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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This paper discusses off-label use in Covid-19 of the FDA-approved medication ivermectin.

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1 **Abstract**

2 **Background**

3 Re-purposed medicines may have a role against the SARS-CoV-2 virus. The antiparasitic ivermectin, with anti-viral
4 and anti-inflammatory properties, has now been tested in numerous clinical trials.

5 **Areas of uncertainty**

6 We assessed the efficacy of ivermectin treatment in reducing mortality, in secondary outcomes, and in chemo-
7 prophylaxis, among people with, or at high risk of, covid-19 infection.

8 **Data sources**

9 We searched bibliographic databases up to April 25 2021. Two review authors sifted for studies, extracted data and
10 assessed risk of bias. Meta-analyses were conducted and certainty of the evidence was assessed using the GRADE
11 approach and additionally in trial sequential analyses for mortality.

12 Twenty-four RCTs involving 3406 participants met review inclusion.

13 **Therapeutic Advances**

14 Meta-analysis of 15 trials found ivermectin reduced risk of death compared with no ivermectin (average Risk Ratio
15 0.38, 95% confidence interval (CI) 0.19 to 0.73; n=2438; I²=49%; moderate-certainty evidence). This result was
16 confirmed in a trial sequential analysis (TSA) using the same DerSimonian-Laird method that underpinned the
17 unadjusted analysis. This was also robust against a TSA using the Biggerstaff-Tweedie method. Low-certainty
18 evidence found ivermectin prophylaxis reduced covid-19 infection by an average 86% (95% CI 79% to 91%).

19 Secondary outcomes provided less certain evidence. Low certainty evidence suggested that that there may be no
20 benefit with ivermectin for 'need for mechanical ventilation', whereas effect estimates for 'improvement' and
21 'deterioration' clearly favoured ivermectin use. Severe adverse events were rare among treatment trials and
22 evidence of no difference was assessed as low certainty. Evidence on other secondary outcomes was very low
23 certainty.

24 **Conclusions**

25 Moderate-certainty evidence finds that large reductions in covid-19 deaths are possible using ivermectin.

26 Employing ivermectin early in the clinical course may reduce numbers progressing to severe disease. The apparent

27 safety and low cost suggest that ivermectin is likely to have a significant impact on the SARS-CoV-2 pandemic
28 globally.

29 **Keywords:** ivermectin, prophylaxis, treatment, covid-19, SARS-CoV-2

30 Introduction

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

35 Ivermectin is a well-known medicine that is approved as an anti-parasitic by the World Health Organization and the
36 US Food and Drug Administration (FDA). It is widely used in low- and middle-income countries (LMICs) to treat
37 worm infections.^{2,3} Also used for the treatment of scabies and lice, it is one of the World Health Organisation's
38 Essential Medicines⁴. With total doses of ivermectin distributed apparently equalling one-third of the present world
39 population,⁵ ivermectin at the usual doses (0.2 mg/kg to 0.4 mg/kg) is considered extremely safe for use in
40 humans.^{6,7} In addition to its anti-parasitic activity, it has been noted to have antiviral and anti-inflammatory
41 properties, leading to an increasing list of therapeutic indications.⁸

42 Since the start of the SARS-CoV-2 pandemic, both observational and randomised studies have evaluated ivermectin
43 as a treatment for, and as prophylaxis against, covid-19 infection. A review by the Front Line Covid-19 Critical Care
44 Alliance (FLCCC) summarised findings from 27 studies on the effects of ivermectin for the prevention and
45 treatment of covid-19 infection, concluding that ivermectin "demonstrates a strong signal of therapeutic efficacy"
46 against Covid-19.⁹ Another recent review found that ivermectin reduced deaths by 75%.¹⁰ Despite these findings,
47 the National Institute of Health in the US recently stated that "there are insufficient data to recommend either for
48 or against the use of ivermectin for the treatment of covid-19",¹¹ and the World Health Organization recommends
49 against its use outside of clinical trials.¹²

50 Ivermectin has exhibited antiviral activity against a wide range of RNA and some DNA viruses, e.g. Zika, Dengue,
51 Yellow Fever, and others.¹³ Caly, *et al.*¹⁴ demonstrated specific action against SARS-CoV-2 *in vitro* with a suggested
52 host-directed mechanism of action being the blocking of the nuclear import of viral proteins^{14,15} which suppress
53 normal immune responses. However, the necessary cell culture EC₅₀ may not be achievable *in vivo*¹⁶. Other
54 conjectured mechanisms include: inhibition of SARS-CoV-2 3CLPro activity^{17,18} (a protease essential for viral
55 replication), a variety of anti-inflammatory effects,¹⁹ and competitive *binding* of ivermectin with the viral S protein
56 as shown in multiple *in silico* studies.²⁰ 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 mechanism²¹ that would be similarly disrupted. Both host-directed and virus-directed mechanisms have thus been proposed, the clinical mechanism may be multi-modal, 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 re-purposed 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 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.

