode (the fixed effect assumpt on s not p aus b e n th s case). he forest p ots show s mp fied dosages for compar son these are the tota dose n the first four days for treatment and the month y dose for prophy ax s for a 70kg person. For fu dosage deta s see be ow.

We rece ved no fund ng th s research s done n our spare t me. We have no affi at ons w th any pharmaceut ca compan es or po t ca part es.

We have c ass fied stud es as ear y treatment f most pat ents are not a ready at a severe stage at the t me of treatment and treatment started w th n 5 days after the onset of symptoms a though a shorter t me may be preferab e. Ant v ra s are typ ca y on y cons dered effect ve when used w th n a shorter t meframe for examp e 0 36 or 0 48 hours for ose tam v r w th onger de ays not be ng effect ve *[McLean, Treanor]*.

Due to the much arger s ze of the contro group n *[Bernigaud]* we m t the s ze of the contro group to be the same as the treatment group for ca cu at on of the number of pat ents.

A summary of study resu ts s be ow. P ease subm t updates and correct ons at https:// vmmeta.com/.

Early treatment

Effect extract on fo ows pre spec fied ru es as deta ed above and g ves pr or ty to more ser ous outcomes. On y the first (most ser ous) outcome s used n ca cu at ons wh ch may d ffer from the effect a paper focuses on.

[Afsar] 12/15/2020 retrospect ve Pak stan South As a prepr nt 6 authors	risk of fever at day 14, 92.2% lower, RR 0.08, *p* = 0.04 treatment 0 of 37 (0.0%) contro 7 of 53

dosage 12mg days 1 6.	(13.2%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm).
[Ahmed] 12/2/2020 Doub e B nd Random zed Contro ed r a Bang adesh South As a peer rev ewed mean age 42.0 15 authors dosage 12mg days 1 5 vermect n + doxycyc ne group took on y a s ng e dose of vermect n.	**risk of unresolved symptoms, 85.0% lower, RR 0.15, *p* = 0.09** treatment 0 of 17 (0.0%) contro 3 of 19 (15.8%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm) day 7 fever vermect n.
	r sk of unreso ved symptoms 62.7% ower RR 0.37 *p* = 0.35 treatment 1 of 17 (5.9%) contro 3 of 19 (15.8%) day 7 fever vermect n + doxycyc ne.
	r sk of no v ro og ca cure 42.5% ower RR 0.58 *p* = 0.01 treatment 11 of 22 (50.0%) contro 20 of 23 (87.0%) day 7 vermect n.
	r sk of no v ro og ca cure 20.0% ower RR 0.80 *p* = 0.28 treatment 16 of 23 (69.6%) contro 20 of 23 (87.0%) day 7 vermect n + doxycyc ne.
	r sk of no v ro og ca cure 62.7% ower RR 0.37 *p* = 0.02 treatment 5 of 22 (22.7%) contro 14 of 23 (60.9%) day 14 vermect n.
	r sk of no v ro og ca cure 35.7% ower RR 0.64 *p* = 0.24 treatment 9 of 23 (39.1%) contro 14 of 23 (60.9%) day 14 vermect n + doxycyc ne.
	t me to v ra 23.6% ower re at ve t me 0.76 *p* = 0.02 treatment 22 contro 23 vermect n.
	t me to v ra 9.4% ower re at ve t me 0.91 *p* = 0.27 treatment 23 contro 23 vermect n + doxycyc ne.
	hosp ta zat on t me 1.0% ower re at ve t me 0.99 vermect n.
	hosp ta zat on t me 4.1% h gher re at ve t me 1.04 vermect n + doxycyc ne.
[Aref] 6/15/2021 Random zed Contro ed r a Egypt M dd e East peer rev ewed 7 authors.	**relative duration of fever, 63.2% lower, relative time 0.37, *p* < 0.001** treatment 57 contro 57.
	r sk of no v ro og ca cure 78.6% ower RR 0.21 *p* = 0.004 treatment 3 of 57 (5.3%) contro 14 of 57 (24.6%).
[Babalola] 1/6/2021 Doub e B nd Random zed Contro ed r a N ger a Afr ca peer rev ewed base ne oxygen requ rements 8.3% 10 authors dosage 12mg or 6mg q84h for two weeks th s	**adjusted risk of viral+ at day 5, 63.9% lower, RR 0.36, *p* = 0.11** treatment 40 contro 20 adjusted per study.
	r sk of no v ro og ca cure 58.0% ower RR 0.42 *p* = 0.01 treatment 20 contro 20 12mg Cox

