South African National Department of Health
Rapid Review Report
Component: COVID-19

TITLE: IVERMECTIN FOR TREATMENT OF COVID-19: EVIDENCE REVIEW OF CLINICAL BENEFITS AND HARMS

Date: 30 July 2021 *(third update of the initial rapid review of 25 January 2021)*

Research question: Should ivermectin be used for the management of COVID-19?

Key findings

- With the completion of further randomised controlled trials (RCTs) and the publication of systematic reviews for ivermectin as treatment for COVID-19, an updated search of two electronic databases (Epistemonikos and the Cochrane Library) was performed on 29 July 2021.
- We found a systematic review by Popp *et al.* of 13 RCTs (n=1374, patients with mild to severe COVID-19) for the use of ivermectin compared to control (placebo, no treatment, or standard of care of no proven benefit). The authors of the review reported that about a third of the included RCTs had a high overall risk of bias, and the studies were small. The systematic review was independently assessed by two reviewers to be of high quality, using the AMSTAR2 tool.
- Three other systematic reviews were excluded. Systematic reviews by Hill *et al*. and Bryant *et al.* were assessed by two independent reviewers using the AMSTAR2 tool, and both were assessed as being of critically low quality. The meta-analysis by Roman *et al.* was excluded, as it only included RCTs up until 22 March 2021; several additional RCTs have since been published. All three of the systematic reviews also included an RCT by Elgazzar *et al*. that has subsequently been withdrawn by a preprint site, due to concerns about the trial's data integrity.
- In the included systematic review by Popp *et al*., amongst **hospitalised** patients, there was a high degree of uncertainty of the effect of ivermectin compared to control on mortality (risk ratio (RR) 0.60, 95% confidence interval (CI) 0.14 to 2.51; 2 RCTs, n=185; *very low-certainty evidence*); the need for invasive mechanical ventilation (RR 0.55, 95% CI 0.11 to 2.59; 2 RCTs, n=185; *very low-certainty evidence*); the need for supplemental oxygen (no participants needed oxygen, 1 RCT, n=45; *very low-certainty evidence*), adverse events within 28 days (RR 1.21, 95% CI 0.50 to 2.97; 1 RCT, n=152; *very low-certainty evidence*), and viral clearance at day seven (RR 1.82, 95% CI 0.51 to 6.48; 2 RCTs, n=159 participants; *very low-certainty evidence*). Ivermectin appeared to have little or no effect compared to control on clinical improvement up to 28 days (RR 1.03, 95% CI 0.78 to 1.35; 1 RCT; n=73 participants; *low certainty evidence*) and duration of hospitalization (mean difference (MD) −0.10 days, 95% CI −2.43 to 2.23; 1 RCT, n= 45; *low certainty evidence*).
- Similarly, amongst **ambulatory** participants, there was high uncertainty regarding the effect of ivermectin (compared to control) on mortality up to 28 days (RR 0.33, 95% CI 0.01 to 8.05; 2 RCTs, n=422; *very low-certainty evidence*), the need for invasive mechanical ventilation (RR 2.97, 95% CI 0.12 to 72.47; 1 RCT, n=398; *very low-certainty evidence*), the need for supplemental oxygen (none needed oxygen; 1 RCT, n=398; *very low-certainty evidence*), and viral clearance at day seven (RR 3.00, 95% CI 0.13 to 67.06; 1 RCT, n=24; *low-certainty evidence*). Ivermectin appeared to have little or no effect on symptom resolution up to 14 days (RR 1.04, 95% CI 0.89 to 1.21; 1 RCT, n=398; *low-certainty evidence*) and adverse events within 28 days (RR 0.95, 95% CI 0.86 to 1.05; 2 RCTs, n=422; *low-certainty evidence*). No data were available for duration of symptoms or hospital admission.
- Quantitative analysis of publication bias was not conducted by Popp *et al*., as the authors believed that it could not be reliably assessed until the large number of ongoing registered RCTs have been completed and published. Publication bias will be assessed in future updates of this review.
- The current very low- to low-certainty evidence does not suggest any clear benefit for the use of ivermectin as treatment for mild to moderate COVID-19. Several studies are underway that may produce clearer answers in future updates of this review.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
Type of recommendation		**X**			

Recommendation: The NEMLC COVID-19 sub-committee suggests that ivermectin not be used in the management of COVID-19, except in the context of a clinical trial.
Rationale: There is currently insufficient evidence to recommend ivermectin for the treatment of COVID-19. Much of the RCT evidence consists of trials of low methodological quality, for the most part with small sample sizes and disparate interventions and controls, limiting the confidence in any conclusions with respect to ivermectin. What evidence does exist does not suggest any clear clinical or virological benefits.
Level of Evidence: Very low to low-certainty evidence.
Review indicator: New high quality evidence of a clinically relevant benefit.

(Refer to Appendix 4 for the evidence to decision framework)

Therapeutic Guidelines Sub-Committee of the COVID-19 Management Clinical Guidelines Committee: Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish *(Chair)*, Helen Rees, Gary Reubenson *(Vice-Chair)*.

Note: Due to the continuous emergence of new evidence, the evidence review will be updated when more relevant evidence becomes available. On 30 July 2021, the International Clinical Trials Registry Platform (ICTRP) lists 80 registered RCTs of ivermectin for the treatment and prevention of COVID-19 that are still in progress/ not completed.

Version	Date	Reviewer(s)	Recommendation and Rationale
First	25 January 2021	TL, JN, HD, AP	There is currently insufficient evidence to support routine use of ivermectin for COVID-19; may be used in a clinical trial setting.
Second	18 June 2021	TL, JN, AP, HD	As before.
Third	30 July 2021	TL, JN, AP, HD, MR	As before.

BACKGROUND

The National Department of Health requested an advisory on ivermectin for COVID-19, following global interest in this medicine in the press and from advocacy groups. A rapid evidence summary which was released on 21 December 2020[1] to inform stakeholders found that the evidence was inconclusive due to methodological flaws and small sample sizes.

The data with respect to treatment of COVID 19 is rapidly evolving and the completion of several registered randomised controlled trials has resulted in the publication of numerous systematic reviews. Therefore, the comprehensive evidence review that was undertaken requires to be updated regularly as new evidence emerges.

Ivermectin is an antiparasitic drug that is commonly used for the treatment and prophylaxis of onchocerciasis and treatment of strongyloidiasis and intractable scabies. Ivermectin is not approved, globally, as an antiviral agent. A topical cream containing ivermectin is registered in South Africa for the treatment of rosacea. Imported, unregistered oral solid dosage forms may be accessed via S21 application. Ivermectin may also be compounded by pharmacists in accordance with section 14(4) of the Medicines and Related Substances Act. Common side effects of ivermectin are diarrhoea, nausea, abdominal pain, fatigue, somnolence and dizziness[2].

Proposed mechanism of action: *In vitro* studies suggest an antiviral and/or anti-inflammatory effect on SARS-CoV-2. *In vitro* inhibition of the host importin alpha and beta-1 nuclear transport proteins has been described; these proteins are used by SARS-CoV-2 to suppress the host antiviral response. In addition, ivermectin may inhibit attachment via the virus's spike protein. Ivermectin also inhibits the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in cell cultures.[3] However, pharmacokinetic and pharmacodynamic studies suggest much higher doses (up to 100-fold more) than those approved for use in humans would be required to achieve *in vitro* antiviral efficacy, casting doubt on whether any direct antiviral effect would be possible at achievable human doses.[4, 5]

Several observational trials have reported on the safety and efficacy of ivermectin in the management of COVID-19. These studies often had small sample sizes, were unblinded, ivermectin dose varied and comparators differed; making the true efficacy of ivermectin difficult to quantify. Many studies did not define the study outcomes or the severity of COVID. An observational cohort study published in preprint format in June 2020[1] suggested a mortality-benefit of single dose ivermectin of 200 mcg/kg, but found no benefit with respect to length of hospital stay or rates of extubation. It was unclear if concomitant medicines contributed to the mortality benefit observed; information on oxygen saturation and radiographic findings was lacking; timing of therapeutic interventions was not standardised which may bias results, and participants were not randomised therefore differences observed may be due to confounding.

We initially reviewed randomised controlled trial (RCT) evidence from COVID-19 living maps and clinical trial registries to evaluate the safety and efficacy of ivermectin in COVID-19 in January 2021. With the subsequent completion of RCTs and the publication of several systematic reviews of RCTs, the report has been updated accordingly.

METHODS

We conducted an updated review of the evidence including systematic searching Epistemonikos Living Overview of the Evidence (LOVE) Platform for Covid-19 evidence (https://app.iloveevidence.com/topics) and the Cochrane Library (https://covid-nma.com/) on 29 July 2021. The search strategy is shown in Appendix 1. Screening of records and data extraction was conducted by two reviewers (TL, MR), with resolution of disagreements through discussion. Relevant record(s) were extracted in a narrative table of results (Table 1) and excluded studies were listed with rationale for exclusion (Table 2) by one reviewer and checked by a second reviewer.

We included systematic reviews of RCTs that were in line with our PICO (Population, Intervention, Comparators, Outcomes) framework (see below). Appraisal of the systematic review(s) were done independently by two reviewers (TL, MR) using the AMSTAR 2 tool[6].

Eligibility criteria for review

Population: Ambulant and hospitalised patients with confirmed COVID-19, >12 years of age.

Intervention: Ivermectin, either alone or in combination with other treatments. No restriction on dose and frequency.

Comparators: Standard of care or placebo.
(Note: In previous rapid review reports, available evidence for ivermectin was reviewed that also included active comparator trials. However, with the emergence of further RCT data, the comparator has now been restricted to placebo or standard of care).

Outcomes: Mortality; duration of hospitalisation; proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis; time to negative SARS-CoV-2 PCR on nasopharyngeal swab; progression to ICU admission; progression to mechanical ventilation; progression to requiring oxygen; duration of ICU stay; adverse reactions and adverse events; clinical improvement on an ordinal scale at chosen time points; and time to clinical improvement.

Study designs: Systematic reviews of randomised controlled trials. Non-randomised studies, case series and single case reports were excluded.

RESULTS

Results of the search: A systematic search of the electronic databases produced 29 records. Screening resulted in the exclusion of 24 records and full-text reviews of the remaining 5 records. Four records were further excluded and one systematic review[7] was identified for evidence synthesis.

Refer to table 1 for details of the included systematic review and table 2 for a list of the excluded studies and supporting rationale for exclusion. Addendum A summarises the results of RCTs included in previous reviews, including active comparator studies. Addenda B and C are appraisals of the excluded systematic reviews by Hill *et al.* and Bryant *et al.,* respectively.

Quality of the evidence:
The systematic review was assessed to be of high quality (refer to appendix 2 for the AMSTAR2 assessment). However, the overall quality of the included RCTs was low- to low-certainty evidence as RCTs generally had few participants, few events and therefore effect estimates had serious imprecision. Seven of the included RCTs for ivermectin as treatment for COVID-19 were open-label, whilst 6 were double-blind placebo-controlled trials. The authors of the review reported that approximately a third of the included RCTs has an overall high risk of bias (assessed using the Cochrane risk of bias 2 tool). Inclusion criteria for RCTs included similar co-interventions in both study arms, whilst RCTs comparing ivermectin to interventions with unproven efficacy were excluded. However, included RCTs were heterogenous with respect to ivermectin's course duration, dosing interval and the dosage administered. Thus, composite measures of effect, such as meta-analyses, should be interpreted with caution.

Furthermore, quantitative analysis for publication bias was not conducted, as the authors stated that this could not be reliably assessed, considering the large number of ongoing registered RCTs that have yet to be completed and published. However, this will be assessed with updates of the systematic review.