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 Bangladesh²³ 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. Additionally, 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 randomised controlled trials (RCTs) up to April 25 2021 (Appendix 1-3); current guidance²⁵ 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 ivermectin⁹, 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. 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 servers *MedRxiv* 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, 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 time to 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.²⁷ 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.

109 We assessed heterogeneity between studies by visual inspection of forest plots, by estimation of the I^2 statistic (I^2
110 $\geq 60\%$ was considered substantial heterogeneity),²⁸ by a formal statistical test to indicate statistically significant
111 heterogeneity²⁹ and, where possible, by subgroup analyses (see below). If there was evidence of substantial
112 heterogeneity, the possible reasons for this were investigated and reported. We assessed reporting biases using
113 funnel plots if more than 10 studies contributed to a meta-analysis.

114 We meta-analysed data using the random effects model (DerSimonian and Laird method)³⁰ using RevMan 5.4.1
115 software.^{27,31} Results used the inverse variance method for weighting.²⁷ Some sensitivity analyses used other
116 methods that are outlined below and some calculations were performed in R ³² through an interface³³ to the
117 *netmeta* package.³⁴ Where possible, we performed subgroup analyses grouping trials by disease severity, inpatients
118 versus outpatients and single dose versus multiple doses. We performed sensitivity analyses by excluding studies at
119 high risk of bias. We conducted further post hoc sensitivity analyses using alternative methods to test the
120 robustness of results in the presence of zero events in both arms in a number of trials³⁵ and estimated odds ratios
121 (and additionally risk ratio for the MH (Mantel-Haenszel) method) using a fixed effects model. The models
122 incorporate evidence from single-zero studies without having to resort to continuity corrections. However double-
123 zero studies are excluded from the analysis so the risk difference (RD) was also assessed using the MH method as
124 this approach can adequately incorporate trials with double zero events. This method can also use a random
125 effects component. A 'treatment-arm' continuity correction was used, where the values 0.01, 0.1 and 0.25 were
126 added where trials reported zero events in both arms. It has been shown that a non-fixed continuity correction is
127 preferable to the usual 0.5.³⁵ Other methods are available but were not considered due to difficulty in
128 interpretation, sensitivity of assumptions or the fact they are rarely used in practice.³⁶⁻⁴⁰

129 *Trial sequential analysis*

130 When a meta-analysis is subjected to repeated statistical evaluation, there is an exaggerated risk that 'naïve' point
131 estimates and confidence intervals will yield spurious inferences. In a meta-analysis it is important to minimise the
132 risk of making a false positive or false negative conclusion. There is a trade-off between the risk of observing a false
133 positive result (type I error) and the risk of observing a false negative result (type II error). Conventional meta-
134 analysis methods (e.g., in RevMan) also do not take into account the amount of available evidence. Therefore, we
135 examined the reliability and conclusiveness of the available evidence using trial sequential analyses (TSA).⁴¹⁻⁴³ The

DerSimonian-Laird (DL) method was used, as this is most often utilised 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, as 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 randomised controlled trial (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, *et al.* (2021)⁴⁴, which was a cause of substantial heterogeneity (but retained in the core analysis as 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 two alternative random effect models; namely, the Biggerstaff-Tweedie (BT) and Sidik-Jonkman (SJ) methods.⁴³

163 All outcomes have been assessed independently by two review authors (TD and AB) using the GRADE approach,⁴⁵
164 which ranks the quality and certainty of the evidence. The results of the TSAs will also form part of the judgement
165 for the primary all-cause mortality outcome. Results are presented in a summary of findings table. Any differences
166 in judgements were resolved by discussion with the wider group. We used Cochrane Effective Practice and
167 Organisation of Care guidance to interpret the evidence.⁴⁶

168 **Role of funding source**

169 The funders who contributed via the crowdfunding initiative on www.gofundme.com had no role in the review
170 design or the analysis and interpretation of the findings.

171 **Results**

172 **Search results and risk of bias assessment**

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

175 The supplementary search for the BEC identified seventeen studies, of which four were retrieved in full. No full
176 trial- or model-based economic evaluations (cost-utility analyses, cost-effectiveness analyses or cost-benefit
177 analyses) were identified.