tr a compares w th another treatment resu ts may be better when compared to p acebo.	proport ona hazard mode .
	r sk of no v ro og ca cure 40.5% ower RR 0.60 *p* = 0.12 treatment 20 contro 20 6mg Cox proport ona hazard mode .
	t me to v ra 49.2% ower re at ve t me 0.51 treatment 20 contro 20 12mg.
	t me to v ra 34.4% ower re at ve t me 0.66 treatment 20 contro 20 6mg.
[Biber] 2/12/2021 Doub e B nd Random zed Contro ed r a Israe M dd e East prepr nt 10 authors dosage 12mg days 1 3 15mg for pat ents >= 70kg.	risk of hospitalization, 70.2% lower, RR 0.30, *p* = 0.34 treatment 1 of 47 (2.1%) contro 3 of 42 (7.1%).
	r sk of no v ro og ca cure 44.8% ower RR 0.55 *p* = 0.04 treatment 13 of 47 (27.7%) contro 21 of 42 (50.0%) adjusted per study odds rat o converted to re at ve r sk mu t var ab e og st c regress on day 6 Ct>30.
	r sk of no v ro og ca cure 70.2% ower RR 0.30 *p* = 0.14 treatment 2 of 47 (4.3%) contro 6 of 42 (14.3%) day 10 non nfect ous samp es (Ct>30 or non v ab e cu ture).
	r sk of no v ro og ca cure 82.1% ower RR 0.18 *p* = 0.01 treatment 2 of 47 (4.3%) contro 10 of 42 (23.8%) day 8 non nfect ous samp es (Ct>30 or non v ab e cu ture).
	r sk of no v ro og ca cure 75.6% ower RR 0.24 *p* = 0.02 treatment 3 of 47 (6.4%) contro 11 of 42 (26.2%) day 6 non nfect ous samp es (Ct>30 or non v ab e cu ture).
	r sk of no v ro og ca cure 65.1% ower RR 0.35 *p* = 0.05 treatment 4 of 28 (14.3%) contro 9 of 22 (40.9%) day 4 non nfect ous samp es (Ct>30 or non v ab e cu ture).
	r sk of no v ro og ca cure 51.9% ower RR 0.48 *p* = 0.08 treatment 7 of 47 (14.9%) contro 13 of 42 (31.0%) day 10 Ct>30.
	r sk of no v ro og ca cure 57.9% ower RR 0.42 *p* = 0.02 treatment 8 of 47 (17.0%) contro 17 of 42 (40.5%) day 8 Ct>30.
	r sk of no v ro og ca cure 44.7% ower RR 0.55 *p* = 0.05 treatment 13 of 47 (27.7%) contro 21 of 42 (50.0%) day 6 Ct>30.
	r sk of no v ro og ca cure 31.9% ower RR 0.68 *p* = 0.16 treatment 13 of 28 (46.4%) contro 15 of

	22 (68.2%) day 4 Ct>30.
[Bukhari] 1/16/2021 Random zed Contro ed r a Pak stan M dd e East prepr nt 10 authors dosage 12mg s ng e dose.	**risk of no virological cure, 82.4% lower, RR 0.18, *p* < 0.001** treatment 4 of 41 (9.8%) contro 25 of 45 (55.6%) day 7.
	r sk of no v ro og ca cure 38.7% ower RR 0.61 *p* < 0.001 treatment 24 of 41 (58.5%) contro 43 of 45 (95.6%) day 3.
[Cadegiani] 11/4/2020 prospect ve Braz South Amer ca prepr nt 4 authors dosage 200µg/kg days 1 3.	**risk of death, 78.3% lower, RR 0.22, *p* = 0.50** treatment 0 of 110 (0.0%) contro 2 of 137 (1.5%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm) contro group 1.
	r sk of mechan ca vent at on 94.2% ower RR 0.06 *p* = 0.005 treatment 0 of 110 (0.0%) contro 9 of 137 (6.6%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm) contro group 1.
	r sk of hosp ta zat on 98.0% ower RR 0.02 *p* < 0.001 treatment 0 of 110 (0.0%) contro 27 of 137 (19.7%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm) contro group 1.
[Carvallo] 9/15/2020 prospect ve Argent na South Amer ca prepr nt mean age 55.7 3 authors dosage 36mg days 1 8 dose var ed depend ng on pat ent cond t on m d 24mg moderate 36mg severe 48mg th s tr a uses mu t p e treatments n the treatment arm (comb ned w th dexamethasone enoxapar n and asp r n) resu ts of nd v dua treatments may vary.	**risk of death for hospitalized cases in study vs. cases in the same hospital not in the study, 87.9% lower, RR 0.12, *p* = 0.05** treatment 1 of 33 (3.0%) contro 3 of 12 (25.0%) the on y treatment death was a pat ent a ready n the ICU before treatment.
[Chaccour] 12/7/2020 Doub e B nd Random zed Contro ed r a Spa n Europe peer rev ewed 23 authors dosage 400µg/kg s ng e dose.	**symptom probability, 52.9% lower, RR 0.47, *p* < 0.05** treatment 12 contro 12 re at ve probab ty of symptoms at day 28 m xed effects og st c regress on data n supp ementary append x.
	v ra oad 94.6% ower re at ve oad 0.05 treatment 12 contro 12 day 7 m d recovery data n supp ementary append x.
[Chahla] 3/30/2021 C uster Random zed Contro ed r a Argent na South Amer ca prepr nt 9 authors dosage 24mg days 1 8 15 22.	**risk of no discharge, 86.9% lower, RR 0.13, *p* = 0.004** treatment 2 of 110 (1.8%) contro 20 of 144 (13.9%) adjusted per study odds rat o converted to re at ve r sk og st c regress on.
[Chowdhury] 7/14/2020 Random zed Contro ed r a Bang adesh South As a peer rev ewed 6 authors dosage 200µg/kg s ng e dose th s tr a compares w th another treatment	**risk of hospitalization, 80.6% lower, RR 0.19, *p* = 0.23** treatment 0 of 60 (0.0%) contro 2 of 56 (3.6%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm).