Effects of the intervention:

Ivermectin compared to placebo or standard of care for inpatient COVID-19 treatment

- **Mortality:** RR 0.60, 95% CI 0.14 to 2.51; 2 studies, 185 participants; *very low-certainty evidence*

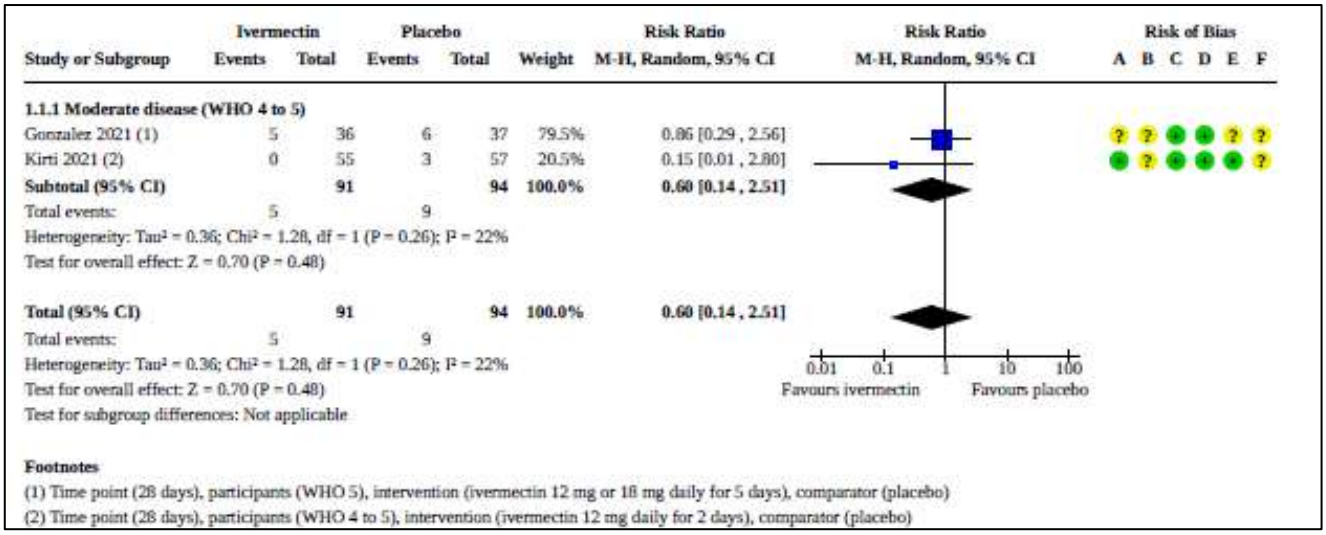

Figure 1: Forest plot for ivermectin vs control for moderate-to severe COVID-19 for outcome: All-cause mortality up to 28 days (primary analysis)

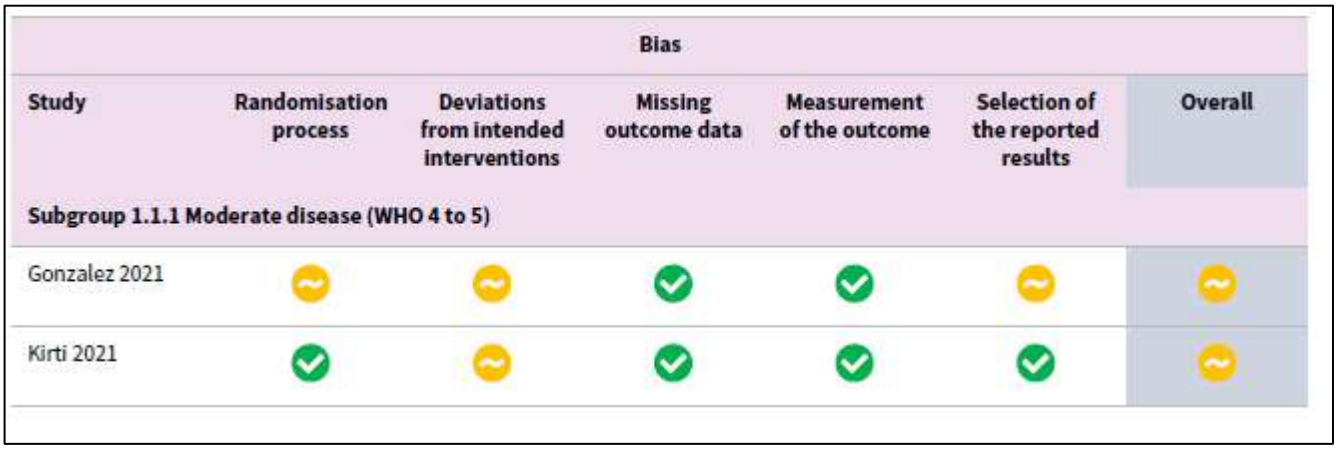

Figure 2: Risk of bias analysis – All-cause mortality up to 28 days (primary analysis). Green – low risk. Yellow – moderate risk.

- **Clinical worsening up to day 28, as measured by needing invasive mechanical ventilation (IMV):** RR 0.55, 95% CI 0.11 to 2.59; 2 studies, 185 participants; *very low-certainty evidence.*

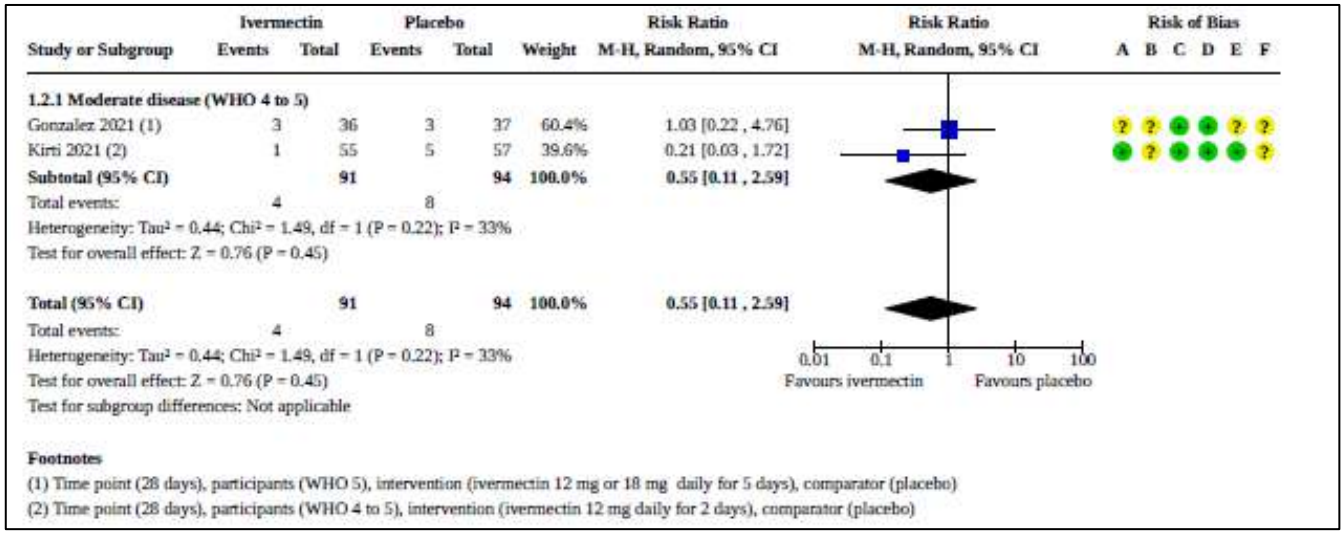

Figure 3: Forest plot for ivermectin vs control for moderate-to severe COVID-19 for outcome: Worsening of clinical status & need for invasive mechanical ventilation up to 28 days (primary analysis)

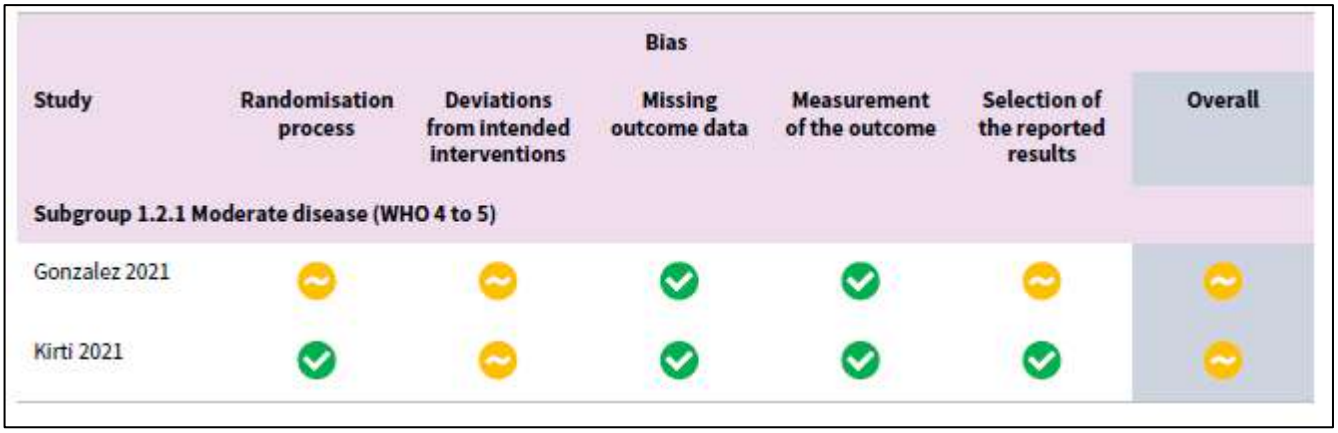

Figure 4: Risk of bias analysis: Worsening of clinical status & need for invasive mechanical ventilation up to 28 days (primary analysis)

- **Need for supplemental oxygen: 0 participants required supplemental oxygen; 1 study, 45 participants;** *very low-certainty evidence.*
- **Viral clearance at day seven:** RR 1.82, 95% CI 0.51 to 6.48; 2 studies, 159 participants; *very low-certainty evidence.*
- **Clinical improvement up to 28 days:** RR 1.03, 95% CI 0.78 to 1.35; 1 study; 73 participants; *low certainty evidence.*
- **Duration of hospitalization:** Mean difference (MD) −0.10 days, 95% CI −2.43 to 2.23; 1 study; 45 participants; *low certainty evidence.*

Ivermectin compared to placebo or standard of care for outpatient COVID-19 treatment

- **Mortality up to 28 days:** RR 0.33, 95% CI 0.01 to 8.05; 2 studies, 422 participants; *very low-certainty evidence.*

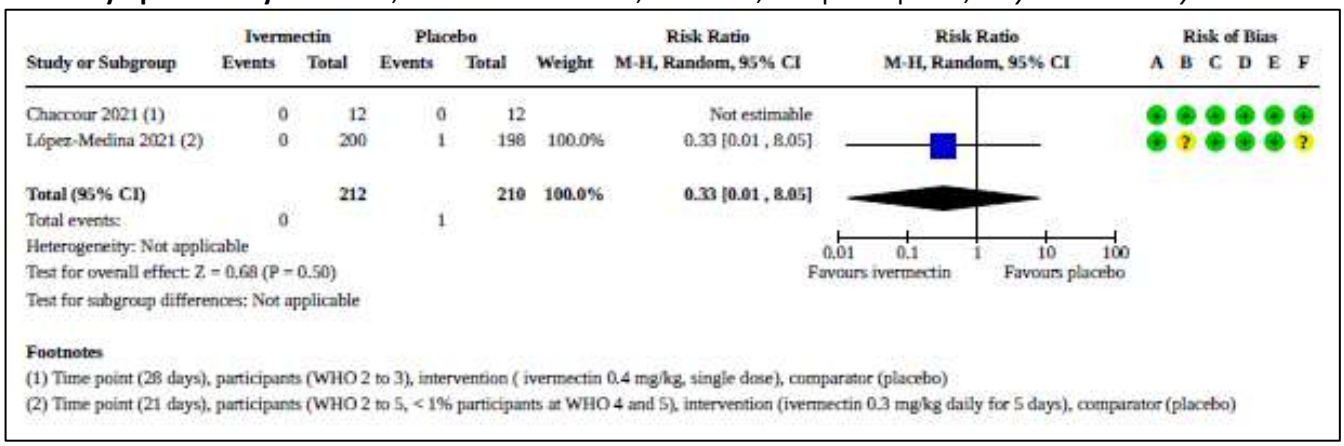

Figure 5: Forest plot of Ivermectin vs control for mild COVID-19 treated in the outpatient setting for outcome: All-cause mortality up to 28 days (primary analysis)

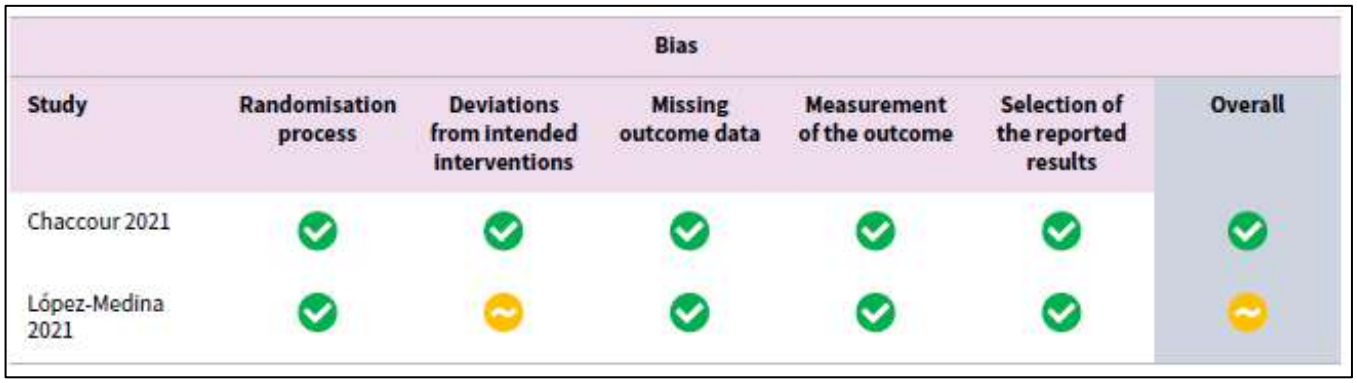

Figure 6: Risk of bias analysis - All-cause mortality up to 28 days (primary analysis)

