Ivermectin for Prevention and Treatment of COVID-19 Infection: a Systematic Review and Meta-analysis

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Research

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Abstract

Background

Re-purposed medicines may have role in combating the SARS-CoV-2 virus. The antiparasitic medicine ivermectin, which has anti-viral and anti-inflammatory properties, has been tested in numerous clinical trials with promising results.

Methods

We assessed the efficacy of ivermectin treatment and/or prophylaxis among people with, or at high risk of covid-19 infection. We searched bibliographic databases up to February 2021 and 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 GRADE approach.

Findings

Twenty-one RCTs involving 2741 participants met review inclusion. Meta-analysis of 13 trials found ivermectin reduced risk of death compared with no ivermectin (average Risk Ratio 0.32, 95% confidence interval (CI) 0.14 to 0.72; n=1892; I^2=57%; low to moderate-certainty evidence. Low-certainty evidence found ivermectin prophylaxis reduced covid-19 infection by an average 86% (95% CI 79% to 91%). Secondary outcomes provided very-low or low certainty evidence. Low certainty evidence suggests that that there may be no benefit with ivermectin for 'need for mechanical ventilation', whereas effect estimates for 'improvement' and 'deterioration' favoured ivermectin use. Severe adverse events were rare and evidence of no difference was assessed as low to very low-certainty. Evidence on other secondary outcomes was very low certainty.

Interpretation

Low to moderate-certainty evidence suggests reductions in covid-19 deaths and infections may be possible by using ivermectin. Employing ivermectin early on may reduce the number of people progressing to severe disease. The apparent safety and low cost suggest that ivermectin could have an impact on the SARS-CoV-2 pandemic globally.

Research In Context

Evidence before this study

In countries across the world, hospitalisations and deaths from covid-19 have increased rapidly over recent months, with estimated total deaths now exceeding 2 million people. The population of developed countries will eventually be given the choice of having a vaccine, but this choice may not be afforded to low- and middle-income countries (LMICs) for a long time. The antiparasitic medicine ivermectin, which is widely available in LMICs, has been tested in numerous clinical trials of prevention and treatment of covid-19 with promising results. To date, three reviews of ivermectin use for covid-19 have been published but only one has been peer-reviewed and limited meta-analyses have been performed on the available data.

Added value of this study

To our knowledge, this is the first systematic review and meta-analysis done using rigorous Cochrane methods. Evidence was assessed using the GRADE approach which judges the certainty of the evidence. We found low- to moderate certainty evidence that ivermectin treatment may reduce the risk of death among people hospitalised with covid-19. Low-certainty evidence also shows that prophylaxis with ivermectin may reduce the risk of getting infected with covid-19 among those with high exposure.

Implications of all the available evidence

The apparent safety and low cost suggest that ivermectin could have an impact on the SARS-CoV-2 pandemic globally. Ivermectin is not a new and experimental drug with safety concerns; it is a WHO 'essential medicine' usually used in different indications. It may be useful for more health professionals to get access to this medicine for use against covid-19 during the ongoing pandemic. Further results from trials are expected soon.

Introduction

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

Ivermectin is a well-known medicine that is approved by the World Health Organization and the US Food and Drug Administration (FDA) for use as an anti-parasitic medication. 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 Organisation's Essential Medicines.[4] With total doses of ivermectin distributed apparently equalling one-third of the present world population,[5] ivermectin at the usual doses (0.2 mg/kg to 0.4 mg/kg) is considered extremely safe for use in humans.[6,7] In addition to its anti-parasitic 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 randomised 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 (FLCCC) summarised 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 Institute of Health in the US recently stated that "there are insufficient data to recommend either for or against the use of ivermectin for the treatment of covid-19".[11]

Ivermectin has antiviral activity against a wide range of RNA and some DNA viruses, e.g. Zika, Dengue, Yellow Fever, and others.[12] Caly et al[13,14] 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[13,14] which suppress normal immune responses. However, the cell culture EC_{50} may not be achievable *in vivo*.[15] Other conjectured mechanisms include: inhibition of SARS-CoV-2 3CLPro activity [16,17] (a protease essential for viral replication), a variety of anti-inflammatory effects,[18] and competitive binding of ivermectin with the viral S protein as shown in multiple *in silico* studies[19]. Analogously to neutralizing antibodies, the latter would inhibit viral binding to ACE-2 receptors suppressing infection. Haemagglutination via viral binding to sialic acid (SA) receptors on erythrocytes is a recently-proposed pathologic mechanism[20] that would be similarly disrupted. Both host-directed and virus-directed mechanisms have thus been proposed, the clinical mechanism may be multi-modal, and a comprehensive review of mechanisms of action is warranted.

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

Ivermectin has now been shown to have anti-viral and anti-inflammatory properties, suggesting that its effect against SARS-CoV-2 requires systematic review. 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 $2.90 for 100 12 mg tablets. [21] A therapeutic course of ivermectin for cases of covid-19 infection in India, for example, has been reported to cost less than PPP$ 53.93 for a dose of 12mg twice daily for 7 days [22] (PPP = purchasing power parity in 2021). This price for ivermectin represents that of a dosage at the upper-end of what has be used to treat covid-19 cases. [22] For these reasons, the exploration of ivermectin’s potential effectiveness against SARS-CoV-2 may be of particular importance for settings with limited resources. [23] 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. Additionally, we aimed to prepare a brief economic commentary (BEC) of ivermectin as treatment and as prophylaxis for covid-19.[24]

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.[25]

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 randomised controlled trials (RCTs) up to February 01 2021 (Appendix 1–3); current guidance[24] for the BEC was followed for a supplementary search of economic evaluations. There were no language restrictions and translations were planned to be carried out when necessary.

We searched the reference list of included studies, and of two other 2021 literature reviews on ivermectin.[9] We contacted experts in the field (Drs. Andrew Hill, Pierre Kory and Paul Marik) for information on new and emerging trial data. Additionally, 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 pre-print publications and unpublished articles were identified from the pre-print sever Medrxiv 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, inclusion/exclusion criteria), setting, participant characteristics (disease severity, age, gender, co-morbidities, smoking, 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 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 (e.g. between a published article and a trial registry record), we contacted the authors for clarification. Assessments were conducted by two reviewers (TL, TD, AB or GG) using the Cochrane RCT risk of bias tool.[26] Discrepancies were resolved by discussion.