resu ts may be better when compared to p acebo th s tr a uses mu t p e treatments n the treatment arm (comb ned w th doxycyc ne) resu ts of nd v dua treatments may vary.	r sk of no recovery 46.4% ower RR 0.54 *p* < 0.001 treatment 27 of 60 (45.0%) contro 47 of 56 (83.9%) m d recovery day 5.
	recovery t me 15.2% ower re at ve t me 0.85 *p* = 0.07 treatment 60 contro 56.
	r sk of no v ro og ca cure 80.6% ower RR 0.19 *p* = 0.23 treatment 0 of 60 (0.0%) contro 2 of 56 (3.6%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm).
	t me to v ra 4.3% ower re at ve t me 0.96 *p* = 0.23 treatment 60 contro 56.
[Elalfy] 2/16/2021 retrospect ve Egypt M dd e East peer rev ewed 15 authors dosage 18mg days 1 4 7 10 13 <90kg 18mg 90 120kg 24mg >120kg 30mg th s tr a uses mu t p e treatments n the treatment arm (comb ned w th n tazoxan de r bav r n and z nc) resu ts of nd v dua treatments may vary.	**risk of no virological cure, 86.9% lower, RR 0.13, *p* < 0.001** treatment 7 of 62 (11.3%) contro 44 of 51 (86.3%) day 15.
	r sk of no v ro og ca cure 58.1% ower RR 0.42 *p* < 0.001 treatment 26 of 62 (41.9%) contro 51 of 51 (100.0%) day 7.
[Espitia Hernandez] 8/15/2020 retrospect ve Mex co North Amer ca peer rev ewed mean age 45.1 5 authors dosage 6mg days 1 2 8 9 th s tr a uses mu t p e treatments n the treatment arm (comb ned w th az thromyc n and cho eca c fero) resu ts of nd v dua treatments may vary.	**risk of viral+ at day 10, 97.2% lower, RR 0.03, *p* < 0.001** treatment 0 of 28 (0.0%) contro 7 of 7 (100.0%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm).
[Faisal] 5/10/2021 Random zed Contro ed r a Pak stan South As a peer rev ewed 3 authors dosage 12mg days 1 5.	**risk of no recovery, 68.4% lower, RR 0.32, *p* = 0.005** treatment 6 of 50 (12.0%) contro 19 of 50 (38.0%) 6 8 days m d recovery.
	r sk of no recovery 27.3% ower RR 0.73 *p* = 0.11 treatment 24 of 50 (48.0%) contro 33 of 50 (66.0%) 3 5 days.
	r sk of no recovery 75.0% ower RR 0.25 *p* = 0.09 treatment 2 of 50 (4.0%) contro 8 of 50 (16.0%) 9 10 days.
[Kirti] 1/9/2021 Doub e B nd Random zed Contro ed r a Ind a South As a prepr nt 11 authors dosage 12mg days 1 2.	**risk of death, 88.7% lower, RR 0.11, *p* = 0.12** treatment 0 of 55 (0.0%) contro 4 of 57 (7.0%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm).
	r sk of mechan ca vent at on 79.3% ower RR 0.21 *p* = 0.09 treatment 1 of 55 (1.8%) contro 5 of 57 (8.8%).
	r sk of ICU adm ss on 13.6% ower RR 0.86 *p* = 0.80 treatment 5 of 55 (9.1%) contro 6 of 57 (10.5%).

	r sk of no v ro og ca cure 11.6% h gher RR 1.12 *p* = 0.35 treatment 42 of 55 (76.4%) contro 39 of 57 (68.4%).
[Krolewiecki] 6/18/2021 Random zed Contro ed r a Argent na South Amer ca peer rev ewed 23 authors dosage 600µg/kg days 1 5.	**risk of mechanical ventilation, 151.9% higher, RR 2.52, *p* = 1.00** treatment 1 of 27 (3.7%) contro 0 of 14 (0.0%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm).
	r sk of d sease progress on 3.7% h gher RR 1.04 *p* = 1.00 treatment 2 of 27 (7.4%) contro 1 of 14 (7.1%).
[Loue] 4/17/2021 retrospect ve quas random zed (pat ent cho ce) France Europe peer rev ewed 2 authors dosage 200µg/kg s ng e dose.	**risk of death, 70.0% lower, RR 0.30, *p* = 0.34** treatment 1 of 10 (10.0%) contro 5 of 15 (33.3%).
	r sk of COVID 19 severe case 55.0% ower RR 0.45 *p* = 0.11 treatment 3 of 10 (30.0%) contro 10 of 15 (66.7%).
[López Medina] 3/4/2021 Doub e B nd Random zed Contro ed r a Co omb a South Amer ca peer rev ewed med an age 37.0 19 authors dosage 300µg/kg days 1 5.	**risk of death, 66.8% lower, RR 0.33, *p* = 0.50** treatment 0 of 200 (0.0%) contro 1 of 198 (0.5%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm).
	r sk of esca at on of care 60.8% ower RR 0.39 *p* = 0.10 treatment 4 of 200 (2.0%) contro 10 of 198 (5.1%) odds rat o converted to re at ve r sk.
	r sk of esca at on of care w th post hoc <12h exc us on 34.3% ower RR 0.66 *p* = 0.51 treatment 4 of 200 (2.0%) contro 6 of 198 (3.0%) odds rat o converted to re at ve r sk.
	r sk of deter orat on by >= 2 po nts on an 8 po nt sca e 43.1% ower RR 0.57 *p* = 0.35 treatment 4 of 200 (2.0%) contro 7 of 198 (3.5%) odds rat o converted to re at ve r sk.
	r sk of fever post random zat on 24.8% ower RR 0.75 *p* = 0.33 treatment 16 of 200 (8.0%) contro 21 of 198 (10.6%) odds rat o converted to re at ve r sk.
	r sk of unreso ved symptoms at day 21 15.3% ower RR 0.85 *p* = 0.53 treatment 36 of 200 (18.0%) contro 42 of 198 (21.2%) odds rat o converted to re at ve r sk Cox proport ona hazard mode .
	hazard rat o for ack of reso ut on of symptoms 6.5% ower RR 0.93 *p* = 0.53 treatment 200 contro 198.
	re at ve med an t me to reso ut on of symptoms 16.7% ower re at ve t me 0.83 treatment 200