178 Twenty-one trials in treatment and two trials in prophylaxis of Covid-19 met review inclusion. One further study⁴⁷
179 reported separate treatment and prophylaxis components; we label this study “Elgazzar” under both questions. In
180 effect, there were 22 trials in treatment and three in prophylaxis. All of these contributed data to at least one
181 review outcome and meta-analysis. Fifteen trials contributed data for the primary outcome for ivermectin
182 treatment (death); three studies reported the primary outcome for prophylaxis (covid-19 infection). Characteristics
183 of included studies are given in Table 1. Seventeen studies⁴⁷⁻⁶³ were excluded as they were not RCTs and we
184 identified 39 ongoing studies⁶⁴⁻¹⁰² and two studies^{103,104} are awaiting classification.

185 A risk of bias summary graph is given in Fig.2. Eleven studies^{23,24,44,47,105-111} used satisfactory random sequence
186 generation and allocation concealment. Two trials described satisfactory sequence generation, but it was unclear
187 whether allocation was concealed.^{112,113}

188 Ten trials reported adequate blinding of the participants/personnel and/or the outcome assessors.^{23,24,44,105,107,109-}
189 ^{111,113,114} The others were either unclear or high risk for blinding. We considered blinding to be a less important
190 criterion for evaluation of evidence related to the review's primary outcomes, namely death and laboratory-
191 confirmed covid-19 infection, which are objective outcomes.

192 We did not consider publication on pre-print websites to constitute a risk of bias, as all studies were scrutinised and
193 peer reviewed by us during the review process and, where additional information was needed, we contacted the
194 authors for clarification.

195 **Main findings**

196 Twenty-four RCTs (including 3 quasi-RCTs) involving 3406 participants were included, with sample sizes ranging
197 from 24 to 473 participants. Twenty-two trials in treatment and three trials in prophylaxis met review inclusion,
198 including the trial of Elgazzar et al which reported both components. For trials of covid-19 treatment, 16 evaluated
199 ivermectin among participants with mild to moderate covid-19 only; six trials included patients with severe covid-
200 19. Most compared ivermectin with placebo or no ivermectin; three trials included an active comparator (Table 1).
201 Three RCTs involving 738 participants were included in the prophylaxis trials. Most trials were registered, self-
202 funded and undertaken by clinicians working in the field. There were no obvious conflicts of interest noted, with
203 the exception of one trial.⁸⁵

204 *Ivermectin treatment vs no ivermectin treatment*

205 Twenty-two trials (2668 participants) contributed data to the comparison ivermectin treatment vs no ivermectin
206 treatment for covid-19 treatment.

207 *All-cause mortality*

208 Meta-analysis of 15 trials, assessing 2438 participants, found that ivermectin reduced the risk of death by an
209 average of 62% (95% CI 27% to 81%) compared with no ivermectin treatment (average risk ratio (aRR) 0.38, 95% CI
210 0.19 to 0.73; $I^2 = 49\%$; risk of death 2.3% versus 7.8% among hospitalised patients in this analysis, respectively
211 (Summary of Findings (SoF) Table 2a and Fig. 3). Much of the heterogeneity was explained by the exclusion of one
212 trial⁴⁴ in a sensitivity analysis (average RR 0.31, 95% CI 0.17 to 0.58, $n = 2196$, $I^2=22\%$), but since this trial was at low
213 risk of bias it was retained in the main analysis. The source of heterogeneity may be due to the use of active
214 comparators in the trial design. The results were also robust to sensitivity analyses excluding two other studies with

an active treatment comparator (average RR 0.41, 95% CI 0.23 to 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 to 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 judgements (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 Fig. 9 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 hospitalised participants with mild to moderate Covid-19 infection.

The TSA was used to calculate the IS required to demonstrate or reject a 62% relative reduction in the risk 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 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 (Fig. 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 Fig. 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 Fig. 8, the z-curve crosses the boundary after reaching the required IS, thereby supporting the previous conclusion in RevMan 5.4.1³¹ using the DL method that ivermectin is superior to control in reducing the risk of death.

243 *Sensitivity analyses*

244 Sensitivity analysis excluding the trial of Fonseca, *et al.*⁴⁴ significantly reduced heterogeneity in the meta-analysis

245 and thus the Diversity estimate in the TSA using the DL model. This strengthened the suggestion in the primary

246 core analysis that the required IS had been reached (Fig 9). Since the DL estimator could potentially underestimate

247 the between-trial variance,⁴³ we performed further sensitivity analyses using two alternative random-effects model

248 approaches. The results of the primary TSA analysis was robust to sensitivity analysis using the BT method with the

249 same parameters, excluding the Fonseca, *et al.* trial,⁴⁴ which was a cause of substantial heterogeneity (Fig. 10). The

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

251 The required IS was not reached in the TSA using the SJ method, largely because Diversity from the model was high

252 (Fig. 11). The SJ estimator may overestimate the between-trial variance in meta-analyses with mild heterogeneity,

253 thus producing artificially wide confidence intervals.⁴³ When the Diversity estimate was reduced to the same as in

254 the DL model, the required IS was reached in the SJ model (data not shown). There was no evidence of futility using

255 the SJ method in any scenario.