- **Clinical worsening up to 14 days assessed as need for IMV:** RR 2.97, 95% CI 0.12 to 72.47; 1 study, 398 participants; *very low-certainty evidence.*

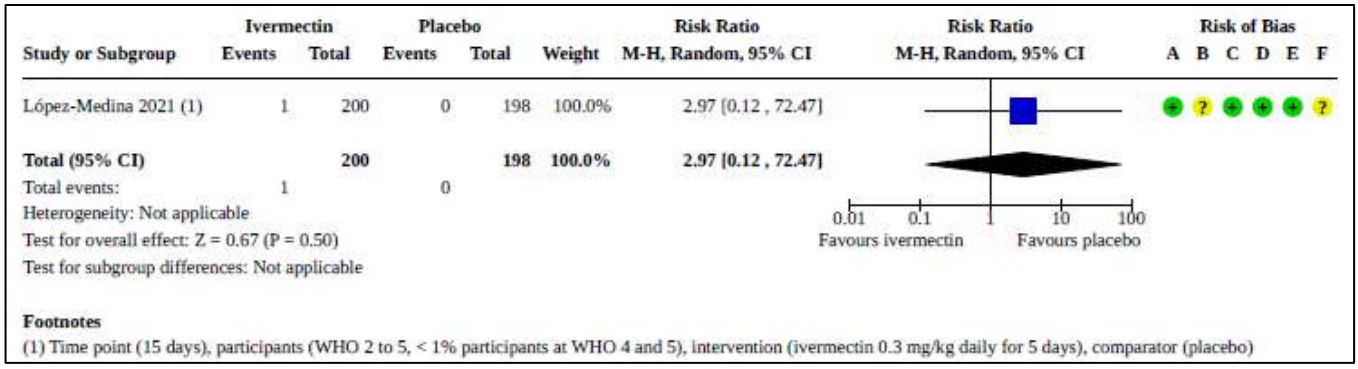

Figure 7: Forest plot of Ivermectin vs control for mild COVID-19 treated in the outpatient setting for outcome: Worsening of clinical status – need for invasive mechanical ventilation up to 14 days (primary analysis)

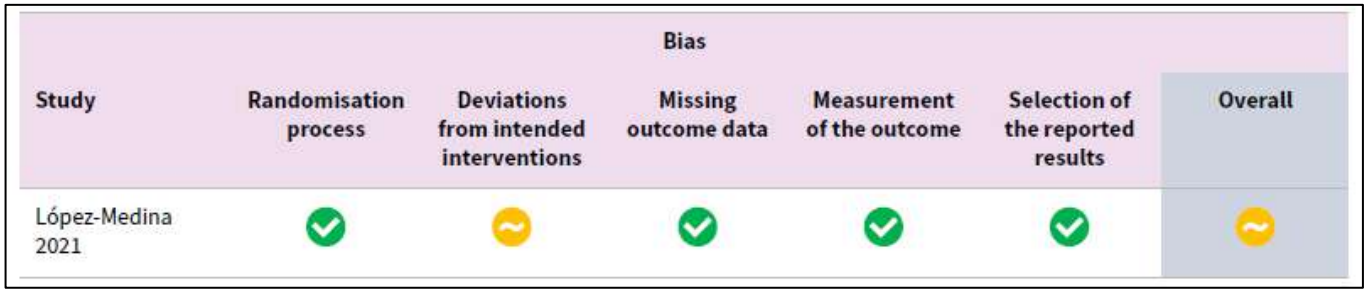

Figure 8: Risk of bias analysis - Worsening of clinical status – need for invasive mechanical ventilation up to 14 days (primary analysis)

- **Need for non-IMV or high flow oxygen requirement:** 0 participants required non-IMV or high flow; 1 study, 398 participants; *very low-certainty evidence.*
- **Viral clearance at seven days:** RR 3.00, 95% CI 0.13 to 67.06; 1 study, 24 participants; *low-certainty evidence*.
- **Symptom resolution up to 14 days:** RR 1.04, 95% CI 0.89 to 1.21; 1 study, 398 participants; *low-certainty evidence*.
- **Duration of symptoms:** No study data**.**
- **Hospital admission:** No study data**.**

Safety

Ivermectin compared to placebo or standard of care for inpatient COVID-19 treatment

- **Adverse events within 28 days:** RR 1.21, 95% CI 0.50 to 2.97; 1 study, 152 participants; *very low-certainty evidence*

Ivermectin compared to placebo or standard of care for outpatient COVID-19 treatment

- **Adverse events within 28 days:** RR 0.95, 95% CI 0.86 to 1.05; 2 studies, 422 participants; *low-certainty evidence.*

In previous rapid review reports, evidence for ivermectin was also compared to active comparators. With the emergence of further RCT data, the comparator has been restricted to placebo or standard of care. The evidence tables from the previous reports for ivermectin compared to active comparators (not shown to have pharmacological benefit) has been included as addendum A.

CONCLUSION

As synthesized in the Cochrane systematic review and meta-analysis, the current evidence for the use of ivermectin in COVID-19 does not suggest any clear benefits in either inpatients or outpatients with respect to mortality, clinical improvement, or viral clearance. All domains were assessed as being of low or very low quality evidence. The included RCTs for the most part have very small sample sizes and suffer from considerable heterogeneity with respect to ivermectin dosing strategy and outcome measures. They also have several methodological limitations, including a lack of allocation concealment, subjective and poorly defined endpoints and patient severity allocations, and baseline imbalances between the various trial arms in co-administered medications and in patients with risk factors for poor outcomes. Many of the trials included have not yet been peer-reviewed, which adds further uncertainty to the evidence base. Lastly, the potential for publication bias cannot be excluded; several trials were only added to trial registries after their completion.

Together, these significant limitations limit the confidence in any conclusions with respect to ivermectin, and thus there is insufficient evidence to recommend ivermectin's use in any patient population outside a clinical trial. Further data from large, well-designed RCTs is needed.

Reviewers: Trudy Leong, Jeremy Nel, Andy Parrish, Halima Dawood, Milli Reddy.

Declaration of interests: TL (National Department of Health, Affordable Medicines Directorate, Essential Drugs Programme), JN (Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand), AP (Walter Sisulu University), HD (Infectious diseases, Greys Hospital and University of KwaZulu-Natal), MR (BHPSA) have no interests with regards to ivermectin.

Table 1: Characteristics of included study

Citation	Study design	Population	Intervention vs comparator	Outcomes	Effect sizes	Comments
Popp M, Stegemann M, Metzendorf M-I, Gould S, Kranke P, Meybohm P, Skoetz N, Weibel S. Ivermectin for preventing and treating COVID-19. Cochrane Database of Systematic Reviews 2021, Issue 7. Art. No.: CD015017. DOI: **10.1002/14651858.CD015017.pub2.**	Systematic Review and Meta-Analysis	14 studies; 1678 participants **Treatment of COVID-19** Confirmed SARS-CoV-2 infection (RT-PCR or antigen testing) **Prevention of SARS-CoV-2 infection** Participants who were not infected with SARS-CoV-2 at enrolment, but were at high risk of developing the infection (e.g., after high-risk exposure), Age, gender, ethnicity, disease severity, and setting (inpatient and outpatients) were not exclusion factors for treatment or prevention	**Intervention:** All doses & regimens of ivermectin **Dosing:** ***Low dose*** (up to 0.2 mg/kg orally, single dose) ***High dose*** (>0.2 mg/kg orally, single dose or > frequency) **Comparators:** no treatment, standard of care, or placebo Ivermectin vs active pharmacological comparator with proven efficacy for prevention/ treatment of COVID-19 (e.g., dexamethasone & remdesivir) - (no studies available for review). Agents e.g., doxycycline, hydroxychloroquine, azithromycin, zinc without proven efficacy excluded	**Ivermectin for treating COVID-19 in inpatient & outpatient settings:** • All-cause mortality up to 28 days • Clinical status, assessed by need for respiratory support with standardized scales (e.g., WHO Clinical Progression Scale) up to 28 days. **Ivermectin for preventing SARS-CoV-2 infection:** • SARS-CoV-2 infection (confirmed by RT-PCR or antigen testing) at 14 days. • Development of clinical COVID-19 symptoms up to 14 days; assessed with WHO scale	**Inpatient COVID-19 treatment: Ivermectin vs placebo or standard of care** • Mortality: (RR) 0.60, 95% (CI) 0.14 to 2.51; 2 studies, n=185; ***very low-certainty evidence***) • Clinical worsening up to day 28 assessed as need for invasive mechanical ventilation (IVM): (RR 0.55, 95% CI 0.11 to 2.59; 2 studies, n=185; very low-certainty evidence) or need for supplemental oxygen (n=0; 1 study, n=45; ***very low-certainty evidence***) • Adverse events within 28 days: (RR 1.21, 95% CI 0.50 to 2.97; 1 study, n=152; ***very low-certainty evidence***) • Viral clearance at day 7: (RR 1.82, 95% CI 0.51 to 6.48; 2 studies, n= 159; ***very low-certainty evidence***) • Clinical improvement up to 28 days: (RR 1.03, 95% CI 0.78 to 1.35; 1 study; n=73 ; ***low certainty evidence***) • Duration of hospitalization (mean difference (MD): −0.10 days, 95% CI −2.43 to 2.23; 1 study; n=45; ***low certainty evidence***) **Outpatient COVID-19 treatment: Ivermectin vs placebo or standard of care** • Mortality up to 28 days (RR 0.33, 95% CI 0.01 to 8.05; 2 studies, n=422; ***very low-certainty evidence***) • Clinical worsening up to 14 days: assessed as need for IMV: (RR 2.97, 95% CI 0.12 to 72.47; 1 study, n=398; ***very low-certainty***	• AMSTAR2 assessment - High quality review (Appendix 1) • 13 studies contributed 41 study results to 23 outcomes – about 1/3 of the results were considered overall high risk of bias. • Graphical representation fo publication bias was not conducted (i.e. funnel plot) as less than 10 RCTs included in the meta-analysis. However, likely to be included when the review is updated as studies are still ongoing or, and results have yet to be published

					evidence) or non-IMV or high flow oxygen (n=0; 1 study, n=398; ***very low-certainty evidence***) • Viral clearance at seven days: (RR 3.00, 95% CI 0.13 to 67.06; 1 study, n=24; ***low-certainty evidence***) • Number with symptoms resolved up to 14 days: (RR 1.04, 95% CI 0.89 to 1.21; 1 study, n=398; ***low-certainty evidence***) • Adverse events within 28 days (RR 0.95, 95% CI 0.86 to 1.05; 2 studies, n=422; ***low-certainty evidence***) • No study reported hospital admission rates. **Prevention of SARS-CoV-2 infection: Ivermectin vs no treatment for** • Mortality up to 28 days: (n=0, died; 1 study, n=304; ***very low-certainty evidence***) • No study reported SARS-CoV-2 infection, hospital admission, & quality of life up to 14 days	

Table 2: Excluded studies

1.	Bartoszko et al. Prophylaxis for covid-19: living systematic review and network meta-analysis, 26 February 2021. https://www.medrxiv.org/content/10.1101/2021.02.24.21250469v1	Ivermectin prophylactic treatment – PICO criteria not met
2. 3.	Murchu et al. Interventions in an Ambulatory Setting to Prevent Progression to Severe Disease in Patients With COVID-19: A Systematic Review. Annals of Pharmacotherapy, 22 June 2021. https://journals.sagepub.com/doi/10.1177/10600280211028242	Databases searched up to 6 January 2021 – later RCTs published
4.	Pan American Health Organisation. Ongoing Living Update of Potential COVID-19 Therapeutics: summary of rapid systematic reviews. Rapid Review, 23 May 2020. https://iris.paho.org/handle/10665.2/52719	Previously excluded – see the previous ivermectin rapid review report, dated 25 January 2021.
5.	Pan American Health Organisation. Ongoing Living Update of Potential COVID-19 Therapeutics: summary of rapid systematic reviews. Rapid Review, 16 June 2020. https://iris.paho.org/handle/10665.2/52719	Previously excluded – see the previous ivermectin rapid review report, dated 25 January 2021.
6.	Bryant et al. Ivermectin for Prevention and Treatment of COVID-19 Infection: a Systematic Review and Meta-analysis. ResearchSquare. 18 March 2021. https://www.researchsquare.com/article/rs-317485/v1	Previously excluded – see the previous ivermectin rapid review report, dated 18 June 2021.
7.	Hill A et al. Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection. ResearchSquare, 19 January 2021. https://www.researchsquare.com/article/rs-148845/v1	Previously excluded – see the previous ivermectin rapid review report, dated 18 June 2021 and see addendum B.
8.	Kow et al. The association between the use of ivermectin and mortality in patients with COVID-19: a meta-analysis. March 2021. https://pubmed.ncbi.nlm.nih.gov/33779964/	Previously excluded – see the previous ivermectin rapid review report, dated 18 June 2021.
9.	Bryant et al. Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines. Am J Ther. 2021 Jun 21;28(4):e434-e460. https://pubmed.ncbi.nlm.nih.gov/34145166/	Previously excluded – see the previous ivermectin rapid review report, dated 18 June 2021 and see addendum C.
10.	Zein et al. Ivermectin and mortality in patients with COVID-19: A systematic review, meta-analysis, and meta-regression of randomized controlled trials. Diabetes Metab Syndr. 2021 Jun 27;15(4):102186. https://pubmed.ncbi.nlm.nih.gov/34237554/	Mixture of 9 RCTs comparing ivermectin to standard of care and/or active comparators
11.	Rodriguez-Gutierrez R, et al. Ivermectin in the Prophylaxis and Treatment of Patients with SARS-CoV-2: A Living Systematic Review and Meta-Analysis. SSRN, 11 March 2021. https://ssrn.com/abstract=3802499	Previously excluded – see the previous ivermectin rapid review report, dated 18 June 2021.