	contro 198.
[Mahmud] 10/9/2020 Doub e B nd Random zed Contro ed r a Bang adesh South As a peer rev ewed 15 authors dosage 12mg s ng e dose th s tr a uses mu t p e treatments n the treatment arm (comb ned w th doxycyc ne) resu ts of nd v dua treatments may vary.	**risk of death, 85.7% lower, RR 0.14, $p = 0.25$** treatment 0 of 183 (0.0%) contro 3 of 183 (1.6%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm).
	r sk of d sease progress on 57.0% ower RR 0.43 $p < 0.001$ treatment 16 of 183 (8.7%) contro 32 of 180 (17.8%) adjusted per study Cox regress on.
	r sk of no recovery 94.0% ower RR 0.06 $p < 0.001$ treatment 72 of 183 (39.3%) contro 100 of 180 (55.6%) adjusted per study day 7 Cox regress on.
	r sk of no recovery 38.5% ower RR 0.61 $p = 0.005$ treatment 40 of 183 (21.9%) contro 64 of 180 (35.6%) day 11.
	r sk of no recovery 96.0% ower RR 0.04 $p < 0.001$ treatment 42 of 183 (23.0%) contro 67 of 180 (37.2%) adjusted per study day 12 Cox regress on.
	t me to recovery 27.0% ower RR 0.73 $p = 0.003$ treatment 183 contro 180 Cox regress on.
	r sk of no v ro og ca cure 39.0% ower RR 0.61 $p = 0.002$ treatment 14 of 183 (7.7%) contro 36 of 180 (20.0%) adjusted per study Cox regress on.
[Merino] 5/3/2021 retrospect ve quas random zed (pat ents rece v ng k t) popu at on based cohort Mex co North Amer ca prepr nt 7 authors dosage 6mg b d days 1 2.	**risk of hospitalization, 74.4% lower, RR 0.26, $p < 0.001$** mode 7 same t me per od pat ents rece v ng k t.
	r sk of hosp ta zat on 68.4% ower RR 0.32 $p < 0.001$ mode 1 d fferent t me per ods adm n strat ve ru e.
[Mohan] 2/2/2021 Doub e B nd Random zed Contro ed r a Ind a South As a prepr nt 27 authors dosage 400µg/kg s ng e dose 200µg/kg a so tested.	**risk of no discharge at day 14, 62.5% lower, RR 0.38, $p = 0.27$** treatment 2 of 40 (5.0%) contro 6 of 45 (13.3%) vermect n 24mg.
	r sk of no d scharge at day 14 43.8% ower RR 0.56 $p = 0.49$ treatment 3 of 40 (7.5%) contro 6 of 45 (13.3%) vermect n 12mg.
	r sk of no v ro og ca cure 10.3% ower RR 0.90 $p = 0.65$ treatment 20 of 36 (55.6%) contro 26 of 42 (61.9%) vermect n 24mg day 7.
	r sk of no v ro og ca cure 3.2% h gher RR 1.03 $p = 1.00$ treatment 23 of 36 (63.9%) contro 26 of 42 (61.9%) vermect n 12mg day 7.

	r sk of no v ro og ca cure 23.8% ower RR 0.76 *p* = 0.18 treatment 21 of 40 (52.5%) contro 31 of 45 (68.9%) vermect n 24mg day 5.
	r sk of no v ro og ca cure 5.6% ower RR 0.94 *p* = 0.82 treatment 26 of 40 (65.0%) contro 31 of 45 (68.9%) vermect n 12mg day 5.
[Mourya] 4/1/2021 retrospect ve Ind a South As a peer rev ewed 5 authors dosage 12mg days 1 7.	**risk of no virological cure, 89.4% lower, RR 0.11, *p* < 0.001** treatment 5 of 50 (10.0%) contro 47 of 50 (94.0%).
[Roy] 3/12/2021 retrospect ve database ana ys s Ind a South As a prepr nt 5 authors dosage not spec fied th s tr a uses mu t p e treatments n the treatment arm (comb ned w th doxycyc ne) resu ts of nd v dua treatments may vary.	**relative time to clinical response of wellbeing, 5.6% lower, relative time 0.94, *p* = 0.87** treatment 14 contro 15.
[Samaha] 1/16/2021 Random zed Contro ed r a Lebanon M dd e East peer rev ewed 16 authors dosage 12mg s ng e dose 45–64kg 65–84kg and >85kg pat ents rece ved 9mg 12mg or 150µg/kg respect ve y.	**risk of hospitalization, 85.7% lower, RR 0.14, *p* = 0.24** treatment 0 of 50 (0.0%) contro 3 of 50 (6.0%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm).
	r sk of fever at day 3 90.9% ower RR 0.09 *p* = 0.004 treatment 1 of 50 (2.0%) contro 11 of 50 (22.0%).
[Szente Fonseca] 10/31/2020 retrospect ve Braz South Amer ca peer rev ewed mean age 50.6 10 authors dosage 12mg days 1 2.	**risk of hospitalization, 13.9% higher, RR 1.14, *p* = 0.45** treatment 340 contro 377 adjusted per study odds rat o converted to re at ve r sk contro preva ence approx mated w th overa preva ence.

Late treatment

Effect extract on fo ows pre spec fied ru es as deta ed above and g ves pr or ty to more ser ous outcomes. On y the first (most ser ous) outcome s used n ca cu at ons wh ch may d ffer from the effect a paper focuses on.