Continuous outcomes were measured as the mean difference (MD) and 95% confidence intervals (CI); 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),[27] by a formal statistical test to indicate statistically significant heterogeneity[28] 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-analysed data using the random effects model (DerSimonian and Laird method)[29] using RevMan 5.4 software.[26,30] Results used the inverse variance method for weighting.[26] Some sensitivity analyses used other methods that are outlined below and some calculations were performed in R[31] through an interface[32] to the netmeta package.[33] 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[34] and estimated odds ratios (and additionally risk ratio for the MH (Mantel-Haenszel) 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 (RD) 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 non-fixed continuity correction is preferable to the usual 0.5.[34] 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.[35–39]

All outcomes have been assessed independently by two review authors (TD and AB) using the GRADE approach,[40] which ranks the quality of the evidence. Results are presented in a summary of findings table. Any differences were resolved by discussion with the wider group. We used Cochrane Effective Practice and Organisation of Care guidance to interpret the evidence.[41]

Role of funding source

There was no funding source for this study.

Results

Search results and risk of bias assessment

The combined and preliminary de-duplicated total was n = 523. We also identified 11 records from other sources (reference lists, etc). See PRISMA flow diagram for inclusion and exclusion details of these references (Fig. 1).

The supplementary search for the BEC identified seventeen studies, of which four 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 met inclusion and all of these contributed data to at least one review outcome and meta-analysis. Thirteen trials contributed data for the primary outcome for ivermectin treatment (death); three studies reported the primary outcome for prophylaxis (covid-19 infection). Characteristics of included studies are given in Table 1. Seventeen studies[42–58] were excluded as they were not RCTs and we identified 39 ongoing studies[59–97] and two studies[98,99] are awaiting classification.

Table 1
Summary of study characteristics

Study ID	Country	Design	Funding	Participants	Sample size	Ivermectin dose and frequency*	Comparator	Origin of data	Main outco repor
covid-19 treatment studies									
Ahmed 2020[100]	Bangladesh	Double-blind	BPL(Pharma); Bangladesh, Canada, Sweden, and UK govt	Mild to moderate covid (inpatients)	72	12mg x 1 day or x 5 days (3 study arms)*	Placebo	Published in PR journal; emailed/responded with data	Time clear -ve), r of fe cough days, of hospi morta failin main > 93% event at 7 a days
Babalola 2020[101]	Nigeria	Double blind	Self-funded	Asymptomatic, mild or moderate covid (45 inpatients and 17 outpatients)	62	6 mg every 84 hrs x 2 wks (arm 1) or 12 mg every 84 hrs x 2 wks (arm 2)	Ritonavir/lopinavir	MedRxiv pre-print: emailed/responded with data. Paper accepted for publication	Time ve, la paran (plate lymp clotti clinic symp paran
Chaccour 2020[23]	Spain	Double blind	Idapharma, ISGlobal and the University of Navarra	Mild covid (outpatients)	24	0.4mg/kg x 1 dose	Placebo	Published in PR journal	PCR + day 7 propo symp at da 4,7,14 progr death event
Chachar 2020[127]	Pakistan	Open label	Self-funded	Mild covid (outpatients)	50	12mg at 0, 12, and 24 hours (3 doses)	SOC	Published in PR journal	Symp at da
Chowdhury 2020[128]	Bangladesh	Quasi-RCT	None reported	Outpatients with a + ve PCR (approx. 78% symptomatic)	116	0.2mg/kg x1 dose*	HCQ 400 mg 1st day then 200mg BID x 9 days + AZM 500 mg daily x 5 days	Research Square pre-print	Time PCR t perio symp recov adver
Elgazzar 2020[50]	Egypt	RCT	None reported	Mild to severe covid (inpatients)	200	0.4mg/kg daily x 4 days	HCQ 400 mg BID x 1 day then 200 mg BID x 9 days	Research Square pre-print: emailed/responded with data	Impro progr died. meas D-dim lymp serun after of tre
Fonseca 2021[102]	Brazil	Double blind	Institution-funded	Moderate to severe (inpatients)	167	14mg daily x 3 days (plus placebos x 2 additional days)	HCQ – 400mg BID on day 0 then daily x 4 days ; CQ -450mg BID day 0 then daily x 4 days	Pre-publication data/ manuscript in progress obtained via email	Death ventil
Hashim 2020[129]	Iran	Quasi-RCT	None reported	Mild to critical (inpatients)	140	0.2mg/kg x 2 days* Some had a 3rd dose a week later	SOC	MedRxiv pre-print	Death time recov disea progr (dete

Footnotes

* Also administered doxycycline

** multi-arm trial

SOC: Standard of care; RCT: Randomised controlled trial; PR: peer review; mg: milligram; kg: kilogram; PCR: polymerase chain reaction; hrs: hours

Study ID	Country	Design	Funding	Participants	Sample size	Ivermectin dose and frequency*	Comparator	Origin of data	Main outco repor
Krolewiecki 2020[103]	Argentina	Open label	None reported	Mild to moderate (inpatients)	45	0.6mg/kg/day x 5 days	Placebo	Published in PR journal	Viral reduc respir secre 5, IVM conc in pla sever event
Mahmud 2020[104]	Bangladesh	Double blind	None reported	Mild to moderate covid (inpatients)	363	12mg x 1 dose*	Placebo + SOC	Data published on clinical trial registry and clarification obtained via email	Impro deteri late c recov persi test +
Mohan 2021[107]	India	Double blind	Institution funded	Mild to moderate	152	12 mg or 24 mg elixir x 1 dose	Placebo	MedRxiv pre-print Research	Conv RT-PC negat declir load from enrol
Niaee 2020[105]	Iran	Double blind	Institution-funded	Mild to severe covid	180	0.2mg/kg x 1 and 3 other dosing options) ~ 14 mg tablet**	HCQ 200mg/kg BID or placebo	Research Square pre-print	Death of sta bioch parar
Okumus 2021[111]	Turkey	Quasi-RCT	None reported	Severe covid	66	0.2mg/kg x 5 days	SOC	Pre-publication data/manuscript in progress obtained via email	Clinic impro deteri death score
Petkov 2021[130]	Bulgaria	Double blind	Pharma funded	Mild to moderate covid	100	0.4mg/kg x 3 days	Placebo	Pre-publication data obtained from another source	Rate conv PCR r
Podder 2020[131]	Bangladesh	Open label	Self-funded	Mild to moderate (outpatients)	62	0.2mg/kg x 1 dose	SOC	Published in PR journal	Durat symp recov to sy free f enrol recov to sy free f symp onset PCR r day 1
Raad 2021[109]	Lebanon	Double blind	Self-funded	Asymptomatic outpatients	100	9 mg PO if 45kg to 64kg, 12mg PO if 65kg to 84kg and 0.15mg/kg if body weight ≥ 85 Kg	Placebo	Pre-publication data/manuscript in progress obtained via email	Viral reduc hospi adver