12.	Hariyanto TI et al. Ivermectin and outcomes from Covid-19 pneumonia: A systematic review and meta-analysis of randomized clinical trial studies. Reviews in medical virology, 6 June 2021. https://onlinelibrary.wiley.com/doi/10.1002/rmv.2265	Databases searched up to 10 May 2021 – later RCTs published
13.	Castañeda-Sabogal A et al. Outcomes of Ivermectin in the treatment of COVID-19: a systematic review and meta-analysis. MedRxiv 27 January 2021. https://www.medrxiv.org/content/10.1101/2021.01.26.21250420v1	Previously excluded – see the previous ivermectin rapid review report, dated 18 June 2021.
14.	Karale S et al. A Meta-analysis of Mortality, Need for ICU admission, Use of Mechanical Ventilation and Adverse Effects with Ivermectin Use in COVID-19 Patients. MedRxiv, 4 May 2021. https://www.medrxiv.org/content/10.1101/2021.04.30.21256415v1	Later RCTs published
15.	Padhy BM et al. Therapeutic potential of ivermectin as add on treatment in COVID 19: A systematic review and meta-analysis. J Pharm Pharm Sci., 23 November 2020. https://pubmed.ncbi.nlm.nih.gov/33227231/	Previously excluded – see the previous ivermectin rapid review report, dated 25 January 2021.
16.	Kalfas et al. The therapeutic potential of ivermectin for COVID-19: a review of mechanisms and evidence . medRxiv. 4 December 2020. https://www.medrxiv.org/content/10.1101/2020.11.30.20236570v1	Previously excluded – see the previous ivermectin rapid review report, dated 25 January 2021.
17.	Roman YM et al. Ivermectin for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials. MedRxiv, 26 May 2021. https://www.medrxiv.org/content/10.1101/2021.05.21.21257595v2	Preprint – publication available in peer-review format – see #19
18.	Roman YM et al. A systematic review and meta-analysis of randomized controlled trials. Clin Infect Dis. 2021 Jun 28. https://pubmed.ncbi.nlm.nih.gov/34181716/	Previously excluded – see the previous ivermectin rapid review report, dated 18 June 2021.
19.	Bhowmick S et al. Safety and Efficacy of Ivermectin and Doxycycline Monotherapy and in Combination in the Treatment of COVID-19: A Scoping Review. Drug Saf. 2021 Jun. https://pubmed.ncbi.nlm.nih.gov/33864232/	Previously excluded – see the previous ivermectin rapid review report, dated 18 June 2021.
20.	Bartoszko JJ et al. Prophylaxis against covid-19: living systematic review and network meta-analysis. BMJ. 2021 Apr 26;373:n949. https://pubmed.ncbi.nlm.nih.gov/33903131/	Previously excluded – see the previous ivermectin rapid review report, dated 18 June 2021.
21.	Marra LP, et al. Ivermectin for COVID-19: rapid systematic review. Hospital Alemão Oswaldo Cruz. Unidade de Avaliação de Tecnologias em Saúde; Hospital Sírio-Libanês. Núcleo de Avaliação de Tecnologias em Saúde. 2020. https://oxfordbrazilebm.com/index.php/2020/05/07/ivermectina-para-otratamento-de-pacientes-com-covid-19-revisao-sistematica-rapida2	Previously excluded – see the previous ivermectin rapid review report, dated 25 January 2021.
22.	Bestetti RB, et al. Pharmacological Treatment of Patients with Mild to Moderate COVID-19: A Comprehensive Review. Int J Environ Res Public Health. 2021 Jul. https://pubmed.ncbi.nlm.nih.gov/34281149/	Three ivermectin RCTs included in the review, later RCTs published.
23.	Malin JJ et al. Key summary of German national treatment guidance for hospitalized COVID-19 patients Key pharmacologic recommendations from a national German living guideline using an Evidence to Decision Framework (last updated 17.05.2021). Infection. 2021 Jul 6. https://pubmed.ncbi.nlm.nih.gov/34228347/	Three ivermectin RCTs included in the review, later RCTs published.
24.	Pan American Health Organisation. Ongoing Living Update of Potential COVID-19 Therapeutics: summary of rapid systematic reviews. Rapid Review, 11 August 2020. https://iris.paho.org/handle/10665.2/52719	Later RCTs published
25.	Kim MS, et al, Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: A systematic review and network meta-analysis. PLoS medicine. 2020;17(12):e1003501. https://pubmed.ncbi.nlm.nih.gov/33378357/	Previously excluded – see the previous ivermectin rapid review report, dated 25 January 2021.
26.	Lawrie T. Ivermectin reduces the risk of death from COVID-19 -a rapid review and meta-analysis in support of the recommendation of the Front Line COVID-19 Critical Care Alliance. Researchgate Jan 2021. http://dx.doi.org/10.13140/RG.2.2.27751.88486	Mixture of RCTs and non-RCTs

Appendix 1: Search strategy

Updated Search performed on 29 July 2021

Database: Cochrane Library
Date: 29 July 2021
Search strategy:

ID	Search	Hits
#1	(ivermectin):ti,ab,kw AND (covid-19):ti,ab,kw (Word variations have been searched)	118
#2	systematic reviews	16589
#3	#1 AND #2	3

3 records retrieved, 2 clinical answers excluded and 1 Cochrane review included in evidence synthesis

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L·OVE for COVID-19

The search terms and databases covered are described on the L·OVE search strategy methods page available at: https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?question_domain=undefined&%20section=methods. The repository is continuously updated, and the information is transmitted in real-time to the L·OVE platform. The searches covered the period from the inception date of each database, and no study design, publication status or language restriction applied.

Search strategy: (title:((title:(ivermectin) OR abstract:(ivermectin))) OR abstract:((title:(ivermectin) OR abstract:(ivermectin)))) AND (title:(COVID-19) OR abstract:(COVID-19))

Search restricted to systematic reviews

26 records retrieved and abstracts screened; 22 records excluded, 4 full-text reviews, all excluded, 0 records included in evidence synthesis

Appendix 2: Evaluating the methodological quality of the Popp et al (2021)[7] systematic review and meta-analysis – AMSTAR 2 tool (Shea 2017)[6]

No.	Criteria	Yes/ Partial Yes/ No	Comment
1	Research questions and inclusion criteria for the review included the components of PICO	Yes	-
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	Partial yes	"*Protocol first published: Issue 4, 2021*", but not clear if the protocol was registered.
3	Review authors explained selection of the study designs for inclusion in the review	Yes	-
4*	Review authors used a comprehensive literature search strategy	Yes	-
5	Review authors perform study selection in duplicate	Yes	-
6	Review authors perform data extraction in duplicate	Yes	Risk of bias assessments done by at least two individuals independently, with disagreements resolved through consensus. GRADE approach used to assess certainty of evidence.
7*	Review authors provided a list of excluded studies and justify the exclusions	Yes	-
8	Review authors described the included studies in adequate detail	Yes	-
9*	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	Yes	Cochrane Risk of Bias Assessment Tool (RoB 2).
10	Review authors reported on the sources of funding for the studies included in the review.	Yes	-
11*	For meta-analyses, review authors used appropriate methods for statistical combination of results	Yes	-
12	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	Yes	-
13*	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	Yes	-
14	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Yes	-
15*	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	n/a	Authors stated, "*But in the current phase of the pandemic, it is impossible to reliably assess the risk of publication bias. Most of the registered studies are still ongoing or, in the case of a completed study status, their results have not yet been published. We will follow the publication and trial history of each ongoing study and study awaiting classification. Currently, we did not suspect publication bias of any outcome included in this review. However, this may change in updates of this review".*
16	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Yes	-

** Critical domains are 2, 4, 7, 9, 11, 13, 15*

Rating overall confidence in the results of the review

- *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
- *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
- *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
- *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

OVERALL ASSESMENT: High quality

Rationale: One non-critical weakness (#2)

Conclusion: The AMSTAR assessment suggests that if the review has no or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

Appendix 3: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ x *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Very low certainty evidence based on small sample sizes and low event rates, methodological issues with the reports available
EVIDENCE OF BENEFIT	**What is the size of the overall effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☐ None ☐ Uncertain ☒ X	RCT evidence consists chiefly of pre-prints of low methodological quality, with small sample sizes and disparate interventions and controls, limiting the confidence in any conclusions with respect to ivermectin . Further data from large, well-designed RCTs is urgently needed.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☐ Small ☐ None ☐ Uncertain ☒ X	Adverse events were not reported for the majority of trials, and where this was done, reporting was sparse. Adverse event reporting may have been clouded by the lack of allocation concealment.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☐ Intervention = Control *or* Uncertain ☒ x	The available evidence is uncertain whether desirable effects outweigh desirable outcomes.
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes ☐ No ☒ X Uncertain ☐	Ivermectin is not SAHPRA registered and requires to be accessed through section 21 approval.
RESOURCE USE	**How large are the resource requirements?** More intensive ☐ Less intensive ☐ Uncertain ☒ X	**Price of medicines/ treatment course :** **Medicine** | **Tender Price** | **SEP** Currently not SAHPRA registered for human consumption | n/a | n/a
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor ☐ Major ☒ X Uncertain ☐ **Is the intervention acceptable to key stakeholders?** Yes ☒ X No ☐ Uncertain ☐	There is no local survey data to determine stakeholder acceptability. However, interest groups support use of ivermectin based on anecdotal data. Some compounding is being done locally. To date, some patients have been given section 21 approval to use imported unregistered oral solid dosage forms, and provision has also been made for importers to hold bulk stock, and for health facilities to hold buffer stock, in anticipation of submitting individual patient applications.
EQUITY	**Would there be an impact on health inequity?** Yes ☒ X No ☐ Uncertain ☐	Access is currently only available through section 21 or as a compounded product.

Appendix 4: Updating of rapid report

Date	Signal	Rationale
24 May 2021	Publication of a number of RCTs	As additional RCTs have been published (including some larger trials), an update is warranted.
28 July 2021	Cochrane review of RCTs published	Systematic review of RCTs now available to review, rather than continuously reporting and appraising individual RCT as they are completed and published (preprint or peer-review format).,

ADDENDUM A: The evidence tables from previous COVID-19 rapid review reports (25 January 2021, 18 June 2021, 2 July 2021) for ivermectin compared to active comparators.