[Abd Elsalam] 6/2/2021 Random zed Contro ed r a Egypt M dd e East peer rev ewed 16 authors dosage 12mg days 1 3.	**risk of death, 25.0% lower, RR 0.75, *p* = 0.70** treatment 3 of 82 (3.7%) contro 4 of 82 (4.9%) odds rat o converted to re at ve r sk og st c regress on.
	r sk of mechan ca vent at on no change RR 1.00 *p* = 1.00 treatment 3 of 82 (3.7%) contro 3 of 82 (3.7%).
	hosp ta zat on t me 19.6% ower re at ve t me 0.80 *p* = 0.09 treatment 82 contro 82.
[Ahsan] 4/29/2021 retrospect ve Pak stan M dd e East peer rev ewed 10 authors dosage 150µg/kg days 1 2 150	**risk of death, 50.0% lower, RR 0.50, *p* = 0.03** treatment 17 of 110 (15.5%) contro 17 of 55 (30.9%).

200µg/kg th s tr a uses mu t p e treatments n the treatment arm (comb ned w th doxycyc ne) resu ts of nd v dua treatments may vary.	
[Budhiraja] 11/18/2020 retrospect ve Ind a South As a prepr nt 12 authors dosage not spec fied.	**risk of death, 99.1% lower, RR 0.009, *p* = 0.04** treatment 0 of 34 (0.0%) contro 103 of 942 (10.9%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm).
[Camprubí] 11/11/2020 retrospect ve Spa n Europe peer rev ewed 9 authors dosage 200µg/kg s ng e dose.	**risk of mechanical ventilation, 40.0% lower, RR 0.60, *p* = 0.67** treatment 3 of 13 (23.1%) contro 5 of 13 (38.5%).
	r sk of ICU adm ss on 33.3% ower RR 0.67 *p* = 1.00 treatment 2 of 13 (15.4%) contro 3 of 13 (23.1%) ICU at day 8.
	r sk of no mprovement at day 8 33.3% h gher RR 1.33 *p* = 1.00 treatment 4 of 13 (30.8%) contro 3 of 13 (23.1%).
[Chachar] 9/30/2020 Random zed Contro ed r a Ind a South As a peer rev ewed 6 authors dosage 36mg 12mg stat 12mg after 12 hours 12mg after 24 hours.	**risk of no recovery at day 7, 10.0% lower, RR 0.90, *p* = 0.50** treatment 9 of 25 (36.0%) contro 10 of 25 (40.0%).
[Elgazzar] 11/13/2020 Random zed Contro ed r a Egypt Afr ca prepr nt 6 authors dosage 400µg/kg days 1 4 th s tr a compares w th another treatment resu ts may be better when compared to p acebo.	**risk of death, 91.7% lower, RR 0.08, *p* < 0.001** treatment 2 of 200 (1.0%) contro 24 of 200 (12.0%).
	r sk of death 88.9% ower RR 0.11 *p* = 0.12 treatment 0 of 100 (0.0%) contro 4 of 100 (4.0%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm) m d/moderate COVID 19.
	r sk of death 90.0% ower RR 0.10 *p* < 0.001 treatment 2 of 100 (2.0%) contro 20 of 100 (20.0%) severe COVID 19.
[Gonzalez] 2/23/2021 Doub e B nd Random zed Contro ed r a Mex co North Amer ca prepr nt mean age 53.8 13 authors dosage 12mg s ng e dose 18mg for pat ents >80kg.	**risk of death, 14.4% lower, RR 0.86, *p* = 1.00** treatment 5 of 36 (13.9%) contro 6 of 37 (16.2%).
	r sk of resp ratory deter orat on or death 8.6% ower RR 0.91 *p* = 1.00 treatment 8 of 36 (22.2%) contro 9 of 37 (24.3%).
	r sk of no hosp ta d scharge 37.0% h gher RR 1.37 *p* = 0.71 treatment 4 of 36 (11.1%) contro 3 of 37 (8.1%).
[Gorial] 7/8/2020 retrospect ve Iraq M dd e East prepr nt 9 authors dosage 200µg/kg s ng e dose.	**risk of death, 71.0% lower, RR 0.29, *p* = 1.00** treatment 0 of 16 (0.0%) contro 2 of 71 (2.8%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm).