256 *Certainty of the evidence for all-cause mortality*

257 Overall, death from any cause, taking into account all composite analyses, was judged to provide moderate-

258 certainty evidence (SoF Table 2a, Fig. 4-11). A funnel plot corresponding to the primary outcome of death from any

259 cause did not appear to suggest any evidence of publication bias (Fig. 7). Furthermore, the ease with which trial

260 reports can be uploaded as preprints should reduce this risk.

261 *Secondary outcomes*

262 Secondary outcomes provided low to very low certainty evidence (SoF Table 2a). Low certainty findings suggested

263 that that there may be no benefit with ivermectin for ‘need for mechanical ventilation’, whereas effect estimates

264 for ‘improvement’ and ‘deterioration’ favoured ivermectin but were graded as low certainty due to study design

265 limitations and inconsistency (Fig. 12 to 14). All other secondary outcome findings were assessed as very low

266 certainty.

267 Meta-analysis of eleven trials, assessing 1533 participants, found that there was no significant difference between

268 ivermectin and control in the risk of severe adverse events (aRR 1.65, 95% CI 0.44 to 6.09; $I^2 = 0\%$; *low certainty*

269 *evidence*, downgraded for imprecision and study design limitations). Seven severe adverse events were reported in

the ivermectin group and two in controls. The SAEs were as follows: two patients in the Mahmud trial¹⁰⁷ 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.*¹⁰⁶ had hyponatraemia (this trial used high-dose ivermectin for 5 days); and two patients in a study from Turkey¹¹⁵ 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. In the Lopez-Medina, *et al.* trial¹⁸⁵, there were two SAEs in each arm (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 three 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% to 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)(Fig. 15). In two trials involving 538 participants, no severe adverse events were recorded (SoF Table 2b).

Discussion

The findings indicate with moderate certainty that ivermectin treatment in covid-19 provides a significant survival benefit. Our certainty of evidence judgement was consolidated by the results of trial sequential analyses which show that the required information size 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 (i) reductions in covid-19 infections when ivermectin was used as prophylaxis, (ii) the more favourable effect estimates for mild to moderate disease compared to severe disease for death due to any cause, and (iii) 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 (0.2mg/kg or 0.4mg/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

298 We restricted the included studies to the highest level of evidence, i.e., RCTs, as a policy. This was despite there
 299 being numerous observational but non-randomised trials of ivermectin, which one could argue could also be
 300 considered in an emergency. We included pre-print and unpublished data from completed but not yet published
 301 trials due to the urgency related to evidence synthesis in the context of a global pandemic.¹¹⁷ Whilst there is the
 302 potential for selective reporting of outcomes and publication bias, we have factored in these considerations in
 303 interpreting results and forming conclusions. We adhered to PRISMA guidelines and the WHO statement on
 304 developing global norms for sharing data and results during public health emergencies.¹¹⁷

305 There are a number of limitations with this review. Several of the studies contributing data did not provide full
 306 descriptions of methods, so assessing risk of bias was challenging. Where descriptions of study methods were
 307 sparse or unclear, we attempted to contact authors to clarify methods, but lack of information led us to downgrade
 308 findings in several instances. Overall interpretation of findings was hampered due to variability in the participants
 309 recruited, treatment regimen, and in the care offered to those in control groups. We have tried to take this
 310 variation into account through subgroup and sensitivity analyses. Nevertheless, dosing and treatment regimens
 311 and the use of ivermectin with other components of “standard care” require further research. We did not include
 312 laboratory outcome measures, such as viral clearance. The latter, as well as other biochemical outcomes have been
 313 reported in several studies and reviews and tend to favour ivermectin.^{10,47,105,108} Several trials reported continuous
 314 data, such as length of hospital stay, as medians and interquartile ranges, therefore, we were unable to include
 315 these data in meta-analysis. As we did not undertake in our protocol to perform narrative evidence synthesis, and
 316 as these data tended to favour ivermectin, the certainty of the effects of ivermectin on these continuous outcomes
 317 may be underestimated.