• **IVERMECTIN + DOXYCYCLINE vs PLACEBO/STANDARD OF CARE – 4 RCTs**						
Citation	**Study design**	**Population**	**Intervention vs comparator**	**Outcomes**	**Effect sizes**	**Comments**
Mahmud et al,[1] Ivermectin in combination with doxycycline for treating COVID-19 symptoms: a randomized trial. Jr of INt Med Res, May 2021. https://journals.sagepub.com/doi/10.1177/03000605211013550 Clinical trial registration: NCT04523831	RCT, double-blinded, single center (Bangladesh) Phase 3 study Follow-up duration (days): 30 Funding/ agreements: No specific funding (No specific grant) Declarations: None	Sample size: n = 400 randomised (200/ group) Disease severity: Mild and moderate COVID-19 infected cases; details not provided Patient characteristics: Mean age: 39.6 years; 235 males (59%) Inclusion criteria: ≥18 years; PCR-confirmed COVID-19 infection within 3 days from enrollment;	*Intervention:* • Ivermectin+Doxycycline (12 mg/100 mg) daily • Co-Intervention: Standard care • Duration : 5 days *Control:* • Placebo • Co-Intervention: Standard care • Duration : 5 days *Standard of care:* Paracetamol, vitamin D, oxygen if indicated, low molecular weight heparin, dexamethasone if indicated.	**Primary outcome(s):** • Number of patients with early clinical improvement at 7 days (defined by WHO and Bangladesh local guideline) • Number of participants with late clinical recovery at 12 days **Secondary outcome(s):** • Number of patients having clinical deterioration at 1 month • Number of patients remaining persistently positive for RT-PCR of Covid-19 **Other reported outcome(s):** • All-cause mortality • SAEs • Adverse events	**Primary outcome(s):** Ivermectin+Doxycycline vs placebo • *Number of patients with early clinical improvement at 7 days*: 111/183 (60.7%) vs 80/180 (44.4%); p<0.03 • *Number of participants with late clinical recovery at 12 day:* 42/183 (23.0%) vs 67/180 (37.2%); p<0.004 **Secondary outcome(s):** Ivermectin+Doxycycline vs placebo • *Number of patients having clinical deterioration at 1 month:* 16/183 (8.7%) vs 32/180 (17.8%); p<0.013 • *Number of patients remaining persistently positive for RT-PCR of Covid-19 at day 14:* 14/183 (7.7%) vs 36/180 (20.0%), p<0.001 **Other reported outcome(s):** Ivermectin+Doxycycline vs placebo • *All-cause mortality:* 00/183 (0.00%) vs 03/180 (1.67%) • *SAEs (erosive oesophagitis)*: 02/183 (1.09%) vs 00/180 (0.00%) • *Adverse events (non-ulcer dyspepsia):* 07/183 (3.83%) vs 00/180 (0.00%)	• No published report, data collected from the online trial registry, protocol and statistical analysis plan. • Target sample size specified in the registry and protocol was achieved. • No deviation between the trial registration and protocol in the intervention and control treatments or in the outcomes. • Registry states that the study uses an ITT analysis, but denominators for SAEs/withdrawal due to AEs and mortality do not seem to include the participants with these outcomes. **Risk of bias assessment: Overall – MODERATE to HIGH RISK** • *Randomisation*: **LOW RISK** - Allocation sequence random. Allocation sequence concealed. Very few baseline characteristics were reported (age, sex) and imbalances appear to be compatible with chance. • *Deviations from intervention*: **LOW RISK** - Blinded study (participants and investigators). Data analysis using available case analysis. • *Attrition:* **MODERATE to HIGH RISK** - 400 randomised/363 analyzed ○ 15 participants lost to follow-up in the intervention and 17 participants in the control arm. ○ 3 participants that died in the control group and 2 in the intervention group due to adverse events, were also excluded. ○ Risk assessed to be high for the outcomes: Mortality; incidence of viral negative conversion; incidence of clinical improvement; time to clinical improvement; adverse event; serious adverse events. • *Measurement of the outcome:* **LOW RISK** - Blinded outcome assessor (risk assessed as low for the outcomes: Mortality; incidence of viral negative conversion; incidence of clinical improvement; time to clinical improvement; adverse event; serious adverse events).

[1] Mahmud RM, Dhaka Medical College. Clinical Trial of Ivermectin Plus Doxycycline for the Treatment of Confirmed Covid-19 Infection, Clinical Trials Registry, NCT04523831. http://clinicaltrials.gov/show/NCT04523831

						• *Selection of the reported results:* **MODERATE RISK -** The trial registry, protocol and statistical analysis plan were available. ○ No information on whether the result was selected from multiple outcome measurements or analyses of the data, or whether the trial was analyzed as pre-specified. ○ Risk assessed to be some concerns for the outcomes: mortality (D28, incidence of viral negative conversion (D7), adverse events, serious adverse events.
Hashim et al.[2] Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq. MedRxiv, 27 October 2020 https://www.medrxiv.org/content/10.1101/2020.10.26.20219345v1 NCT04591600	RCT , parallel, single-blinded (outcome assessors), single-center (Alkarkh and Alforat hospitals in Baghdad, Iran) Phase 1/2 study Follow-up duration: 8 weeks Funding: Alkarkh Health Directorate-Baghdad Declarations: No conflicts of interest declared	Sample size: n=140 (70/study gp – ivermectin+ doxycycline and standard care gps); hospital outpatients and inpatients Disease severity: *(defined as per WHO criteria)* Mild-moderate:96 (48 vs 48) Severe: 33 (11vs 22) Critical: 11 (11 vs 0) Patient characteristics: Mean age: 48.7±8.6 years 73 male s (52%) Inclusion criteria: 16-86 years, COVID-19 patients at any stage of this disease (diagnosed by clinical, radiological and laboratory PCR testing) Exclusion criteria: Allergy to ivermectin or to doxycycline	*Intervention:* • Ivermectin 200mcg/kg, oral daily • Duration: 2-3 days **PLUS** • Doxycycline 100mg, oral 12 hrly • Duration: 5-10 days **PLUS** • Standard therapy *Control:* • Standard therapy *Standard therapy:* Acetaminophen 500mg as needed, vitamin C 1000mg 12 hrly, zinc 75-125 mg daily, vitamin D3 5000IU daily, azithromycin 250mg daily (5 days), oxygen/ C-pap as needed, dexamethasone 6 mg daily or methylprednisolone 40mg 12 hrly as needed,	**Primary outcome(s):** ○ Mortality rate ○ Progression of the disease **Secondary outcome(s):** ○ Time to recovery	**Primary outcome(s):** Ivermectin+ doxycycline vs standard care *Mortality rate (%):* • Total: 2/70 (2.85%) vs 6/70 (8.57); p=0.14; OR 0.31; p=0.16 • Mild-moderate: 0/48 (0%) vs 0/48 (0%); p=1 • Severe: 0/11 (0%) vs 6/22 (27.27%); p= 0.052; OR 0.11; p=0.14 • Critical: 2/11 (18.2%) vs n/a *Rate of progression of disease (%):* • Total: 3/70 (4.28%) vs 7/70 (10%); p=0.19; OR 0.4; p=0.2 • Mild-moderate: 0/48 (0%) vs 0/48 (0%); p=1 • Severe: 1/11 (9%) vs 7/22 (31.81%); p=0.15; OR 0.21; p=0.17 • Critical: 2/11 (18.2%) vs n/a **Secondary outcome(s):** Ivermectin+ doxycycline vs standard care *Mean time to recovery (days):* • Total: 10.61± 5.3 vs 17.9±6.8; p<0.0001 • Mild-moderate: 6.34±2.4 vs 13.66±6.4; p<0.001 • Severe: 20.27±7.8 vs 24.25±9.5; p=0.29 • Critical: 19.77±9.2 vs n/a	• Data extracted from preprint and online trial registry. Protocol and statistical analysis plan not available • Target sample size specified in the registry and protocol was achieved. • Standard therapy administered to both groups included azithromycin • Baseline comorbidities of patients not provided for; to determine confounding. **Risk of bias assessment: Overall – HIGH RISK** • *Randomisation*: **HIGH RISK –** Allocation sequence concealment and allocation concealment unlikely and study gps were "*age-and sex-matched*" – "*COVID-19 patients were randomly allocated to one of the study groups depending on a simple method. Patients recruited at dates with odd number were allocated to Ivermectin-Doxycycline group while other patients were allocated to the control group*". • *Deviations from intervention*: **HIGH RISK –** Single blinded study (outcome assessors and not participants and investigators). • *Attrition:* **LOW RISK** - 140 randomised/140 analyzed • *Measurement of the outcome:* **UNCLEAR RISK -** Blinded outcome assessor, but) - protocol and statistical plan not available for further review.. • *Selection of the reported results:* **UNCLEAR RISK -** The protocol and statistical analysis plan were not available for further review. Authors concluded that, "*Nevertheless, these observational findings still need confirmation by a large randomized controlled study*".

[2] Hashim HA, Maulood MF, Rasheed AM *et al*. Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq. MedRxiv, 27 October 2020. https://www.medrxiv.org/content/10.1101/2020.10.26.20219345v1

			mechanical ventilation as needed			
Ahmed S et al., 2020.[3] A five day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. International journal of infectious diseases, 26 Nov 2020 https://dx.doi.org/10.1016/j.ijid.2020.11.191 Clinical trial registration: NCT04407130	RCT, double-blinded, single center (Bangladesh) Phase of study not reported Follow-up duration (days): 14 Funding: Beximco Pharmaceutical Limited, Bangladesh – supplier of ivermectin 12 mg tablets Declarations: Authors reported no conflicts of interest to declare.	Sample size: n = 72 randomised (n=24/group: ivermectin +doxycycline vs control vs ivermectin) Disease severity: Mild Inclusion criteria: 18-65 years; admitted to hospital ≤ 7 days [with either fever (>37.5C); cough or sore throat; and diagnosed positive for SARS-CoV-2 by rRT-PCR]; Patient characteristics: Mean age: 42 years; 46% male; Duration of illness before assessment was an average of 3.83 days.	*Intervention:* • Ivermectin+doxycycline (12 mg/100 mg) daily • Co-Intervention: Standard care • Duration : 5 days *Control 1:* • Placebo • Co-Intervention: Standard care • Duration : 5 days *Control 2:* • Ivermectin (12 mg) daily • Co-Intervention: Standard care • Duration: 5 days *Standard of care:* Not reported	**Primary outcome(s):** Time required for virological clearance (a negative rRT-PCR result on nasopharyngeal swab); remission of fever (>37.5°C) and cough within 7 days	**Primary outcome(s):** Ivermectin+doxycycline vs placebo • *The mean duration to viral clearance:* ○ Ivermectin+doxycycline: 11.5 days (95% CI 9.8 to 13.2 days); p=0.27 ○ Placebo: 12.7 days (95% CI 11.3 to 14.2 days); no p-value reported ○ Ivermectin: 9.7 days (95% CI 7.8 to 11.8 days); p=0.02 • *Viral clearance at 7 days:* ○ Ivermectin vs placebo: HR = 4.1, 95% CI 1.1 to 14.7; p = 0.03 ○ Ivermectin+doxycycline vs placebo: HR 2.3, 95% CI 0.6 to 9.0; p=0.22 • *Viral clearance at 14 days:* ○ Ivermectin vs placebo: HR = 4.1, 95% CI 1.1 to 14.7; p=0.03 ○ Ivermectin+doxycycline vs placebo: HR 1.7, 95% CI 0.8 to 4.0; p=0.19 • *Clinical symptoms of fever, cough, and sore throat at day 7:* Comparable among the three groups *Severe adverse drug events:* None recorded in the study.	• The protocol and statistical analysis plan were not available. The registry was available. • The study achieved its stated sample size. • Pharmaceutical industry sponsored study (supplier of ivermectin). • Baseline demographic characteristics were not reported by study group. • Some efficacy outcomes were not reported in the results section of the paper although they were listed in the methods section (i.e. failure to maintain an SpO_2 >93% despite oxygenation and days on oxygen support, the duration of hospitalization, all-cause mortality, adverse events, and the discontinuation of the study drug during the trial) – however, data on all outcomes except time to viral negative conversion were requested from the authors. • Mortality, reported as a study outcome in the methods, was not clearly reported. **Risk of bias assessment: Overall – MODERATE RISK** • *Randomisation*: **LOW RISK** - Allocation sequence with allocation sequence concealment: *"the allocated sequence was concealed all through the study until the blinded analysis was done.* *1. The randomization was performed centrally.* *2. The allocation sequence was sequentially numbered and preserved in sealed envelope which was retained by the independent statistician.* *3. In addition, coded drug containers were provided to the trial site".* • *Blinding*: **LOW RISK** - Blinded study, "*randomized, double-blind, placebo-controlled trial".* • *Attrition:* **LOW RISK** – 68 of 72 randomised patients were analyzed. ○ 1 patient from each of the ivermectin+doxycycline and placebo arms and 2 from the 5-day ivermectin arm withdrew their consent. ○ Risk assessed as low for the outcomes: Time to viral negative conversion; WHO score 7 and above (D28); adverse events and serious adverse events. • *Measurement of the outcome:* **LOW RISK** - Blinded outcome assessor (risk assessed as low for the outcomes: Time to viral negative conversion; serious adverse events

[3] Ahmed S, Karim MM, Ross AG, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis. 2020 Dec 2;103:214-216. https://dx.doi.org/10.1016/j.ijid.2020.11.191