Footnotes

* Also administered doxycycline

** multi-arm trial

SOC: Standard of care; RCT: Randomised controlled trial; PR: peer review; mg: milligram; kg: kilogram; PCR: polymerase chain reaction; hrs: hours

Study ID	Country	Design	Funding	Participants	Sample size	Ivermectin dose and frequency*	Comparator	Origin of data	Main outco repor
Ravikirti 2021[106]	India	Double blind	Self-funded	Mild to moderate covid (inpatients)	112	12mg x 2 days + SOC	Placebo + SOC	Published in PR journal	A neg PCR r day 6 symp on da disch day 1 admi ICU, r invas mech ventil morta
Rezai 2020[108]	Iran	Double blind	None reported	Mild to moderate (inpatient)	60	0.2 mg/kg x 1 dose	SOC	Pre-publication data obtained from another source	Clinic symp respi and C satur
Schwartz 2021[110]	Israel	Double blind	None reported	Mild to moderate (outpatients)	94	0.15 to 0.3 mg/ kg x 3 days	Placebo	Pre-publication data obtained from another source	Viral at da and 1 hospi
covid-19 prophylaxis studies									
Chala 2021[132]	Argentina	Open label	None reported	Health care workers	234	12 mg (in drops) weekly + lota-carrageenan 6 sprays daily x 4 wks	SOC	Pre-publication data/manuscript in progress obtained via email	Covic infect clear meas PCR symp
Elgazzar 2020[50]	Egypt	Open label	Self-funded	Health care and family contacts	200	0.4mg/kg, weekly x 2 weeks	SOC	Research Square pre-print: emailed/responded with data	Posit test
Shouman 2020[133]	Egypt	Open label	Self-funded	Family contacts	303	2 doses (15mg – 24 mg depending on weight) on day 1 and day 3	SOC	Published in PR journal	Symp and/ covid test w days; event
Footnotes									
* Also administered doxycycline									
** multi-arm trial									
SOC: Standard of care; RCT: Randomised controlled trial; PR: peer review; mg: milligram; kg: kilogram; PCR: polymerase chain reaction; hrs: hours									

A risk of bias summary graph is given in Fig. 2. Eleven studies[23,50,100–108] used satisfactory random sequence generation and allocation concealment. One study described satisfactory sequence generation, but it was unclear whether allocation was concealed.[109]

Ten trials reported blinding of the participants/personnel and/or the outcome assessors.[23, 100–102,104, 106–110] 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 pre-print websites to constitute a risk of bias, as all studies were scrutinised and peer reviewed by us during the review process and, where additional information was needed, we contacted the authors for clarification. Most trials were self-funded or did not report funding and we did not note any apparent conflicts of interest among the trialists.

Main findings

Twenty-one RCTs (including 2 quasi-RCTs) involving 2741 participants were included, with sample sizes ranging from 24 to 363 participants. For trials of covid-19 treatment, 14 evaluated ivermectin among participants with mild to moderate covid-19 only; four trials included patients with severe covid-19. Most compared ivermectin with placebo or no ivermectin; four trials included an active comparator (Table 1). Three RCTs involving 738 participants were included in the prophylaxis studies. Most studies were registered, self-funded and undertaken by clinicians working in the field. There were no obvious conflicts of interest noted.

Ivermectin treatment vs no ivermectin treatment

Nineteen studies (2003 participants) contributed data to the comparison ivermectin treatment vs no ivermectin treatment for covid-19 treatment.

Meta-analysis of 13 trials, assessing 1892 participants, found that ivermectin reduced the risk of death by an average of 68% (95% CI, 28–86%) compared with no ivermectin treatment (average risk ratio (aRR) 0.32, 95% CI 0.14 to 0.72; I^2 = 57%; risk of death 2.5% versus 9.1% among hospitalised patients in this analysis, respectively (Summary of Findings (SoF) Table 2a and Fig. 3). Heterogeneity was explained by the exclusion of one trial[102] in a sensitivity analysis (average RR 0.25, 95% CI 0.13 to 0.48, n = 1725, I^2 = 12%), but since 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 three other studies with an active treatment comparator (average RR 0.45, 95% CI 0.21 to 0.98, n = 1083, I^2 = 0%). The results were also not sensitive to the exclusion of studies that were potentially at higher risk of bias (average RR 0.28, 95% CI 0.09 to 0.85, 11 studies, n = 1697, I^2 = 67%), 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 judgements (Table 3). Overall, death from any cause, taking into account all composite analyses, was judged to provide low to moderate-certainty evidence (SoF Table 2a and Fig. 4–6). A funnel plot corresponding to the primary outcome of death from any cause did not appear to suggest any evidence of publication bias (Fig. 7). Furthermore, the ease with which trial reports can be uploaded as preprints should reduce this risk.

Table 2a

Summary of findings table of ivermectin versus no ivermectin for covid-19 treatment in any setting

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No ivermectin	Ivermectin			
Death from any cause	91 per 1000 (all disease severity)	62 fewer deaths per 1000 (25 to 78)	RR = 0.32 (0.14 to 0.72)	1892 (13)	Low to moderate[1,2]
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[1,3,4]
Time to clinical recovery, in days (outpatients)			(MD = -1.06 (-1.63 to -0.49)	176 (2)	Very low[1,3,4]
Time to clinical recovery, in days (mild to moderate covid-19 inpatients)			MD = -7.32 (-9.25 to -5.39)	96 (1)	Very low[1,5]
Time to clinical recovery, in days (severe covid-19 inpatients)			MD = -3.98 (-10.06 to 2.10)	33 (1)	Very low[1,5]
Admission to ICU			RR = 1.22 (0.75 to 2.00)	379 (2)	Very low[5,6]
Need for mechanical ventilation			RR = 0.66 (0.14 to 3.00)	431 (3)	Low[4,6]
Length of hospital stay, in days			MD = 0.13 (-2.04 to 2.30)	68 (2)	Very low[1,5]
Admission to hospital			RR 0.16 (0.02 to 1.32)	194 (2)	Very low[1,5]
Duration of mechanical ventilation	Not reported				
Improvement (mild to moderate covid-19)*	543 improved per 1000	185 more per 1000 (from 119 more to 260 more)	RR 1.34 (1.22 to 1.48)	681 (4)	Low[1,3]
Deterioration (any disease severity)	189 per 1000	140 fewer per 1000 (from 77 fewer to 166 fewer)	RR 0.26 (0.12 to 0.59)	1041 (5)	Low[1,3]
Serious adverse events	5/542 (1%) had an SAE in ivermectin group and 0/370 (0%) in control		RR = 3.23 (0.55 to 18.87)	728 (8)	Low[1,3]