	hosp ta zat on t me 42.0% ower re at ve t me 0.58 *p* < 0.001 treatment 16 contro 71.
[Hashim] 10/26/2020 S ng e B nd Random zed Contro ed r a Iraq M dd e East prepr nt 6 authors dosage 200µg/kg days 1 2 some pat ents rece ved a th rd dose on day 8 th s tr a uses mu t p e treatments n the treatment arm (comb ned w th doxycyc ne) resu ts of nd v dua treatments may vary.	**risk of death, 66.7% lower, RR 0.33, *p* = 0.27** treatment 2 of 70 (2.9%) contro 6 of 70 (8.6%) a pat ents.
	r sk of death 91.7% ower RR 0.08 *p* = 0.03 treatment 0 of 59 (0.0%) contro 6 of 70 (8.6%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm) exc ud ng cr t ca pat ents.
[Huvemek] 3/25/2021 Doub e B nd Random zed Contro ed r a Bu gar a Europe prepr nt 1 author dosage 400µg/kg days 1 3.	**risk of no improvement, 31.6% lower, RR 0.68, *p* = 0.28** treatment 13 of 50 (26.0%) contro 19 of 50 (38.0%) day 7 pat ents w th mprovement on WHO sca e.
	r sk of no mprovement 34.5% ower RR 0.66 *p* = 0.07 treatment 19 of 50 (38.0%) contro 29 of 50 (58.0%) day 4 pat ents w th mprovement on WHO sca e.
[Khan] 9/24/2020 retrospect ve Bang adesh South As a prepr nt med an age 35.0 8 authors dosage 12mg s ng e dose.	**risk of death, 87.0% lower, RR 0.13, *p* < 0.05** treatment 1 of 115 (0.9%) contro 9 of 133 (6.8%).
	r sk of ICU adm ss on 89.5% ower RR 0.11 *p* = 0.007 treatment 1 of 115 (0.9%) contro 11 of 133 (8.3%).
	t me to v ra 73.3% ower re at ve t me 0.27 *p* < 0.001 treatment 115 contro 133.
[Kishoria] 8/31/2020 Random zed Contro ed r a Ind a South As a peer rev ewed 7 authors dosage 12mg s ng e dose.	**risk of no hospital discharge, 7.5% higher, RR 1.08, *p* = 1.00** treatment 11 of 19 (57.9%) contro 7 of 13 (53.8%).
	r sk of no v ro og ca cure 7.5% h gher RR 1.08 *p* = 1.00 treatment 11 of 19 (57.9%) contro 7 of 13 (53.8%) day 3.
	r sk of no v ro og ca cure 220.0% h gher RR 3.20 *p* = 0.45 treatment 1 of 5 (20.0%) contro 0 of 6 (0.0%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm) day 5.
[Lima Morales] 2/10/2021 prospect ve Mex co North Amer ca peer rev ewed 9 authors dosage 12mg s ng e dose th s tr a uses mu t p e treatments n the treatment arm (comb ned w th az thromyc n monte ukast and asp r n) resu ts of nd v dua treatments may vary.	**risk of death, 77.7% lower, RR 0.22, *p* < 0.001** treatment 15 of 481 (3.1%) contro 52 of 287 (18.1%) adjusted per study odds rat o converted to re at ve r sk mu t var ate.
	r sk of hosp ta zat on 67.4% ower RR 0.33 *p* < 0.001 treatment 44 of 481 (9.1%) contro 89 of 287 (31.0%) adjusted per study odds rat o converted to re at ve r sk mu t var ate.

	r sk of no recovery 58.6% ower RR 0.41 *p* < 0.001 treatment 75 of 481 (15.6%) contro 118 of 287 (41.1%) adjusted per study odds rat o converted to re at ve r sk recovery at day 14 after symptoms mu t var ate.
[Niaee] 11/24/2020 Doub e B nd Random zed Contro ed r a Iran M dd e East peer rev ewed mean age 56.0 14 authors dosage 400µg/kg s ng e dose dose var es n d fferent groups.	**risk of death, 81.8% lower, RR 0.18, *p* = 0.001** treatment 4 of 120 (3.3%) contro 11 of 60 (18.3%) A IVM vs. a contro .
	r sk of death 94.3% ower RR 0.06 *p* = 0.01 treatment 0 of 30 (0.0%) contro 11 of 60 (18.3%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm) IVM s ng e dose 200mcg/kg vs. a contro .
	r sk of death 45.5% ower RR 0.55 *p* = 0.37 treatment 3 of 30 (10.0%) contro 11 of 60 (18.3%) IVM three dose 200mcg/kg vs. a contro .
	r sk of death 94.3% ower RR 0.06 *p* = 0.01 treatment 0 of 30 (0.0%) contro 11 of 60 (18.3%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm) IVM s ng e dose 400mcg/kg vs. a contro .
	r sk of death 81.8% ower RR 0.18 *p* = 0.06 treatment 1 of 30 (3.3%) contro 11 of 60 (18.3%) IVM three dose 400/200/200mcg/kg vs. a contro .
[Okumuş] 1/12/2021 Doub e B nd Random zed Contro ed r a urkey M dd e East peer rev ewed 15 authors dosage 200µg/kg days 1 5 36 50kg 9mg 51 65kg 12mg 66 79kg 15mg >80kg 200µg/kg.	**risk of death, 33.3% lower, RR 0.67, *p* = 0.55** treatment 6 of 30 (20.0%) contro 9 of 30 (30.0%).
	r sk of no mprovement at day 10 42.9% ower RR 0.57 *p* = 0.18 treatment 8 of 30 (26.7%) contro 14 of 30 (46.7%).
	r sk of no mprovement at day 5 15.8% ower RR 0.84 *p* = 0.60 treatment 16 of 30 (53.3%) contro 19 of 30 (63.3%).
	r sk of no v ro og ca cure 80.0% ower RR 0.20 *p* = 0.02 treatment 2 of 16 (12.5%) contro 5 of 8 (62.5%) day 10.
[Podder] 9/3/2020 Random zed Contro ed r a Bang adesh South As a peer rev ewed 4 authors dosage 200µg/kg s ng e dose.	**recovery time from enrollment, 16.1% lower, relative time 0.84, *p* = 0.34** treatment 32 contro 30.
[Pott Junior] 3/9/2021 Random zed Contro ed r a Braz South Amer ca peer rev ewed 10 authors dosage 200µg/kg s ng e dose dose var es n three arms 100 200 400µg/kg.	**risk of mechanical ventilation, 85.2% lower, RR 0.15, *p* = 0.25** treatment 1 of 27 (3.7%) contro 1 of 4 (25.0%).
	r sk of ICU adm ss on 85.2% ower RR 0.15 *p* =