						• *Selection of the reported results*: **MODERATE RISK** - The protocol and statistical analysis plan were not available. The registry was available. But, data on all outcomes except time to viral negative conversion were requested from the authors. ○ Unclear whether the result was selected from multiple outcome measurements or analyses of the data and if the trial was analyzed as pre-specified. ○ Results for mortality (D28); incidence of viral negative conversion (D7); WHO score 7 and above (D28); adverse events; serious adverse events risk assessed as low analyzed as pre-specified and not selected from multiple outcome measurements or analyses of the data. ○ Risk assessed to be some concerns for time to viral negative conversion, as was not pre-specified in the registry and unclear whether the outcome was selected from multiple outcome measurements or analyses of the data. • Authors conclude that *"A concentration dependent antiviral activity of oral high dose IVM was identified in this pilot trial at a dosing regimen that was well tolerated. Large trials with clinical endpoints are necessary to determine the clinical utility of IVM in COVID-19".*

• **IVERMECTIN vs LIPONAVIR/RITONAVIR – 1 RCT**						
Citation	**Study design**	**Population**	**Intervention vs Comparator**	**Outcomes**	**Effect sizes**	**Comments**
Babalola et al,[4] Ivermectin shows clinical benefits in mild to moderate Covid19 disease: A randomised controlled double blind dose response study in Lagos. MedRxiv, 6 January 2021 https://www.medrxiv.org/content/10.1101/2021.01.05.21249131v1	RCT, parallel, double-blinded, dose-response, single-center (Lagos University Teaching Hospital, Nigeria) Phase 3 study Follow-up duration: 14 days	Sample size: n=63 (21/study gp – randomised 1:1:1) Disease severity: Mild: 57 Moderate: 3 None required ventilator; 5 needed intranasal oxygen (3 in the ivermectin, IV 12mg arm and 2 in the control arm)	*Intervention (s):* **Gp A:** Ivermectin 6 mg, IV every 84 hrs for 2 consecutive weeks; n=21 **Gp B:** Ivermectin 12 mg, IV every 84 hrs for 2 consecutive weeks; n=21	**Primary outcome(s):** • Viral RNA load (measured using quantitative branched DNA (bDNA), reverse transcriptase-polymerase chain reaction (RT-PCR), & qualitative transcription-mediated amplification at baseline and 1, 2, 4, 7, 10, 12, 14 days) –	**Primary outcome(s):** *Mean days-to- negative PCR:* • **Gp A:** Ivermectin 6mg IV = 6.0 (95% CI 4.61 to 7.38) • **Gp A:** Ivermectin 12mg IV = 4.65 (95%CI 3.15 to 6.15) • **Gp C:** Control (LPV/r) oral = 9.15 (95%CI 5.68 to 12.62)	• Data extracted from preprint, trial registry and protocol. • *"..a proof of concept (PoC) randomized, double blind placebo controlled, dose response, parallel group study of IV efficacy in RT - PCR proven COVID 19 positive patients".* • Target sample size specified in the registry and protocol was achieved. • Conflicting information between preprint and protocol: ○ In the preprint, no placebo is described clearly (mentioned in the abstract); patients in the control arm received LPV/r, which was not allowed for

[4] Babalola OE, Bode CO, Ajayi AA *et al*, Ivermectin shows clinical benefits in mild to moderate Covid19 disease: A randomised controlled double blind dose response study in Lagos. MedRxiv, 6 January 2021. https://www.medrxiv.org/content/10.1101/2021.01.05.21249131v1

Clinical trial registration: ISRCTN40302986 http://www.isrctn.com/ISRCTN40302986	Funding: Rachel Eye Center, Lagos University Teaching Hospital Declarations: No conflicts of interest reported	Characteristics of participants: Mean age 44.1years (range:20-82 years). 43(68%) males Inclusion criteria: COVID 19 PCR proven positive patients, who gave informed, written consent to participate in the study, and were either asymptomatic or had mild/moderate symptoms Exclusion criteria: COVID 19 negative patients, patients who had COVID pneumonia or requiring ventilator therapy, renal failure, thromboembolic complications, or unconscious by reduced Glasgow Coma Scale	*Control:* **Gp C:** LPV/r, oral daily for 2 consecutive weeks; n=20 *(dosing not provided)* *Supplemental medicines:* Zinc, vitamin C, vitamin D, azithromycin; and as required – dexamethasone and enoxaparin The total duration of follow up will be about 4 weeks after dosing in the first instance but long-term follow-up will continue as the clinical situation dictates.	*reported in registry but not in the preprint* **Secondary outcome(s):** *Measured on days 0, 2, 4, 7, 10, 12, 14:* • Body temperature measured using infrared temperature sensor • Heart Rate measured using a pulse oximeter device • Respiratory rate measured using respiratory movement method • PaO2 measured using pulse oximeter • Symptoms especially: Anosmia/cacosmia, cough frequency, intensity, dyspnea, nausea, vomiting, diarrhoea, abdominal pain, blood in stool or vomit, dysuria, urine colour, frothiness, chest pain, palpitations, tiredness, lassitude, dyspnea on exertion headache, as reported by the patient, and change in consciousness level (Glasgow Coma Scale)	Faster viral clearance was seen in ivermectin group, which was dose-dependent. **Secondary outcome(s):** *Change fm day 7-baseline (unless otherwise stated)* Ivermectin (Gp A/GpB) vs control: • Platelet count (000/ml): 20.05 vs -64.00; Mean Difference (MD) 84.06 (95% CI 5.56 to 162.55; p=0.0369 • SpO2 %: 0.125 vs -1.444; MD 1.56 (95% CI -0.85 to - 3.99); p 0.0975 (change fm day 1 -2) • Platelet count: 20.05 vs -64.00; MD 84.06 (95% CI 5.56 to 162.55); p= 0.0369 ○ Platelet count increase was inversely correlated to days to negative PCR (r = -0.52, p = 0.005). No SAEs reported.	patients in the Ivermectin arms. In the protocol and registry, patients in the control arm were to receive an inactive placebo. The protocol also describes the administration of lopinavir/ritonavir to those in the control arm. As a result of lopinavir/ritonavir not being allowed for patients in the ivermectin arms, this treatment difference not only plausibly affected outcomes, but also compromised the blinding of physicians and study personnel. Furthermore, the number of tablets given to the patients would also likely reveal the treatment assignment to patients, since 2 tablets were given to those in the 3mg ivermectin group and 4 tablets to those in the 12mg group. • Well matched groups but 12 mg arm slightly younger but not statistically significant and more baseline comorbid hypertension in control arm, whilst comorbid diabetes only in treatment arms. • Baseline Ct values for EN and N genes was lower for ivermectin group compared to control, suggesting that the viral load was lower. Viral load was included as the primary outcome. • Only a few patients were administered dexamethasone (Gp A:1 patient; Gp B:1 patient; Gp C: 2 patients). **Risk of bias assessment: Overall – MODERATE RISK** • *Randomisation*: **MODERATE RISK –** ○ Protocol: *"A statistician not directly involved in the analysis of the study results will prepare the folded paper. The schedule will be provided to the pharmacist and sealed envelopes containing the treatment allocation to assign to each participant. Participants will be expected to pick a folded paper out of 60 folded papers which gives them an equal chance of belonging to any of three arms"* - allocation sequence random. Unclear allocation concealment (i.e., unclear if opaque envelopes and if sequential). ○ Preprint: No information on randomization procedure. • *Deviations from intervention*: **MODERATE RISK –** ○ Preprint: *"We conducted a translational proof of concept (PoC) randomized, double blind placebo controlled dose response trial"; "The study was a proof of concept (PoC), double blind, randomized controlled trial"* ○ Protocol: "*This is designed as a double-blind trial. The tablets for the three arms of the study will look alike and labeled ABC"; "The 3mg tablets will be used meaning those to receive 6mg will have 2 tablets and those to receive 12mg will have 4 tablets"; "With*

						blinding, the drugs will be labeled as assigned by the statistician. The data will be entered against the label of the drug being taken. The name of the drug will only be revealed at the end of the study after data has been collated." ○ Conflicting information between the preprint and protocol regarding the control/ placebo. ○ Despite being a double-blind trial, patients could have been aware of the treatment assignment due to the number of tablets given. LPV/r not administered to patients in treatment arms and this treatment difference likely compromised the blinding of physicians and study personnel. ○ No participant cross-over. ○ Only co-administration of corticosteroids were reported (balanced between groups); but there was no information on administration of other co-interventions. ○ ITT analysis as per protocol. • *Attrition:* **LOW RISK** - 140 randomised/140 analyzed • *Measurement of the outcome:* **LOW RISK** - Unclear blinding; no information on blinding of outcome assessor; but risk assessed to be low for the outcomes: Mortality, time to viral negative conversion. • *Selection of the reported results:* **LOW RISK** - The protocol, statistical analysis plan and registry were available. ○ Mortality was not an outcome pre-specified in the protocol or registry but should be reported even if not planned. ○ Time to viral negative conversion was pre-specified as reported. ○ Results were not selected from multiple outcome measurements or analyses of the data. ○ Trial analyzed as pre-specified.

• **IVERMECTIN vs HYDROXYCHLOROQUINE – 3 RCTs**						
Citation	**Study design**	**Population**	**Intervention vs Comparator**	**Outcomes**	**Effect sizes**	**Comments**
Elgazzar et al.[5] Efficacy and Safety of Ivermectin for Treatment and prophylaxis of COVID-19 Pandemic. Research Square 28 Dec 2020.	Preprint publication retracted, as trial data fraudulent.					

[5] Elgazzar A, Hany B, Youssef SA *et al*. Efficacy and Safety of Ivermectin for Treatment and prophylaxis of COVID-19 Pandemic. Research Square 28 Dec 2020. https://doi.org/10.21203/rs.3.rs-100956/v3

https://doi.org/10.21203/rs.3.rs-100956/v3 Clinical trial registration: NCT04668469						
Beltran-Gonzalez et al., 2021[6]. Efficacy and safety of Ivermectin and Hydroxychloroquine in patients with severe COVID-19. A randomized controlled trial. MedRxiv, 23 February 2021. https://www.medrxiv.org/content/10.1101/2021.02.18.21252037v1 Clinical trial registration: NCT04391127	RCT, blinded, single centre (Mexico) Phase 3 study Follow-up duration (days): not clear Funding: Public/non profit (Aguascalienes State Health Institute) Declarations: None	Sample size: n=106 (n_1=36/ n_2=37/ n_3=33) Disease severity: Hospitalised patients Patient characteristics: Mean age: 53 years 66 (62%) males Inclusion criteria: 16 to 90 years; hospitalized; positive RT-PCR for SARS-CoV-2 by nasal and oropharyngeal swabbing; pneumonia, diagnosed by X-ray or CT scan, with a pattern suggesting involvement due to coronavirus; recent hypoxemic respiratory failure or acute clinical deterioration of pre-existing lung or heart disease. Exclusion Criteria: Required high oxygen volumes (face mask > 10 L/ min); had predictors of a poor response to high-flow oxygen nasal prong therapy ; required mechanical ventilation	Intervention: Ivermectin (n_1=36) Control: Placebo (n_2=37) Treatment 2: Hydroxychloroquine (n_3=33) Concomitant medicines: Not reported.	**Primary outcome(s):** *In the report* Not reported In the registry: • Mean days of hospital stay at 3 months • Rate of Respiratory deterioration, requirement of invasive mechanical ventilation or dead, at 3 months Mean of oxygenation findex delta, at 3 months	**Primary outcome(s):** Ivermectin vs control vs HCQ: • *Average hospital stay: days (IQR):* ○ 6 (4 to 11) vs 5 (4 to 7) vs 7 (3 to 9), p=0.43 • *Respiratory deterioration/death (n):* ○ 8 (22.2%) vs 9 (24.3%) vs 6 (18.1%), p=0.83 • *Death (n):* ○ 5 (13.8%) vs 6 (16.25)% vs 2 (6%), p=0.42	• Pre-print article and trial registry was used in data extraction and assessment of risk of bias (Neither study protocol nor statistical analysis plan was available). • Inclusion criteria in registry and the pre-print article differ slightly - pre-print article also included hypoxemic respiratory failure or acute clinical deterioration of pre-existing lung or heart disease. • Some pre-stated primary (i.e., mean of oxygenation index delta) and secondary (i.e., mean time to negative PCR) outcomes were not reported. • Patients considered at high risk of development of QT interval prolongation due to hydroxychloroquine were only randomized to the ivermectin or placebo arms. • The trial was terminated due to a reduction in eligible participants. As a result, the target sample size was not achieved. **Risk of bias assessment: Overall – MODERATE RISK** • *Randomisation*: **MODERATE RISK** - Allocation sequence random, but allocation sequence concealment unclear. • *Deviations from intervention:* **LOW RISK –** double-blinded study. • *Attrition:* **LOW RISK –** 106/106 patients analyzed. • *Measurement of the outcome:* **LOW RISK -** Blinded study (outcome assessor). • *Selection of the reported results:* **MODERATE RISK** ○ Only the trial registry was available. ○ Outcomes not pre-specified in the registry ○ No information on whether the result was selected from multiple outcome measurements or analyses of the data. ○ Risk assessed to be some concerns for the outcomes: mortality (D28) and clinical improvement (D28). • Authors concluded that, *"In non-critical hospitalized patients with COVID-19 pneumonia, neither ivermectin nor hydroxychloroquine decreases the number of in-hospital days, respiratory deterioration, or deaths".*