*Only one study contributed to the 'severe' covid-19 subgroup and subgroup data were not pooled due to subgroup differences

[1] Downgraded − 1 for study design limitations

[2] Downgraded − 1 each for discrepancies in composite sensitivity analyses

[3] Downgraded − 1 for inconsistency

[4] Downgraded − 1 for imprecision

[5] Downgraded − 2 for imprecision/sparse data

[6] Downgraded − 1 for indirectness

Table 2b
Summary of findings table of ivermectin versus no ivermectin for covid-19 prophylaxis in healthy population (people without covid-19 infection)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No ivermectin	Ivermectin			
covid-19 infection	296 per 1000	245 fewer infections per 1000 (234 to 269)	RR = 0.14 (0.09 to 0.21)	738 (3)	Low[1]
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.				
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).					
CI: Confidence interval; **RR**: Risk Ratio; RCT: Randomised controlled trial; NNT: number needed to treat.					
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.					
[1] Downgraded − 2 for study design limitations					

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	0.33 (0.21 to 0.50)	Handles single zero trials
M-H	OR	FE	0.33 (0.21 to 0.50)	Handles single zero trials
M-H	OR	RE	0.28 (0.11 to 0.66)	Handles single zero trials
M-H	RR	FE	0.39 (0.27 to 0.58)	Handles single zero trials
M-H	RR	RE	0.32 (0.14 to 0.73)	Handles single zero trials
M-H	RD	FE	-0.05 (-0.07 to -0.03)	Handles double zero trials
M-H	RD	RE	-0.04 (-0.07 to -0.00)	Handles double zero trials
IV	RD	FE	-0.02 (-0.03 to -0.01)	Handles double zero trials
IV	RD	RE	-0.03 (-0.05 to -0.01)	Handles double zero trials
Treatment arm continuity correction methods using IV			Accounting for double zeros	Accounting for all zeros
0.01	RR	FE	0.51 (0.34 to 0.77)	0.55 (0.36 to 0.85)
0.01	RR	RE	0.36 (0.19 to 0.68)	0.47 (0.27 to 0.81)
0.1	RR	FE	0.51 (0.34 to 0.77)	0.53 (0.35 to 0.82)
0.1	RR	RE	0.37 (0.20 to 0.69)	0.38 (0.19 to 0.76)
0.25	RR	FE	0.51 (0.34 to 0.77)	0.52 (0.34 to 0.79)
0.25	RR	RE	0.38 (0.20 to 0.70)	0.38 (0.20 to 0.72)
0.5	RR	FE	0.52 (0.35 to 0.77)	0.52 (0.35 to 0.78)
0.5	RR	RE	0.39 (0.22 to 0.71)	0.41 (0.23 to 0.71)
M-H: Mantel-Haenszel; IV: Inverse variance; TACC: Treatment arm continuity correction; OR: odds ratio; RR: Risk ratio; RD: Risk difference; FE: fixed effects; RE: Random effects; CI: Confidence interval				

Secondary outcomes provided low to very low certainty evidence (SoF Table 2a). Low certainty findings suggested that that there may be no benefit with ivermectin for 'need for mechanical ventilation', whereas effect estimates for 'improvement' and 'deterioration' favoured ivermectin but were graded as low

certainty due to study design limitations and inconsistency (Fig. 8 to 10). All other secondary outcome findings were assessed as very low certainty.

Meta-analysis of eight trials, assessing 728 participants, found that there was no significant difference between ivermectin and control in the risk of severe adverse events (aRR 3.23, 95% CI 0.55 to 18.87; I^2 = 0%; *low certainty evidence*, downgraded for imprecision and study design limitations). Five severe adverse events were reported in the ivermectin group and none in controls. The SAEs were as follows: two patients in the Mahmud 2020 trial[104] had oesophagitis (this is a known side effect of doxycycline, which was co-administered with ivermectin in this trial); one patient in Krolewiecki et al[103] had hyponatraemia (this trial used high-dose ivermectin for 5 days); and two patients in a study from Turkey[111] had serious "delirium-like behaviour, 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 (see SoF Table 2a).

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 covid-19 infection by an average of 86% (79–91%) (3 trials, 738 participants; aRR 0.14, 95% CI 0.09 to 0.21; 5.0% vs 29.6% contracted covid-19, respectively; *low-certainty evidence*; downgraded due to study design limitations and few included trials). In two trials involving 538 participants, no severe adverse events were recorded (SoF Table 2b; Fig. 11).

Discussion

These findings suggest low to moderate-certainty evidence showing a survival benefit without harm of ivermectin for treatment against covid-19. Low certainty evidence on improvement and deterioration support the possibility of clinical benefit with ivermectin. Low certainty evidence also suggest it could be a useful prophylaxis. Overall, therefore, the evidence suggests that early use of ivermectin may reduce morbidity and mortality from covid-19, based on reductions in covid-19 infections when ivermectin was used as post-exposure prophylaxis, more favourable point estimates for mild to moderate disease compared with severe disease for death due to any cause, and on the evidence demonstrating reductions in the number of patients deteriorating.

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. However, evidence from a recent systematic review of ivermectin use among people with parasitic infections suggests that ivermectin administered at the usual doses (0.2mg/kg or 0.4mg/kg) is safe and could be safe at higher doses.[7,112] A recent World Health Organization document on ivermectin use for scabies found that adverse events with ivermectin were primarily minor and transient.[21]

We decided to restrict the included studies to the highest level of evidence, i.e. RCTs, despite the use of observational evidence being potentially used in times of emergency,[113] and the numerous observational studies on ivermectin for covid-19. We included pre-print 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.[114] Whilst 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.[114]

There are a number of limitations with this review. Several of the studies contributing data did not 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 in 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, as well as other biochemical outcomes have been reported in several studies and reviews and tend to favour ivermectin.[10,50,101,105] 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. As we did not undertake in our protocol to perform narrative evidence synthesis, and as these data tended to favour ivermectin, the certainty of the effects of ivermectin on these continuous outcomes may be underestimated.