	0.25 treatment 1 of 27 (3.7%) contro 1 of 4 (25.0%).
	re at ve mprovement n Ct va ue 0.8% ower RR 0.99 *p* = 1.00 treatment 27 contro 3.
	r sk of no v ro og ca cure 11.1% h gher RR 1.11 *p* = 1.00 treatment 10 of 27 (37.0%) contro 1 of 3 (33.3%).
	t me to v ra 16.7% ower re at ve t me 0.83 treatment 27 contro 3.
[Rajter] 10/13/2020 retrospect ve propens ty score match ng USA North Amer ca peer rev ewed 6 authors dosage 200µg/kg s ng e dose.	**risk of death, 46.0% lower, RR 0.54, *p* = 0.04** treatment 13 of 98 (13.3%) contro 24 of 98 (24.5%) adjusted per study odds rat o converted to re at ve r sk PSM.
	r sk of death 66.9% ower RR 0.33 *p* = 0.03 treatment 26 of 173 (15.0%) contro 27 of 107 (25.2%) adjusted per study odds rat o converted to re at ve r sk mu t var ate.
	r sk of mechan ca vent at on 63.6% ower RR 0.36 *p* = 0.10 treatment 4 of 98 (4.1%) contro 11 of 98 (11.2%) matched cohort exc ud ng ntubated at base ne.
[Shahbaznejad] 1/19/2021 Doub e B nd Random zed Contro ed r a Iran M dd e East peer rev ewed 8 authors dosage 200µg/kg s ng e dose.	**risk of death, 197.1% higher, RR 2.97, *p* = 1.00** treatment 1 of 35 (2.9%) contro 0 of 34 (0.0%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm) pat ent d ed w th n 24 hours of adm ss on.
	r sk of mechan ca vent at on 94.3% h gher RR 1.94 *p* = 1.00 treatment 2 of 35 (5.7%) contro 1 of 34 (2.9%).
	recovery t me 31.6% ower re at ve t me 0.68 *p* = 0.05 treatment 35 contro 34 durat on of dsypnea.
	recovery t me 19.2% ower re at ve t me 0.81 *p* = 0.02 treatment 35 contro 34 durat on of a symptoms.
	hosp ta zat on t me 15.5% ower re at ve t me 0.85 *p* = 0.02 treatment 35 contro 34.
[Soto Becerra] 10/8/2020 retrospect ve database ana ys s Peru South Amer ca prepr nt med an age 59.4 4 authors dosage 200µg/kg s ng e dose.	**risk of death, 17.1% lower, RR 0.83, *p* = 0.01** treatment 92 of 203 (45.3%) contro 1438 of 2630 (54.7%) IVM vs. contro day 43 (ast day ava ab e) we ghted KM from figure 3 per the pre spec fied ru es the ast ava ab e day morta ty resu ts have pr or ty.

	r sk of death 39.0% h gher RR 1.39 *p* = 0.16 treatment 47 of 203 (23.2%) contro 401 of 2630 (15.2%) adjusted per study day 30 ab e 2 IVM wHR.
[Spoorthi] 11/14/2020 prospect ve Ind a South As a peer rev ewed 2 authors dosage not spec fied th s tr a uses mu t p e treatments n the treatment arm (comb ned w th doxycyc ne) resu ts of nd v dua treatments may vary.	**recovery time, 21.1% lower, relative time 0.79, *p* = 0.03** treatment 50 contro 50.
	hosp ta zat on t me 15.5% ower re at ve t me 0.84 *p* = 0.01 treatment 50 contro 50.

Prophylaxis

Effect extract on fo ows pre spec fied ru es as deta ed above and g ves pr or ty to more ser ous outcomes. On y the first (most ser ous) outcome s used n ca cu at ons wh ch may d ffer from the effect a paper focuses on.

[Alam] 12/15/2020 prospect ve Bang adesh South As a peer rev ewed 13 authors dosage 12mg month y.	**risk of COVID 19 case, 90.6% lower, RR 0.09, *p* < 0.001** treatment 4 of 58 (6.9%) contro 44 of 60 (73.3%).
[Behera (B)] 2/15/2021 prospect ve Ind a South As a prepr nt 13 authors dosage 300µg/kg days 1 4.	**risk of COVID 19 case, 83.0% lower, RR 0.17, *p* < 0.001** treatment 45 of 2199 (2.0%) contro 133 of 1147 (11.6%) two doses.
	r sk of COVID 19 case 4.0% h gher RR 1.04 *p* = 0.85 treatment 23 of 186 (12.4%) contro 133 of 1147 (11.6%) pat ents on y rece v ng the first dose.
[Behera] 11/3/2020 retrospect ve Ind a South As a peer rev ewed 13 authors dosage 300µg/kg days 1 4.	**risk of COVID 19 case, 53.8% lower, RR 0.46, *p* < 0.001** treatment 41 of 117 (35.0%) contro 145 of 255 (56.9%) adjusted per study odds rat o converted to re at ve r sk mode 2 2+ doses cond t ona og st c regress on.
	r sk of COVID 19 case 44.5% ower RR 0.56 *p* < 0.001 treatment 41 of 117 (35.0%) contro 145 of 255 (56.9%) odds rat o converted to re at ve r sk matched pa r ana ys s.
[Bernigaud] 11/28/2020 retrospect ve France Europe peer rev ewed 12 authors dosage 200µg/kg days 1 8 15 400µg/kg days 1 8 15 two d fferent dosages.	**risk of death, 99.4% lower, RR 0.006, *p* = 0.08** treatment 0 of 69 (0.0%) contro 150 of 3062 (4.9%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm).
	r sk of COVID 19 case 55.1% ower RR 0.45 *p* = 0.01 treatment 7 of 69 (10.1%) contro 692 of 3062 (22.6%).
[Carvallo (C)] 11/17/2020 prospect ve Argent na South Amer ca peer rev ewed 4 authors dosage 12mg week y th s tr a uses mu t p e treatments n the	**risk of COVID 19 case, 99.9% lower, RR 0.001, *p* < 0.001** treatment 0 of 788 (0.0%) contro 237 of 407 (58.2%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm).