318 At least five other reviews of ivermectin use for covid-19 have been published, including one co-authored with
 319 Nobel Laureate Professor Satoshi Ōmura, discoverer of ivermectin,^{9,10,118-120} but only three have been peer-
 320 reviewed^{9,118,120} and only two attempt full systematic review.^{10,119} We applied AMSTAR 2¹²¹, a critical appraisal tool
 321 for systematic reviews of healthcare interventions, to the two non-peered systematic reviews^{10,119} and both were
 322 judged to be of low quality (Table 4). However, there was also a suggestion that ivermectin reduced the risk of
 323 death in treatment of covid-19 in these reviews.

324 The recently updated WHO therapeutics guidelines,¹² included seven trials and 1419 people in the analysis of
 325 mortality. Reporting a risk reduction of 81% (odds ratio 0.19, 95% CI 0.09 to 0.36), the effect estimate favouring

ivermectin was downgraded by two levels for imprecision, although the justification for this is unclear as the reported confidence interval is precise (64% to 91%).

In addition to the evidence from systematic reviews, the findings of several controlled observational studies 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 healthcare workers in India¹²⁴ 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-analysis⁵ 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 (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.^{50,127} A letter on positive experience in seven elder care facilities in Virginia covering 309 patients was sent to NIH¹²⁷ 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 eight states were reduced between 64% to 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 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.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.^{129,131-134} A recent survey of global trends¹¹⁸ 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 organisations 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 two 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.

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

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

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List of Figure Titles

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

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Fig. 3. Death due to any cause

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

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

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

Fig. 7. Funnel plot of ivermectin vs control for covid-19 treatment for all cause death (subgrouped by severity)

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

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

Fig. 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%

Fig. 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%

Fig. 12. Need for mechanical ventilation

Fig. 13. Improvement

Fig. 14. Deterioration

Fig. 15. Covid-19 infection (prophylaxis studies)

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	12mg x 1 day or x 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 hospitalisation, 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 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 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 x 1 dose	SOC	MedRxiv pre-print	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	0.4mg/kg x 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	12mg 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 (31pprox..	116	0.2mg/kg x1 dose*	HCQ 400 mg 1 st day then 200mg	Research Square pre-print	Time to –ve PCR test; period to symptomatic recovery; adverse events

				78% symptomatic)			BID x 9 days + AZM 500 mg daily x 5 days		
Elgazzar 2020 ⁴⁷	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	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	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, invasive mechanical ventilation
Gonzalez 2021 ¹³⁷	Mexico	Double blind	Institution funded	Moderate to severe (inpatients)	108	12mg x 1 dose	Placebo	MedRxiv pre-print	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	0.2mg/kg x 2 days* Some had a 3 rd dose a week later	SOC	MedRxiv pre-print	Death, mean time to recovery, disease progression (deterioration)
Krolewiecki 2020 ¹⁰⁶	Argentina	Open label	None reported	Mild to moderate (inpatients)	45	0.6mg/kg/day x 5 days	Placebo	Published in PR journal	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	0.3mg/kg elixir x 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	12mg x 1 dose*	Placebo + SOC	Data published on clinical trial registry and clarification obtained via email	Improvement, deterioration, late clinical recovery, persistent PCR test +ve

Mohan 2021 ¹¹⁰	India	Double blind	Institution funded	Mild to moderate	152	12 mg or 24 mg elixir x 1 dose	Placebo	MedRxiv pre-print Research	Conversion of RT-PCR to negative result, decline of viral load at day 5 from enrolment
Niaee 2020 ¹⁰⁸	Iran	Double blind	Institution- funded	Mild to severe covid	180	0.2mg/kg x 1 and 3 other dosing options) ~ 14 mg tablet**	Placebo	Research Square pre-print	Deaths, length of stay, biochemical parameters
Okumus 2021 ¹¹⁵	Turkey	Quasi- RCT	None reported	Severe covid	66	0.2mg/kg x 5 days	SOC	Pre-publication 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	0.4mg/kg x 3 days	Placebo	Pre-publication data obtained from another source	Rate of conversion to PCR negative
Podder 2020 ¹⁴⁰	Bangladesh	Open label	Self-funded	Mild to moderate (outpatients)	62	0.2mg/kg x 1 dose	SOC	Published in PR journal	Duration of symptoms, recovery time to symptom free from enrolment, 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 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 load reduction, hospitalisation, adverse effects
Ravikirti 2021 ¹⁰⁹	India	Double blind	Self-funded	Mild to moderate covid (inpatients)	112	12mg x 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 x 1 dose	SOC	Pre-publication 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 to 0.3 mg/kg x 3 days	Placebo	Pre-publication data obtained from another source	Viral clearance at day 4, 6, 8 and 10), hospitalisation
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 x 4 wks	SOC	Pre-publication 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	0.4mg/kg, weekly x 2 weeks	SOC	Research Square pre-print: emailed/responded with data	Positive PCR test
Shouman 2020 ¹⁴³	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	Symptoms and/or positive covid-19 PCR test within 14 days; adverse events