To date, three other reviews of ivermectin use for covid-19 have been published[9,10,115] but only one has been peer-reviewed.[9] We applied AMSTAR 2,[116] a critical appraisal tool for systematic reviews of healthcare interventions, to the two non-peered systematic reviews[10,115] and both were judged to be of low quality (Table 4). However, there was also a suggestion that ivermectin may reduce risk of death in treatment of covid-19 in these reviews.

In addition to these reviews, the findings of several controlled observational studies are consistent with existing evidence and suggest improved outcomes with ivermectin treatment.[49,52,54] 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.[42,48]

Clarifying ivermectin safety in pregnancy is a key question in patient acceptability for pregnant women contracting covid-19. One source[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.[117,118] In addition to safety and relative efficacy, different risk-benefit judgments may be presented for prophylaxis (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, though 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 two recent reports suggesting that ivermectin may be efficacious as prevention and treatment of covid-19 in this age group.[44,119]

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.[120] Based on observational evidence, the Peruvian government approved ivermectin for use against covid-19 in May 2020.[120] After implementation, death rates in eight states reduced by 64–91% over a two-month period.[120] 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.[121] However, factors such as change in behaviour, 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.[122] 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.[122]

Ivermectin may be equitable, acceptable and feasible global intervention against covid-19. 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.[121,123–126] 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 may potentially have an impact on health and economic outcomes of the pandemic across many countries. Ivermectin is not a new and experimental drug with safety concerns. It is a WHO ‘Essential Medicine’ used in several different indications. Health professionals should consider its use against Covid-19 in both treatment and prophylaxis.

Declarations

Contributors

Tess Lawrie and Andrew Bryant co-wrote 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 amongst Tess Lawrie, Andrew Bryant and Therese Dowswell. Therese Dowswell and Andrew Bryant graded the evidence. Edmund Fordham prepared the text on ivermectin mechanisms, use in pregnancy and among the elderly. Sarah Hill prepared the brief economic commentary. Clinicians Scott Mitchell and Tony Tham contributed to the interpretation of the evidence in the discussion and conclusions. All authors reviewed and approved the final version of the manuscript.

Ethical Approval and Consent to participate

Not applicable

Consent for publication

Not applicable

Availability of supporting data

All data are presented in this review and references to included and ongoing trials are provided.

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Tess Lawrie and Andrew Bryant co-wrote 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 amongst Tess Lawrie, Andrew Bryant and Therese Dowswell. Therese Dowswell and Andrew Bryant graded the evidence. Edmund Fordham prepared the text on ivermectin mechanisms, use in pregnancy and among the elderly. Sarah Hill prepared the brief economic commentary. Clinicians Scott Mitchell and Tony Tham contributed to the interpretation of the evidence in the discussion and conclusions. All authors reviewed and approved the final version of the manuscript.

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Tables

Due to technical limitations, table 4 docx is only available as a download in the Supplemental Files section.