treatment arm (comb ned w th ota carrageenan) resu ts of nd v dua treatments may vary.	
[Carvallo (B)] 10/19/2020 prospect ve Argent na South Amer ca prepr nt 1 author dosage 1mg days 1 14 th s tr a uses mu t p e treatments n the treatment arm (comb ned w th ota carrageenan) resu ts of nd v dua treatments may vary.	**risk of COVID 19 case, 96.3% lower, RR 0.04, *p* < 0.001** treatment 0 of 131 (0.0%) contro 11 of 98 (11.2%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm).
[Chahla (B)] 1/11/2021 Random zed Contro ed r a Argent na South Amer ca prepr nt 1 author dosage 12mg week y th s tr a uses mu t p e treatments n the treatment arm (comb ned w th ota carrageenan) resu ts of nd v dua treatments may vary.	**risk of COVID 19 case, 95.2% lower, RR 0.05, *p* = 0.002** treatment 0 of 117 (0.0%) contro 10 of 117 (8.5%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm) moderate/severe COVID 19.
	r sk of COVID 19 case 84.0% ower RR 0.16 *p* < 0.001 treatment 4 of 117 (3.4%) contro 25 of 117 (21.4%) adjusted per study odds rat o converted to re at ve r sk a cases.
	r sk of COVID 19 case 84.0% ower RR 0.16 *p* < 0.001 treatment 4 of 117 (3.4%) contro 25 of 117 (21.4%) a cases.
[Elgazzar (B)] 11/13/2020 Random zed Contro ed r a Egypt Afr ca prepr nt 6 authors dosage 400µg/kg week y.	**risk of COVID 19 case, 80.0% lower, RR 0.20, *p* = 0.03** treatment 2 of 100 (2.0%) contro 10 of 100 (10.0%).
[Hellwig] 11/28/2020 retrospect ve eco og ca study mu t p e countr es Afr ca peer rev ewed 2 authors dosage 200µg/kg dose var ed typ ca y 150 200µg/kg.	**risk of COVID 19 case, 78.0% lower, RR 0.22, *p* < 0.02** Afr can countr es PC I vs. no PC re at ve cases per cap ta.
	r sk of COVID 19 case 80.0% ower RR 0.20 *p* < 0.001 wor dw de PC I vs. no PC re at ve cases per cap ta.
[Morgenstern] 4/16/2021 retrospect ve propens ty score match ng Dom n can Repub c Car bbean prepr nt 16 authors dosage 200µg/kg week y.	**risk of hospitalization, 80.0% lower, RR 0.20, *p* = 0.50** treatment 0 of 271 (0.0%) contro 2 of 271 (0.7%) cont nu ty correct on due to zero event (w th rec proca of the contrast ng arm) PSM.
	r sk of COVID 19 case 74.0% ower RR 0.26 *p* = 0.008 treatment 5 of 271 (1.8%) contro 18 of 271 (6.6%) adjusted per study PSM mu t var ate Cox regress on.
[Seet] 4/14/2021 C uster Random zed Contro ed r a S ngapore As a peer rev ewed 15 authors dosage 12mg s ng e dose 200µg/kg max mum 12mg th s tr a compares w th another treatment resu ts may be better when compared to p acebo.	**risk of COVID 19 severe case, 49.8% lower, RR 0.50, *p* = 0.01** treatment 32 of 617 (5.2%) contro 64 of 619 (10.3%).
	r sk of COVID 19 case 5.8% ower RR 0.94 *p* = 0.61 treatment 398 of 617 (64.5%) contro 433 of 619 (70.0%) adjusted per study odds rat o converted to re at ve r sk mode 6.

[Shouman] 8/28/2020 Random zed Contro ed r a Egypt Afr ca peer rev ewed 8 authors dosage 18mg days 1 3 dose var es depend ng on we ght 40 60kg: 15mg 60 80kg: 18mg >80kg: 24mg.	risk of symptomatic case, 91.3% lower, RR 0.09, $p < 0.001$ treatment 15 of 203 (7.4%) contro 59 of 101 (58.4%) adjusted per study mu t var ate.
	r sk of COVID 19 severe case 92.9% ower RR 0.07 $p = 0.002$ treatment 1 of 203 (0.5%) contro 7 of 101 (6.9%) unadjusted.
[Tanioka] 3/26/2021 retrospect ve eco og ca study mu t p e countr es Afr ca prepr nt 3 authors dosage 200µg/kg dose var ed typ ca y 150 200µg/kg.	risk of death, 88.2% lower, RR 0.12, $p = 0.002$ re at ve mean morta ty per m on.
[Vallejos] 12/20/2020 retrospect ve Argent na South Amer ca prepr nt 1 author dosage 12mg week y.	risk of COVID 19 case, 73.4% lower, RR 0.27, $p < 0.001$ treatment 13 of 389 (3.3%) contro 61 of 486 (12.6%).

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Table 1. Evidence base used for other COVID-19 approvals

Source: https://ivmmeta.com

(Ivermectin for COVID-19: real-time meta analysis of 60 studies

Covid Analysis, Nov 26, 2020 (Version 94, **Jul 2, 2021 — updated Niaee**))

Evidence base used for other COVID-19 approvals			
Medication	Studies	Patients	Improvement
Budesonide (UK)	1	1,779	17%
Remdesivir (USA)	1	1,063	31%
Casiri/imdevimab (USA)	1	799	66%
Ivermectin evidence	60	18,931	71% [62-77%]