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

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	78 per 1000 (all disease severity)	48 fewer deaths per 1000 (21 to 63)	RR=0.38 (0.19 to 0.73)	2438 (15)	Moderate ¹
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 ^{1,2,3}
Time to clinical recovery, in days (outpatients)			(MD = -1.06 (-1.63 to -0.49)	176 (2)	Very low ^{1,2,3}
Time to clinical recovery, in days (mild to moderate covid-19 inpatients)			MD = -7.32 (-9.25 to -5.39)	96 (1)	Very low ^{1,4}
Time to clinical recovery, in days (severe covid-19 inpatients)			MD = -3.98 (-10.06 to 2.10)	33 (1)	Very low ^{1,4}
Admission to ICU			RR=1.22 (0.75 to 2.00)	379 (2)	Very low ^{4,5}
Need for mechanical ventilation			RR=0.66 (0.14 to 3.00)	431 (3)	Low ^{3,5}
Length of hospital stay, in days			MD= 0.13 (-2.04 to 2.30)	68 (1)	Very low ^{1,4}
Admission to hospital			RR 0.16 (0.02 to 1.32)	194 (2)	Very low ^{1,4}
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 to 1.45)	681 (5)	Low ^{1,2}
Deterioration (any disease severity)	143 per 1000	93 fewer per 1000 (from 50 fewer to 116 fewer)	RR 0.35 (0.19 to 0.65)	1587 (7)	Low ^{1,2}
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 to 6.09)	1533 (11)	Low ^{1,2}

*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 for inconsistency

³ Downgraded -1 for imprecision

⁴ Downgraded -2 for imprecision/sparse data

⁵ 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	0.35 (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 to 0.88)
0.01	RR	RE	0.43 (0.25 to 0.72)	0.58 (0.39 to 0.88)
0.1	RR	FE	0.54 (0.37 to 0.79)	0.56 (0.38 to 0.84)
0.1	RR	RE	0.43 (0.26 to 0.73)	0.46 (0.26 to 0.80)
0.25	RR	FE	0.54 (0.37 to 0.79)	0.55 (0.37 to 0.81)
0.25	RR	RE	0.44 (0.26 to 0.73)	0.45 (0.26 to 0.76)
0.5	RR	FE	0.54 (0.37 to 0.79)	0.55 (0.35 to 0.78)
0.5	RR	RE	0.45 (0.27 to 0.74)	0.47 (0.29 to 0.75)

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

Table 4. 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	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 <i>et al.</i> 2021¹⁰	+	-	+	+	?	?	- ^a	? ^b	- ^c	-	- ^d	- ^a	- ^e	- ^a	NA	-
Castañeda-Sabogal <i>et al.</i> 2021¹¹⁹	+ ^f	?	-	? ^g	+	+	- ^a	+	- ^h	-	- ⁱ	- ^j	- ^a	+	NA	+

Footnotes

Assessed using AMSTAR 2¹²¹; + adequately assessed; - inadequately assessed; ? unclear assessment; NA= not applicable (less than 10 included studies in meta-analysis)

^a Not documented or inadequately reported

^b Participant population, description of comparator interventions and time frame for follow-up was not described or inadequately reported

^c 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 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.

^d 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 two 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 guidelines¹⁴⁴

^e 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.

^f Outcomes were reported but lacked definitions

^g A significant number of pertinent randomised controlled trials have not been included in the review. Given the adequate due diligence of review process the comprehensive nature of the search strategy is questionable

^h No description of risk of bias assessment in any domain apart from missing outcome data but attrition rates not documented to justify judgement

ⁱ Authors did not report data from RCTs which we obtained from various sources and some conclusions were not reflective of the observed data. It was reported that an analysis of four pre-print retrospective studies at high risk of bias, that ivermectin was not associated with reduced mortality (logRR 0.89, 95% CI 0.09 to 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 this results as not demonstrating a potential association based on the observed result. Furthermore, the high risk of bias judgement is not adequately justified.