Figures

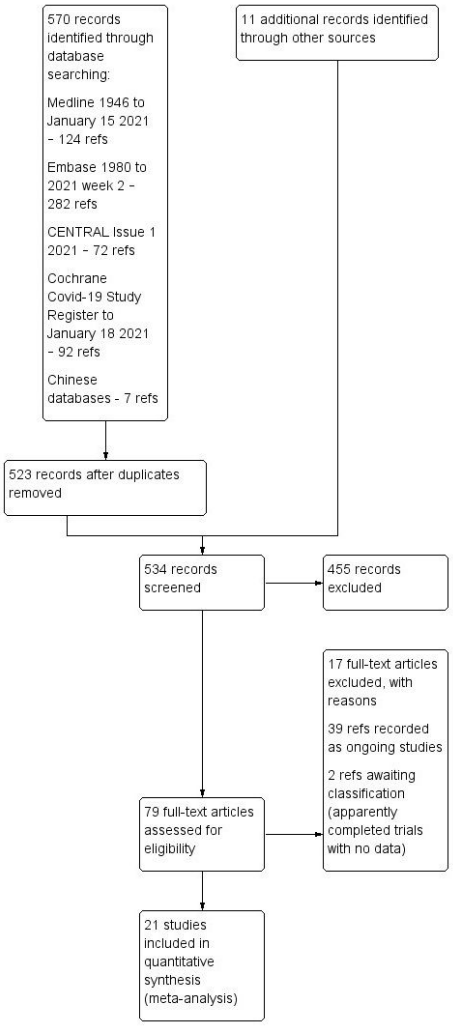


Figure 1

Study flow diagram from search conducted on 01 February 2021

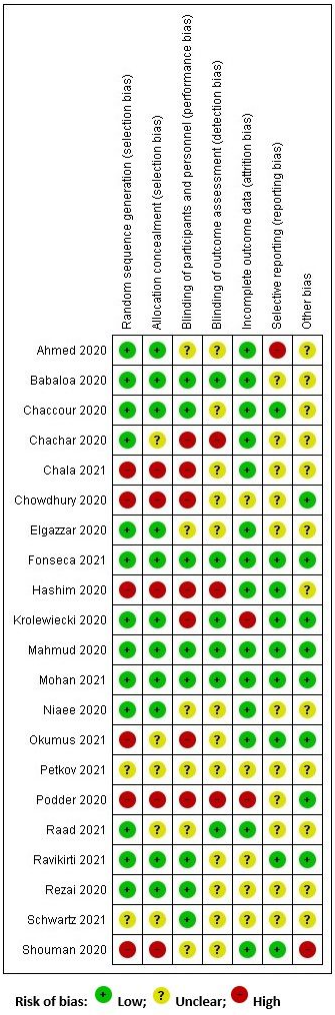


Figure 2

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

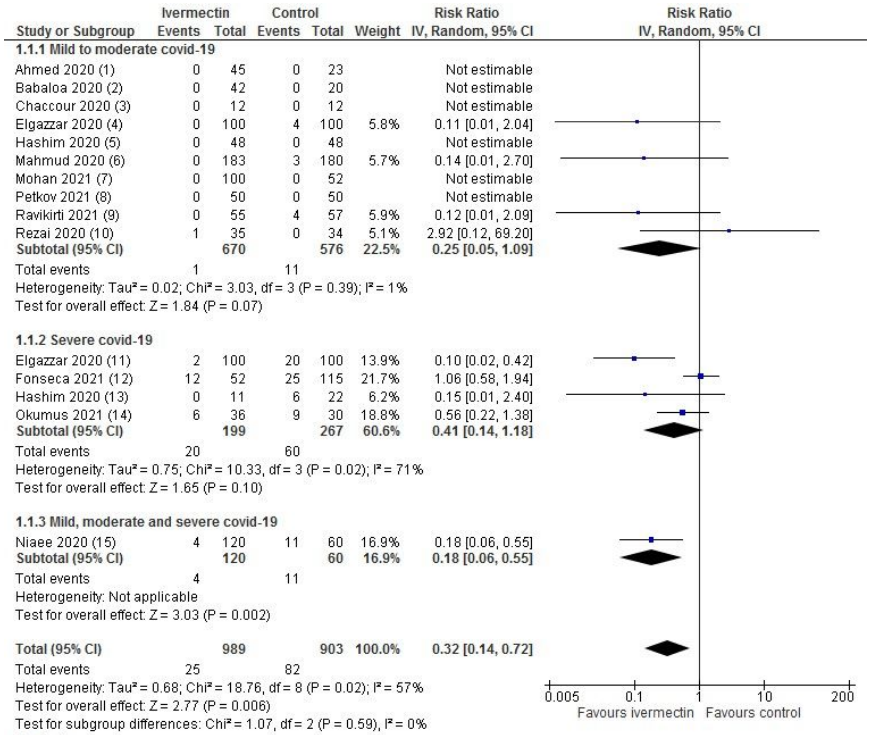


Figure 3

Death due to any cause

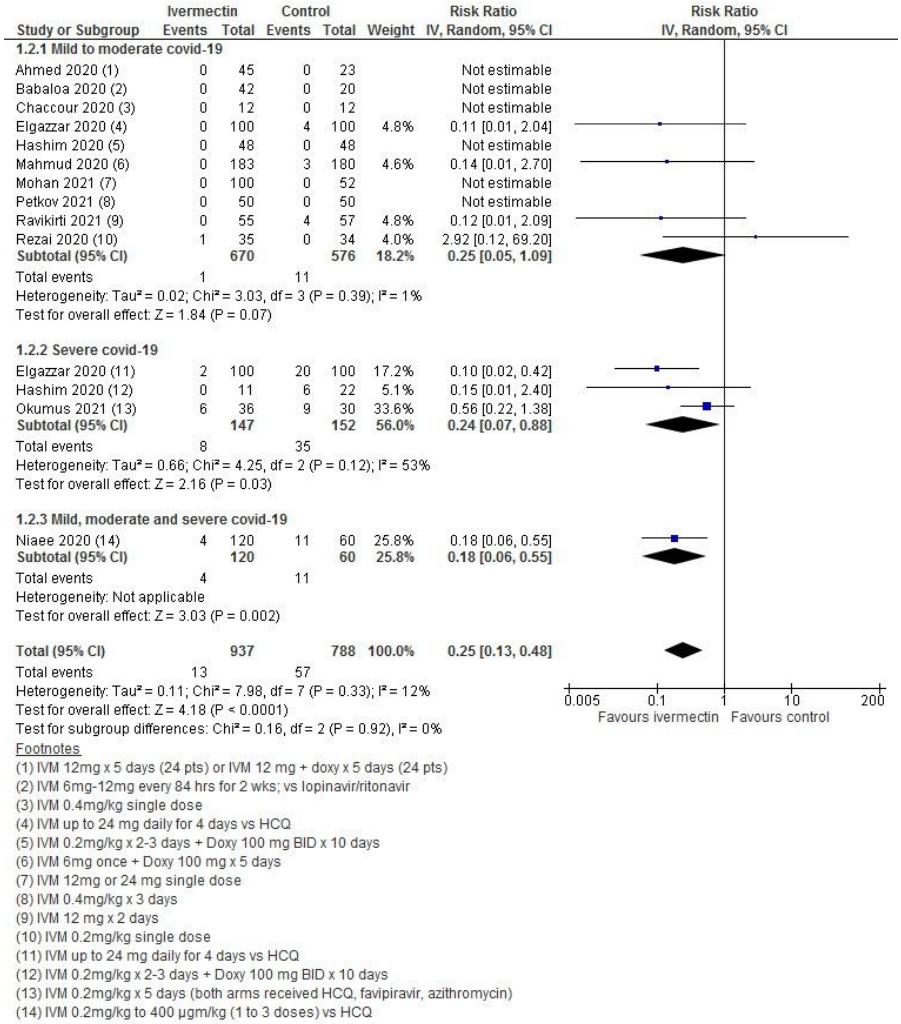


Figure 4