[6] Beltran Gonzalez JL, González Gámez M, Mendoza Enciso EA, et al. Efficacy and safety of Ivermectin and Hydroxychloroquine in patients with severe COVID-19. A randomized controlled trial. MedRxiv, 23 February 2021. https://www.medrxiv.org/content/10.1101/2021.02.18.21252037v1

Galan L et al, 2021[7]. Phase 2 randomized study on chloroquine, hydroxyl-chloroquine or ivermectin in hospitalized patients with severe manifestations of SARS-CoV-2 infection. Pathogens and Global Health, 8 March 2021. https://www.tandfonline.com/doi/full/10.1080/20477724.2021.1890887 Clinical trial registration: RBR-8h7q82	RCT , double-blinded, single-center (Brazil) Phase 2 study Follow-up duration: 90 days Funding: Public/non profit (Universidade Federal de Roraima) Declarations: None	Sample size: n=168 (n_1=53, n_2=54, n_3=61) Disease severity: Unclear Patient characteristics: Mean age: 53.2 years 95 male s (57%) Inclusion criteria: Laboratory test confirming SARS-CoV-2 infection (serologic IgM or rt-PCR); hospitalized with a clinical, epidemiological, and radiological picture compatible with COVID-19; > 18 years; severe disease characterized by one of the following: dyspnea, tachypnea (>30 bpm), peripheral oxygen saturation <93% (pulse oximeter evaluation), PaO2/FiO2 ratio <300, or infiltrate pulmonary>50% of the parenchyma seen on chest tomography or chest radiography. Exclusion criteria: < 18 years; indigenous people; patients not fluent in Portuguese; unable to understand the objectives and methods of the study; critically ill patients not accompanied by legal representatives; those who reject participation in the study; cardiac arrhythmia that include prolongation of the QT interval; previous use of medicines surveyed for > 24 h.	*Intervention:* • Ivermectin (n_1=53) *Control 1:* • Hydroxychloro-quine (n_2=54) *Control 2:* • Chloroquine (n_3=61) *Concomitant medicines:* Corticosteroids, anticoagulants or antibiotics	**Primary outcome(s):** Not reported in the report, but listed in the register as: • Need for supplemental oxygen, • Need for invasive ventilation, • Need for admission to the intensive care unit (ICU)	**Primary outcome(s):** HCQ vs Chloroquine vs Ivermectin • *Oxygen supplementation*: ○ 90.2% vs 88.5% vs 88.4%, ns • *Need for invasive ventilation:* ○ 21.1% vs 20.6% vs 23.5%, ns • *ICU admission:* ○ 21.1% vs 22.4% vs 26.0%, ns Other outcome(s): • *Mortality:* ○ 22.2% vs 21.3% vs 23.0% , ns	• The prospective trial registry was available. There were no differences between the published article and the registry in population or interventions. • The study achieved its target sample size. • No study protocol or statistical analysis plan was available. • A phase 2 study. • High number of exclusions (61%), mostly due to previous use of investigated medications before hospitalisations. **Risk of bias assessment: Overall – MODERATE RISK** • *Randomisation*: **LOW RISK** – *"An electronically generated randomization list was prepared by an independent statistician. This randomization list linked the participant in chronological order of inclusion to the numbered treatment bottle, blindly. A non-blinded pharmacist was responsible to assign the intervention. The bottles were numbered, and they contained an equal number of tablets, equally arranged in blister sheet with the daily intake schedule"* - Allocation sequence concealment and allocation concealment appears sufficient. • *Deviations from intervention*: **LOW RISK –** Double blinded study. ○ Anticoagulants and corticosteroids administered to all 3 study group, but no detailed information on antibiotics or biologics. ○ ITT analysis • *Attrition:* **LOW RISK** - 168 randomised/168 analyzed • *Measurement of the outcome:* **MODERATE RISK –** Double-blinded study, but unclear whether outcome assessor was blinded - protocol and statistical plan not available for further review. • *Selection of the reported results:* **MODERATE RISK –** Primary outcomes not clearly described in the report, but described in the register. The protocol and statistical analysis plan were not available for further review. Authors concluded that, *"Although CQ, HCQ or ivermectin revealed a favorable safety profile, the tested drugs do not reduce the need for supplemental oxygen, ICU admission, invasive ventilation or death, in patients hospitalized with a severe form of COVID-19".*

[7] Galan LEB, Santos NMD, Asato MS, *et al*. Phase 2 randomized study on chloroquine, hydroxychloroquine or ivermectin in hospitalized patients with severe manifestations of SARS-CoV-2 infection. Pathog Glob Health. 2021 Jun;115(4):235-242. https://pubmed.ncbi.nlm.nih.gov/33682640/

• IVERMECTIN+DOXYCYCLINE vs HYDROXYCHLOROQUINE+AZITHROMYCIN – 1 RCT						
Citation	**Study design**	**Population**	**Intervention vs Comparator**	**Outcomes**	**Effect sizes**	**Comments**
Chowdhury et al. [8]A comparative study on Ivermectin- Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients. EJMO, 2021 https://ejmo.org/10.14744/ejmo.2021.16263/ Clinical trial registration NCT04434144	RCT, single centre (health complex in Bangladesh; though registered as an observational study on clinicaltrials.gov. Study phase not reported, as registered as an observational study in trial registry Follow-up duration (days): 35 Funding: No specific funding Declarations: None	Sample size: n=125 (ivermectin+ doxycyline gp: n=63; HCQ+azithromycin gp n=62) Enrolled patients treated as outpatients. Disease severity: Mild Characteristics of participants: Mean age: 33.8 years 90 males Inclusion criteria: SARS-CoV-2 infection diagnosed by RT PCR with/without symptom(s) at a health complex; ≥95% oxygen saturation (pulse oximeter measurement); normal or near-normal chest radiograph in patients with respiratory symptoms Exclusion criteria: Unstable comorbid conditions (bronchial asthma, COPD, ischemic heart disease, uncontrolled diabetes mellitus, advanced renal and hepatic disease, carcinoma); hospitalised and Immuno-compromised patients	*Intervention:* • Ivermectin + doxycycline (200 mcg/kg/100 mg) • Co-Intervention: Standard care • Duration : Once-off+10 day *Control:* • HCQ + azithromycin (200 mg/500 mg) • Duration: 10 days+5 days *Standard of care:* Not reported and symptomatic treatment for fever, headache, cough, myalgia, etc provided to all, details not provided.	**Primary outcome(s):** A negative PCR and resolution of symptoms. Adverse events.	**Primary outcome(s):** Ivermectin+doxycycline group vs HCQ+azithromycin: • *Negative PCR for SARS-CoV-2*: Ivermectin + doxycycline gp (100%) at a mean of 8.93 days (8 to 13days) *vs* of HCQ+azithromycin gp (96.36%; 54/56) at a mean of 9.33 days (5 to 15 days); p= 0.2314 • *Resolution of symptoms*; Mean duration of symptomatic recovery was 5.93days (5 to 10 days) vs 6.99days (4 to 12 days), p=0.071. • *Adverse events:* ○ Possible ADRs: 31.67% vs 46.43% ○ Ivermectin + doxycycline gp: lethargy in 14(23.3%), nausea in 11(18.3%), and occasional vertigo in 7(11.66%) ○ HCQ+azithromycin gp: 13(23.21%) mild blurring of vision and headache; 22(39.2%) increased lethargy and dizziness, 10(17.85%) occasional palpitation, and 9(16.07%) nausea and vomiting.	• Study registered as an observational single center study, retrospectively after enrollment was already completed (NCT04434144). However, methodology describes a RCT. • Study information including study results are available as pre-print format and in the trial registry. • Outcomes not registered in the registry were reported in the article. • There is no change from the trial registration in the intervention and control treatments. • Results submitted to ClinicalTrials.gov by the sponsor or investigator is not posted, pending quality control review for apparent errors, deficiencies, or inconsistencies (results returned to investigator 19 August 2020). • Baseline comorbidities of patients not provided for; to determine confounding. • New signals of harm[26] associated with chloroquine-azithromycin in the control group may have contributed to the apparent benefit of ivermectin. • New signals of harm associated with chloroquine-azithromycin in the control group may have contributed to the apparent benefit of ivermectin. **Risk of bias assessment: Overall – HIGH RISK** • *Randomisation*: **HIGH RISK** – Allocation of study participants probably not concealed as "*Randomization was done using an odd-even methodology applied to registration numbers, in a consecutive fashion in a 1:1 ratio, by the hospital registration office".* • *Deviations from intervention*: **MODERATE RISK** - Unblinded study. ○ No participant cross-over. ○ No information reported on co-interventions (i.e. antivirals, corticosteroids, biologics). ○ Patients analyzed according to intervention assignment. • *Attrition:* **LOW RISK** – 116/ 125 patients analyzed. ○ 7% missing data - 5%(3/63) in ivermectin + doxycycline arm; 10%(6/62) in HCQ + azithromycin arm, due to LTFU.

[8] Chowdurry ATMM, Shahbaz M, Karim MR *et al*. A Comparative Study on Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin Therapy on COVID-19 Patients. EJMO 2021;5(1):63–70. https://ejmo.org/10.14744/ejmo.2021.16263/

						○ Risk assessed to be low for the outcomes: Incidence of viral negative conversion, adverse events. • *Measurement of the outcome:* **MODERATE RISK -** Unblinded study. ○ Risk assessed to be low for the outcome: Incidence of viral negative conversion, an observer-reported outcome not involving judgement. ○ Risk assessed to be some concerns for the outcome: Adverse events - contains clinically-reported events which can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic. • *Selection of the reported results:* **LOW RISK -** trial registry available, protocol and statistical analysis plan not available. ○ Reported outcomes in the preprint were aligned with the trial registry. ○ Trial probably analyzed as pre-specified. ○ Risk assessed to be low for the outcomes: Incidence of viral negative conversion, adverse events. Authors concluded that, *"Further study is required on a larger scale with an increase in the duration of Ivermectin treatment".*

ADDENDUM B: APPRAISAL OF THE SYSTEMATIC REVIEW BY HILL *et al*.[8] ON USE OF IVERMECTIN FOR TREATMENT AND PREVENTION OF COVID-19

Date: 18 June 2021

Evaluating the methodological quality of the Hill et al (2020)[8] systematic review and preliminary meta-analysis – AMSTAR 2 tool (Shea 2017[9])

No.	Criteria	Yes/ Partial Yes/ No
1	Research questions and inclusion criteria for the review included the components of PICO	Yes
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	Partial yes
3	Review authors explained selection of the study designs for inclusion in the review	Yes
4*	Review authors used a comprehensive literature search strategy	Partial yes
5	Review authors perform study selection and data extraction in duplicate	No
6	Review authors provided a list of excluded studies and justify the exclusions	No
7*	Review authors described the included studies in adequate detail	No
8	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	Partial yes
9*	Review authors reported on the sources of funding for the studies included in the review?	No
10	For meta-analyses, review authors used appropriate methods for statistical combination of results	No
11*	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	No
12	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	No
13*	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	No
14	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	No
15*	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Yes**

** Critical domains*

***Review authors declared no conflict of interest, but the authors for this preliminary meta-analysis also included the investigators from the studies included in this review – and there may be reservations regarding the independence of this analysis.*

Rating overall confidence in the results of the review

• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

• *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

OVERALL ASSESMENT: Critically low

Rationale: Four flaws in critical domains (#7, 9, 11, 13)

Conclusion: The AMSTAR assessment suggests that the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

Small study effects: Pooling of small studies with sparse numbers in the endpoints is vulnerable to incomplete data acquisition. Publication bias is one contributor to this, where small negative studies remain unpublished, but similarly powered studies with positive results are identified by search strategies. For the ivermectin mortality endpoint, a funnel plot illustrates all the reported studies lying on one side of null, pointing to the potential of 'missing' studies on the other side. (With small numbers of studies, this technique may also produce this pattern by chance.)