^j 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 four 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

Fig. 1. Study flow diagram from search conducted on 25 April 2021

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ahmed 2020	+	+	?	?	+	-	?
Babalola 2020	+	+	+	+	+	?	?
Bukhari 2021	?	?	-	?	?	?	?
Chaccour 2020	+	+	+	?	+	+	?
Chachar 2020	+	?	-	-	+	?	?
Chala 2021	-	-	-	?	+	?	?
Chowdhury 2020	-	-	-	?	?	?	+
Elgazzar 2020	+	+	?	?	+	?	?
Fonseca 2021	+	+	+	+	+	+	+
Gonzalez 2021	-	-	?	?	?	?	-
Hashim 2020	-	-	-	-	+	+	?
Krolewiecki 2020	+	+	-	+	-	+	+
Lopez-Medina 2021	?	?	?	?	?	-	?
Mahmud 2020	+	+	+	+	+	+	+
Mohan 2021	+	+	+	+	+	+	+
Niaee 2020	+	+	?	?	+	?	?
Okumus 2021	-	?	-	?	+	+	+
Petkov 2021	?	?	?	?	?	?	?
Podder 2020	-	-	-	-	-	?	+
Raad 2021	+	?	?	+	+	?	?
Ravikirti 2021	+	+	+	?	?	+	+
Rezai 2020	+	+	+	?	?	?	?
Schwartz 2021	?	?	+	?	?	?	?
Shouman 2020	-	-	?	?	+	+	-

Risk of bias: + Low; ? Unclear; - High

Fig. 3. Death due to any cause

Footnotes

- (1) IVM 12mg x 5 days (24 pts) or IVM 12 mg + doxy x 5 days (24 pts)
- (2) IVM 6mg-12mg every 84 hrs for 2 wks; vs lopinavir/ritonavir
- (3) IVM 0.4mg/kg single dose
- (4) IVM up to 24 mg daily for 4 days vs HCQ
- (5) IVM 0.2mg/kg x 2-3 days + Doxy 100 mg BID x 10 days
- (6) IVM 0.3mg/kg 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 µg/kg (1 to 3 doses) vs HCQ

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

Footnotes

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

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

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

Footnotes

- (1) IVM 12mg x 5 days (24 pts) or IVM 12 mg + doxy x 5 days (24 pts)
- (2) IVM 0.4mg/kg single dose
- (3) IVM 0.2mg/kg x 2-3 days + Doxy 100 mg BID x 10 days
- (4) IVM 0.3mg/kg solution for 5 days vs placebo solution
- (5) IVM 6mg once + Doxy 100 mg x 5 days
- (6) IVM 12mg or 24 mg single dose
- (7) IVM 0.4mg/kg x 3 days
- (8) IVM 12 mg x 2 days
- (9) IVM 0.2mg/kg single dose
- (10) IVM single dose 12mg or 18mg depending on weight
- (11) IVM 0.2mg/kg x 2-3 days + Doxy 100 mg BID x 10 days
- (12) IVM 0.2mg/kg x 5 days (both arms received HCQ, favipiravir, azithromycin)
- (13) IVM 0.2mg/kg to 400 µg/kg (1 to 3 doses) vs HCQ

Fig. 7. Funnel plot of ivermectin vs control for covid-19 treatment for all cause death (subgrouped by severity)

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

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

Fig. 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%

Fig. 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%

Fig. 12. Need for mechanical ventilation

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"

Fig. 13. Improvement

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

Fig. 14. Deterioration

Footnotes

- (1) IVM 0.4mg/kg single dose
- (2) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine
- (3) IVM 200µg/kg + Doxy 100 mg BID x 10 days
- (4) IVM 0.3mg/kg x 5 days
- (5) IVM 6mg once + Doxy 100 mg x 5 days
- (6) IVM 12mg or 24mg
- (7) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine
- (8) IVM 12mg or 18mg single dose
- (9) IVM 200µg/kg + Doxy 100 mg BID x 10 days

Fig. 15. Covid-19 infection (prophylaxis studies)

Footnotes

(1) IVM 12 mg weekly + Iota-Carrageenan 6 sprays/day

(2) IVM up to 24mg weekly depending on weight x 2 doses

(3) IVM up to 24 mg depending on weight, given in 2 doses 72 hours apart

Appendices

1 MEDLINE search strategy

1. exp Ivermectin/
2. (stromectol* or mectizan* or soolantra* or sklice* or ivermectin* or ivomec or acarexx or bimectin* or cardomec or equimectrin or eqvalan or heartgard* or hyvermectin or Ivermax or noromectin or oramec or pandex or phoenectin or stromectal or uvemec or vermic or vetmec or zimecterin).ti,ab,kw.
3. (Dihydroavermectin* or "cardotek-30" or "CCRIS 8839" or "EINECS 274-536-0" or "L 640471" or "MK 933" or "MK-0933" or "UNII-8883YP2R6D" or "agri-mectin").ti,ab,kw.
4. 1 or 2 or 3
5. exp Severe Acute Respiratory Syndrome/
6. covid-19.mp.
7. covid.mp.
8. SARS-CoV-2.mp.
9. severe acute respiratory syndrome coronavirus 2.mp.
10. 2019-nCoV.mp.
11. 2019 novel coronavirus.mp.
12. Wuhan coronavirus.mp.
13. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 4 and 13