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

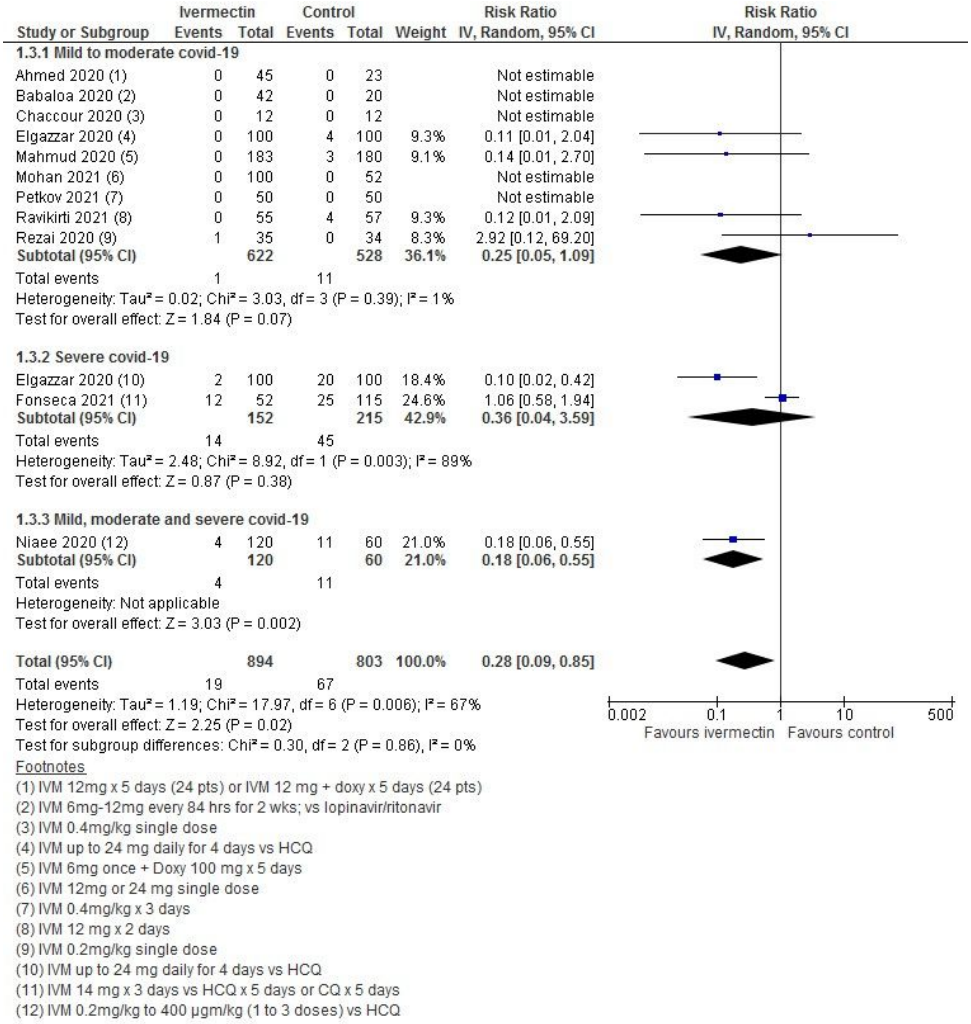


Figure 5

Death due to any cause, excluding high risk of bias studies

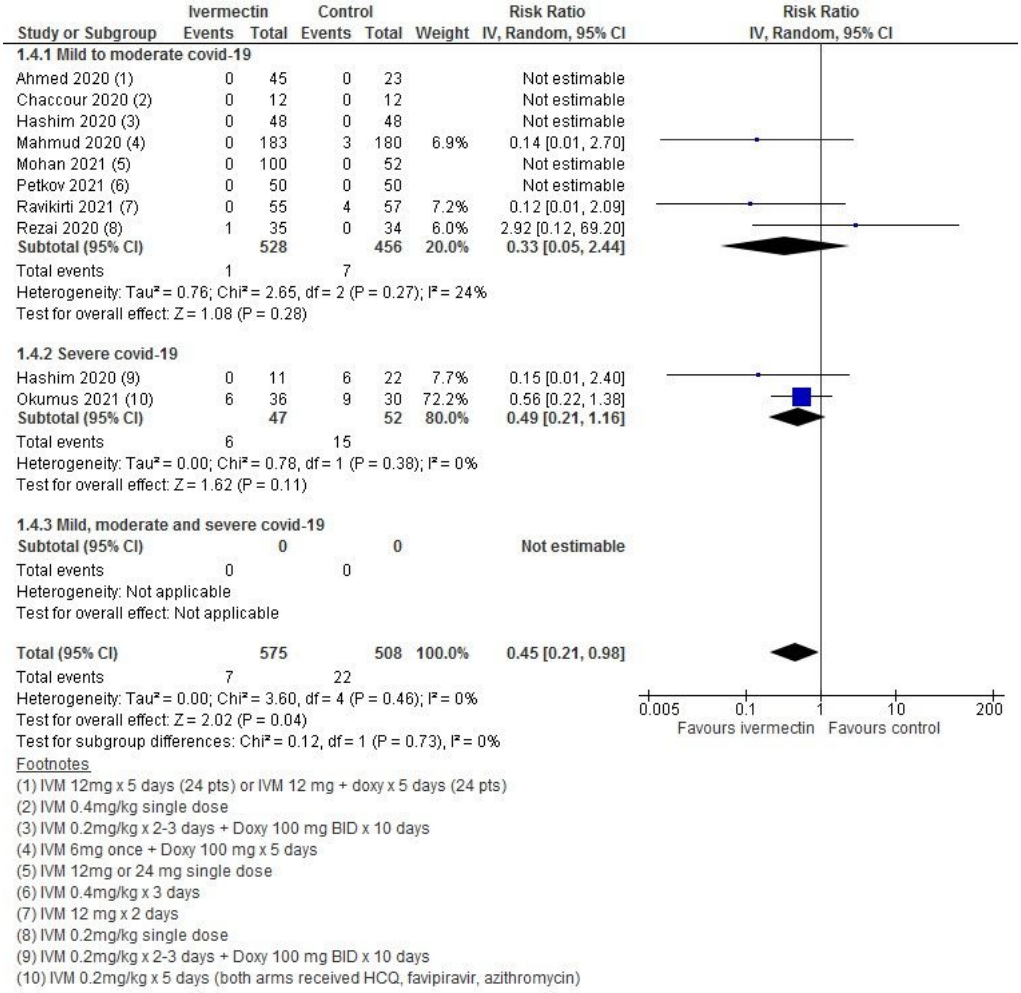


Figure 6

Death due to any cause, excluding studies with active controls

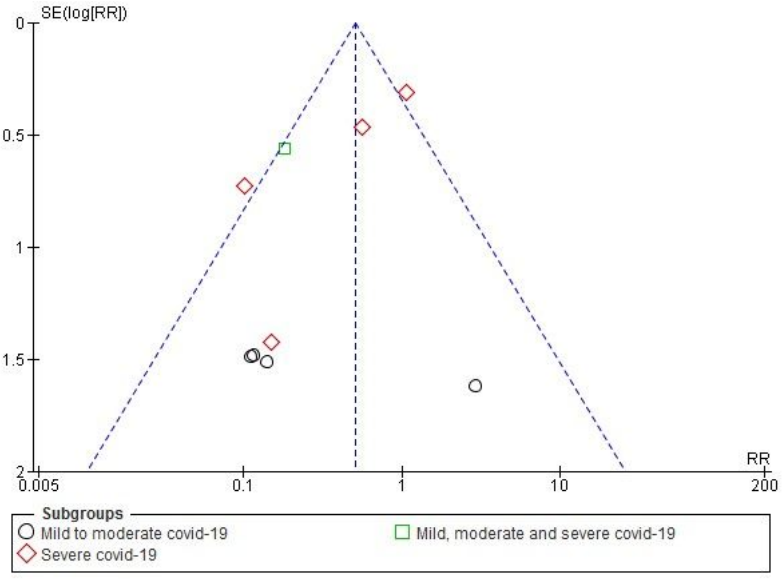
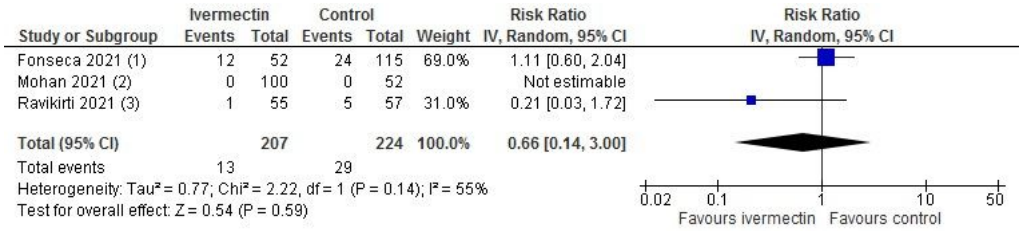