[9] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

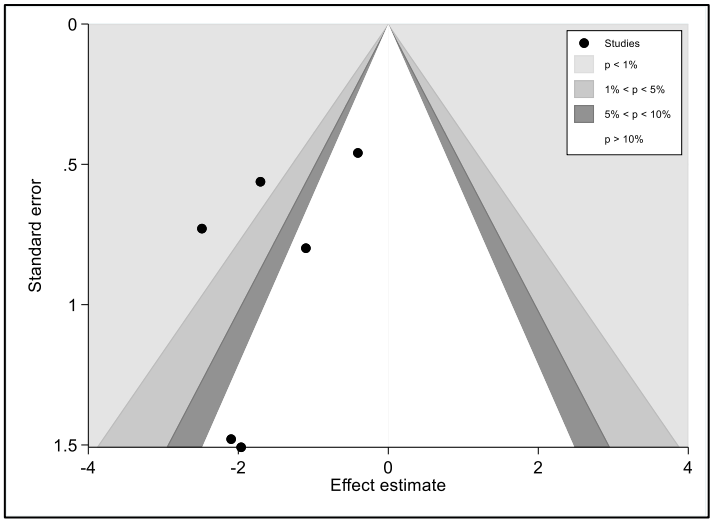

Figure 1: Funnel plot of RCTs included in the meta-analysis by Hill *et al*.

Heterogeneity: Statistical heterogeneity can be estimated, but with small numbers of studies and patients in endpoints, the techniques are insensitive. Clinical heterogeneity is more subjective, but the studies included in Hill's meta-analysis had dissimilar population selection criteria, and mortality in the control group varied from less than 2% to 30%. Clinical effects may still be consistent across different study populations, but in combining small studies, the influence of unmeasured variables is of concern.

This study had therefore not been included in the review.

ADDENDUM C: APPRAISAL OF THE SYSTEMATIC REVIEW BY BYRANT *et al*[9]. ON USE OF IVERMECTIN FOR TREATMENT AND PREVENTION OF COVID-19

Date: 2 July 2021

Overview:

Rosenthal[10] on meta-analysis: combining apples and oranges makes sense if your goal is to produce a fruit salad.

In the last few decades, reaching conclusions about the efficacy and safety of medical interventions has moved from reliance on expert opinion and narrative reviews to a more transparent and formalized collaborative process of searching, quality appraisal, and synthesis of all relevant evidence. The conclusions reached are critically dependent on unbiased adherence to all steps, and on the quality of the underlying evidence. A critical final process entails transforming conclusions about strength and direction of evidence into clinically useful recommendations, often by groups independent of the review process. A key principle is that decisions can and should be made using the best available evidence, even when this is imperfect.

Considerable time and effort goes into conducting high quality systematic reviews, and when done well, they are a valuable resource. Like any human endeavor, they still have vulnerabilities. The more obvious issues can be detected using quality appraisal tools such as AMSTAR2 which evaluate whether a review meets the main reporting requirements, however the tool does not address the content of the review. There are other more subtle ways in which bias can occur rendering results less reliable. The rigour of the Cochrane process, and formal collaborative use of software such as RevMan[11] are specifically designed to address many of these issues.

Issues which may render the conclusions of a systematic review unreliable include undeclared intellectual conflicts of interest (where reviewers may not approach a research question entirely objectively), inconsistent rigour in risk of bias assessment (where studies supporting a particular viewpoint may be reviewed more leniently), inclusion of studies of low reliability, and issues with meta-analytic methods. This last point is particularly problematic in an era where software allows almost instantaneous iterative data analysis, which makes it difficult to determine whether a submitted data analysis plan is truly based on *a priori* scientific considerations or *post hoc* adoption of the model found to yield preferred results. Other issues in meta-analytic technique, such as the handling of studies that observed no outcome events in either arm, weighting methodologies, and the handling of heterogeneity and potential small study effects, engender vigorous debate, as in many other evolving areas of statistics.

The Bryant *et al.* review raises a number of concerning methodological issues. Some of these are described in more detail below, but the key issue is that no matter how rigorous and detailed the review and statistical analysis, the evidence pool is currently too small for reliable decision making. This review focuses only on mortality as findings for all other endpoints were listed by the authors as based on low or very low quality evidence. The mortality endpoint was the only endpoint considered by the authors to be based on moderate quality evidence. For mild or moderate COVID-19, despite 11 trials, information on mortality was only available in five trials with a total of 13 deaths, and for severe COVID-19, on 5 trials, with a total of 539 patients, 200 of which were contributed by Elgazzar *et al*.'s study - reviewed below. The Naiee *et al.* study, in COVID-19 of undifferentiated severity, was not included in these two subgroup analyses, but contributed to the total analysis.

Authors of reviews can draw their own conclusions from their analysis, but the aim of scientific scrutiny is to allow others to look at the same information and potentially reach different interpretations. A responsible interpretation is not that this data is irrefutable proof of efficacy, but simply that information of this quality renders efficacy conclusions highly vulnerable to change as further data becomes available.

A few specific points:

1. The data search section states that that Kory and Malik were consulted as 'experts in the field'. As members of Front Line COVID-19 Critical Care Alliance (FLCCC), a group with previously demonstrated views supporting ivermectin use, they have taken a partisan and potentially biased, position as evident in their own narrative review in the same journal. There seems little evidence of a search for experts who might hold equivocal or negative views about ivermectin.

[10] Introduction to Meta-Analysis. Michael Borenstein, L. V. Hedges, J. P. T. Higgins and H. R. Rothstein © 2009 John Wiley & Sons, Ltd. ISBN: 978-0-470-05724-7 Chapter 40

[11] Review Manager (RevMan) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020.

2. The table of included studies contain several situations where 'prepublication data/manuscript in progress/ obtained via email' was stated as the origin of the data. From the perspective of scientific method, this information is not currently available for public scrutiny and has not completed a peer-review process. (Some information listed in this way in the table is now published.) This leaves the reader with little opportunity to check validity. Including all available evidence is, in principal, a good practice. However the authors specifically state that they have not considered these data as adding potential risk of bias or decreasing certainty in the findings, a position that that would not be consistently held by reviewers.
3. The Elgazzar *et al.* study remains in the analysis despite some other studies at high risk of bias having been removed. Elgazzar *et al*. studied the effect of ivermectin vs hydroxychloroquine in a 6-arm trial that included both patients and contacts. The two arms that received ivermectin had deaths in 0/100 and 2/100, whereas those that received hydroxychloroquine had deaths in 4/100 and 20/100. Both arms received azithromycin as part of standard of care, so effectively the comparison was ivermectin and azithromycin versus hydroxychloroquine and azithromycin. Both of the latter agents are associated with QT prolongation. In addition, allocation concealment was unclear and randomisation procedures were not described in sufficient detail, it is unclear whether any blinding occurred, and the outcomes reported in the preprint differ from those in the trial registry. Studies with an active comparator may reduce apparent efficacy if the comparator is also active against the disease, or may flatter the trial medication if the comparator causes harm. Combining such studies with studies having a placebo control may introduce uncertainty.
4. A sub-analysis of studies was done removing studies at high risk of bias. This means that the primary analysis contained such studies. It is difficult to reconcile this with a statement that this constitutes moderate quality evidence.
5. The confidence interval for ivermectin's effect on mortality in mild to moderate COVID-19 ranges from 0.06 to 0.94, reflecting the paucity of events (1 death in the intervention arm and 12 in the control, out of 11 included studies, 6 of which (55%) observed no deaths in either arm). The confidence interval for use in severe COVID-19 includes 1, and thus is not statistically significant, even when including data from Elgazzar *et al.* Most of the other endpoints were contributed by the Fonseca study, one of only three considered at low risk of bias. Overall, one of the challenges with reviews of small trials is recognizing the 'fragility' of the results. When the number of deaths is so low, shifting one or two events from the ivermectin group to the control would change the result substantially from statistically significant to not[12].
6. Another way of demonstrating the frailty of the evidence is using the authors' own study assessments. In the main forest plot, they include trials they indicate are at high risk of bias. In sensitivity analysis, these are removed. Another sensitivity analysis removes trials with active comparators. If both are done together (removing studies at high risk of bias and those with active comparators), no studies on severe COVID-19 remain, and the three remaining studies in mild COVID-19 together with the single study on mixed severity have a total of 24 events, with two thirds of the weight then provided by the Niaee *et al*. study.

Conclusion

Using evidence in clinical decision making requires meticulous attention to assessing both the quality of individual trials and how the information is pooled in a meta-analysis. Trials can be considered potentially misleading if their design, conduct, or reporting raise concerns; there is sound empiric evidence that failure to exercise caution in the face of these warning quality signs makes it highly likely that any conclusions drawn will be overturned by subsequent evidence.

As Guyatt *et al*.[6] stated, "Early trials addressing a particular question will, particularly if small, substantially overestimate the treatment effect. A systematic review of these early trials will also generate a spuriously large effect estimate. These considerations argue for skepticism regarding evidence summaries that generate apparent benefits, or harms, of therapy with what appear to be satisfactorily narrow CIs on the basis of small trials with relatively few events."

The Bryant *et al.* review contains data not yet available for peer review, includes in the primary analysis studies labeled by the authors themselves as at high risk of bias, and found low or very low quality evidence for all endpoints except mortality. After removal of trials at high risk of bias or with active comparators, the few remaining studies, with very few total events, are insufficient to provide reliable information. The sensible and responsible conclusion from this review is not that ivermectin is likely to be effective, but rather that there is currently insufficient evidence to justify recommending widespread use of this agent.

[12] Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. 2011;64(12):1283-93.

Evaluating the methodological quality of the Bryant et al (2021)[9] systematic review and meta-analysis – AMSTAR 2 tool (Shea 2017[6])

No.	Criteria	Yes/ Partial Yes/ No	Comment
1	Research questions and inclusion criteria for the review included the components of PICO	Yes	There is no PICO in the review report.
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	No	Inclusion/exclusion criteria omitted, study protocol not registered.
3	Review authors explained selection of the study designs for inclusion in the review	No	No clear explanation provided why RCTs, Quasi-RCTs and Cluster RCTs were selected.
4*	Review authors used a comprehensive literature search strategy	Yes	-
5	Review authors perform study selection in duplicate	Yes	-
6	Review authors perform data extraction in duplicate	Yes	-
7*	Review authors provided a list of excluded studies and justify the exclusions	No	Excluded studies were merely referenced (ref# *47-63*), stating that they were not RCTs. However, ref# 47, Elgazzar et al is included in the analysis.
8	Review authors described the included studies in adequate detail	Partial yes	-
9*	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	Partial yes	-
10	Review authors reported on the sources of funding for the studies included in the review?	Yes	-
11*	For meta-analyses, review authors used appropriate methods for statistical combination of results	No	The authors did not sufficiently justify combining the data in the meta- analysis, and why the Quasi-RCTs were not categorized as non-RCTs.
12	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	Yes	-
13*	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	No	This was not adequately reported in the interpretation and discussion of the results of the review.
14	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Partial yes	-
15*	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	Yes	-
16	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	No	Report states that *"authors have no conflicts of interest to declare"*, but have participated in initiatives promoting ivermectin.

** Critical domains = 2, 4, 7, 9, 11, 13, 15*

Rating overall confidence in the results of the review

• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

• *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

OVERALL ASSESMENT: Critically low

Rationale: Four flaws in critical domains (#2, 7, 11, 13)

Conclusion: The AMSTAR assessment suggests that the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

REFERENCES:

[1] South African Department of Health. Rapid evidence summary of ivermectin for COVID-19, 20 Dec 2020. http://www.health.gov.za/covid-19-rapid-reviews/

[2] South African Medicines Formulary, 2016 edition.

[3] Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*. Antiviral Res. 2020;178:104787. https://www.ncbi.nlm.nih.gov/pubmed/32251768

[4] Chaccour C, Hammann F, Ramon-Garcia S, Rabinovich NR. Ivermectin and COVID-19: keeping rigor in times of urgency. Am J Trop Med Hyg. 2020;102(6):1156-1157. https://www.ncbi.nlm.nih.gov/pubmed/32314704

[5] Guzzo CA, Furtek CI, Porras AG, *et al*. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. J Clin Pharmacol. 2002;42(10):1122-1133. https://www.ncbi.nlm.nih.gov/pubmed/12362927

[6] Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008. https://pubmed.ncbi.nlm.nih.gov/28935701/

[7] Popp_M, Stegemann_M, Metzendorf_M-I, et al. Ivermectin for preventing and treating COVID-19. Cochrane Database of Systematic Reviews 2021, Issue 7. Art. No.: CD015017. doi: 10.1002/14651858.CD015017.pub2

[8] Hill A, on behalf of the International Ivermectin Project Team. Preliminary meta-analysis of randomized trials of ivermectin to treat SARSCoV-2 infection, Red Square, 19 January 2021. https://www.researchsquare.com/article/rs-148845/v1

[9] Bryant A, Lawrie TA, Dowswell T, et al. Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines. Am J Ther. 2021 Jun 17. https://pubmed.ncbi.nlm.nih.gov/34145166/