2 Embase search strategy

1. exp Ivermectin/
2. stromectol*.ti,ab,kw.
3. mectizan*.ti,ab,kw.
4. soolantra*.ti,ab,kw.
5. sklice*.ti,ab,kw.
6. ivermectin*.ti,ab,kw.
7. ivomec*.ti,ab,kw.
8. acarexx*.ti,ab,kw.
9. bimectin*.ti,ab,kw.
10. cardomec*.ti,ab,kw.
11. equimectrin*.ti,ab,kw.
12. eqvalan*.ti,ab,kw.
13. heartgard*.ti,ab,kw.
14. hyvermectin*.ti,ab,kw.
15. Ivermax*.ti,ab,kw.
16. noromectin*.ti,ab,kw.
17. oramec*.ti,ab,kw.
18. pandex*.ti,ab,kw.
19. phoenectin*.ti,ab,kw.
20. stromectal*.ti,ab,kw.
21. uvemec*.ti,ab,kw.
22. vermic*.ti,ab,kw.
23. vetmec*.ti,ab,kw.
24. zimecterin*.ti,ab,kw.
25. Dihydroavermectin*.ti,ab,kw.
26. cardotek-30.ti,ab,kw.
27. CCRIS 8839.ti,ab,kw.
28. EINECS 274-536-0.ti,ab,kw.
29. L 640471.ti,ab,kw.
30. MK 933.ti,ab,kw.
31. MK-0933.ti,ab,kw.

32. UNII-8883YP2R6D.ti,ab,kw.
33. agri-mectin.ti,ab,kw.
34. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. Coronaviridae/
36. Coronavirinae/
37. Coronaviridae infection/
38. coronavirus infection/
39. 'coronavirus disease 2019'.ti,ab,kw.
40. SARS-related coronavirus/
41. Severe acute respiratory syndrome coronavirus 2.ti,ab,kw.
42. 2019 nCoV.ti,ab,kw.
43. 2019nCoV.ti,ab,kw.
44. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw.
45. coronavir*.ti,ab,kw.
46. coronovir*.ti,ab,kw
47. covid.ti,ab,kw.
48. covid19.ti,ab,kw.
49. CoV*.ti,ab,kw.
50. nCov 2019.ti,ab,kw.
51. SARS CoV2.ti,ab,kw.
52. SARS CoV 2.ti,ab,kw.
53. SARSCoV2.ti,ab,kw.
54. SARSCoV 2.ti,ab,kw.
55. 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56. 34 and 55

3 CENTRAL

Central Ivermectin for prevention and treatment of covid-19

- #1 MeSH descriptor: [Ivermectin] explode all trees
- #2 stromectol*
- #3 mectizan*
- #4 soolantra*
- #5 sklice*
- #6 ivermectin*
- #7 ivomec*
- #8 acarexx*
- #9 bimectin*
- #10 cardomec*
- #11 equimectrin*
- #12 eqvalan*
- #13 heartgard*
- #14 hyvermectin*
- #15 Ivermax*
- #16 noromectin*
- #17 oramec*
- #18 pandex*
- #19 phoenectin*
- #20 stromectal*
- #21 uvemec*
- #22 vermic*
- #23 vetmec*
- #24 zimecterin*
- #25 Dihydroavermectin*

- #26 cardotek-30
- #27 CCRIS 8839
- #28 EINECS 274-536-0
- #29 L 640471
- #30 MK 933
- #31 MK-0933
- #32 UNII-8883YP2R6D
- #33 agri-mectin
- #34 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33
- #35 2019 nCoV
- #36 "2019-nCoV"
- #37 2019nCoV
- #38 corona virus
- #39 corona viruses
- #40 coronavirus
- #41 coronaviruses
- #42 covid
- #43 covid19
- #44 nCov 2019
- #45 SARS-CoV2
- #46 SARS CoV-2
- #47 SARSCoV2
- #48. SARSCoV-2
- #49 covid-19
- #50 MeSH descriptor: [Coronavirus] this term only
- #51 #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50
- #52 #34 and #51