Figure 7

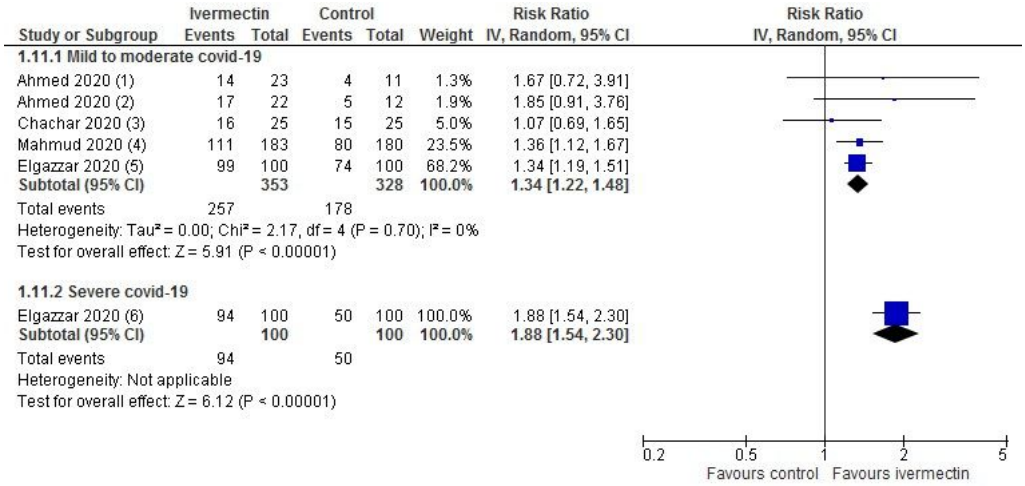
Funnel plot of Ivermectin vs control for covid-19 treatment for all cause death (subgrouped by severity)



Footnotes
(1) IVM 14 mg x 3 days vs HCQ x 5 days or CQ x 5 days
(2) IVm 12mg or 24mg
(3) IVM 12 mg x 2 days; data for "invasive ventilation"

Figure 8

Need for mechanical ventilation



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

Figure 9

Improvement

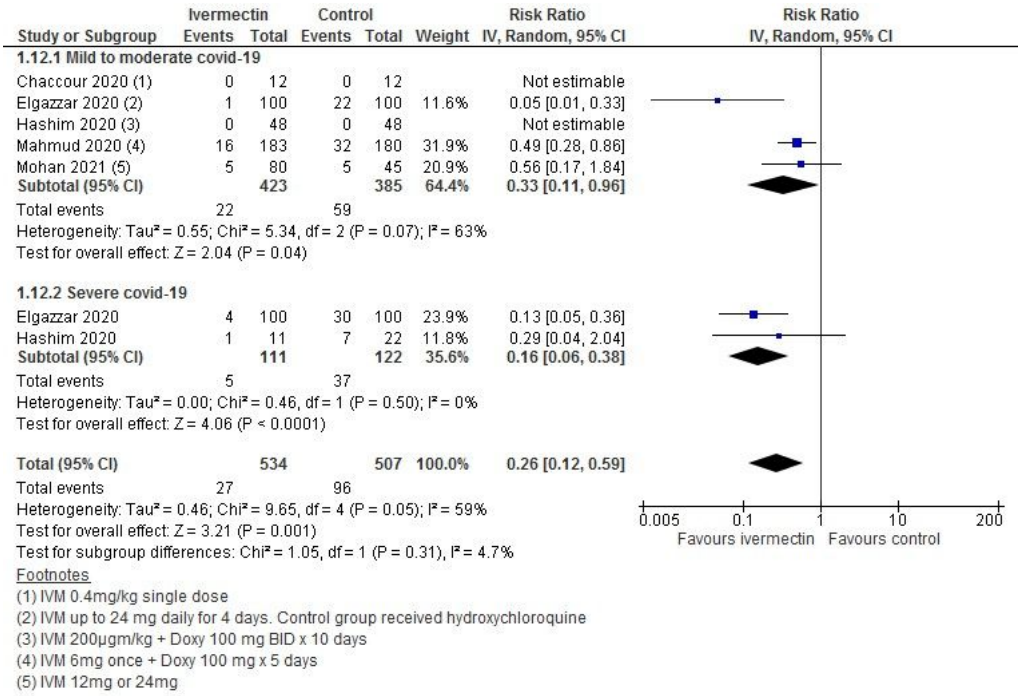


Figure 10

Deterioration

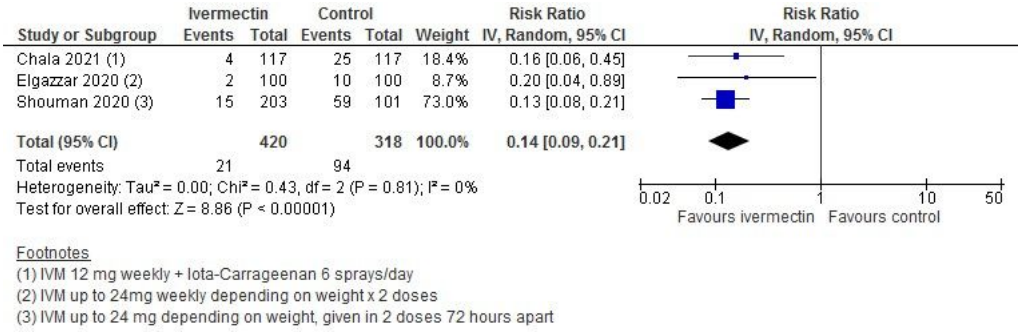


Figure 11

Covid-19 infection (prophylaxis studies)

Supplementary Files

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- Appendices.docx
- Table4.docx