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Rapid review of ivermectin for COVID 19

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**South African National Department of Health
Evidence summary
Component: COVID-19**

EVIDENCE SUMMARY

Date: 21 December 2020

Research question: Should ivermectin be used for managing COVID-19 patients compared to no intervention or an alternative intervention?

Key findings

- ➔ The overall quality of the randomized trials involving ivermectin in COVID-19 patients is extremely low.
- ➔ From the available randomised control trial evidence, ivermectin is not superior to placebo in terms of viral load reduction or clinical progression. There is no evidence from randomised control trials for any reduction in mortality.
- ➔ Eligible patients with COVID-19 in South Africa should be considered for enrolment in relevant therapeutic trials.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative (strong)	We suggest not to use the option or to use the alternative (conditional)	We suggest using either the option or the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
		X			
<p>Recommendation: The Sub-committee suggests that ivermectin not be used for adults with COVID-19. Eligible patients with COVID-19 in South Africa should be considered for enrolment in relevant therapeutic trials.</p> <p>Rationale: The evidence of efficacy and safety is very uncertain at this point. Early phase studies were of very low quality and do not demonstrate any clear evidence of efficacy or safety.</p> <p>Level of Evidence: Very low certainty evidence</p> <p>Review indicator: Evidence of safety and efficacy that is sufficient to change the recommendation.</p>					

Therapeutic Guidelines Sub-Committee for COVID-19: Andy Parrish (chair), Gary Reubenson (vice-chair), Marc Blockman, Karen Cohen,), Andy Gray, Tamara Kreda, Renee De Waal, Gary Maartens, Jeremy Nel, Helen Rees.

Background: The National Department of Health requested an advisory on ivermectin for COVID-19, following global interest in this medicine in the lay press. Wide dissemination of the results of a retrospective cohort study¹ through social media is promoting use of ivermectin as a repurposed medicine for hospitalised COVID-19 adult patients.

The observational study results published in preprint format in June 2020 suggested a mortality-benefit of single dose ivermectin of 200 mcg/kg (n=173; with a repeat dose administered in 7 patients on day 7) compared to usual care (n=103), with an aOR 0.27 (95% CI 0.09 to 0.85, p=0.03) for mortality. The mortality benefit appeared to be limited to patients with severe disease, but there was no difference between the cohorts for length of hospital stay or the rates of extubation. Concomitant hydroxychloroquine with/without azithromycin was administered to patients in both treatment arms. All retrospective analyses are at risk of bias with confounding, but this analysis also presented the following limitations – it is unclear whether concomitant medicines contributed to the mortality benefit or whether patients received other interventions such as corticosteroids or remdesivir; information on oxygen saturation and radiographic findings is lacking; timing of therapeutic interventions was not standardised resulting in timing bias; no virologic assessments determining ivermectin’s effect on viral load, was performed.

Furthermore, there is uncertainty regarding the appropriate dose of ivermectin. Ivermectin inhibits the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in cell cultures². Ivermectin is a host directed agent and has broad-spectrum activity against many RNA viruses *in vitro*. Host directed agents could reduce viral loads by inhibiting the key cellular process that the virus hijacks to enhance infection and suppress host response. 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^{3,4}. Ivermectin is not approved globally, as an antiviral agent and neither is the product registered in South Africa for human consumption, but may be accessed via S21 application. Common side effects associated with ivermectin are diarrhoea, nausea, abdominal pain, fatigue, somnolence and dizziness⁵.

The Front-Line Covid-19 Critical Care Alliance’s narrative review⁶ and meta-analysis by Hill⁷ are duly noted, but currently there is insufficient data available for review and evidence synthesis.

International Guidelines recommend against the use of ivermectin for the treatment of COVID-19, except in a clinical trial setting^{8,9}.

Therefore, randomised controlled trial (RCT) evidence from COVID-19 living maps were reviewed to determine the safety and efficacy of ivermectin in COVID-19.

EVIDENCE REVIEW:

Living meta-analyses:

• Ivermectin vs Standard care/Placebo

A Cochrane supported meta-analysis¹⁰ of two RCTs (n=107) showed that there remains significant uncertainty whether ivermectin is more effective and safer than standard care or placebo in treating patients with mild or moderate COVID-19 (see Table 1 for characteristics of the included studies).

Krolewecki et al⁹ performed a pilot study in Argentina to assess the antiviral activity of intravenous ivermectin in hospitalised adult COVID-19 patients with mild or moderate disease (stages 3-5 on WHO’s ordinal scale). Forty-five patients were enrolled in total – 30 in the ivermectin group and 15 in the control group, and given ivermectin at a dose of 0.6mg/kg for 5 days or standard care. The standard care for symptomatic treatment included antipyretics, cough suppressants and oral doxycycline to treat possible community-acquired pneumonia; whilst those on other antibiotics or hydroxychloroquine were excluded from the study. The trial showed no significant proportionate difference in viral load reduction from baseline to day 5 between control and ivermectin groups (no figures are given by the authors for this however; the authors state only that “Viral load reduction between baseline and day-5 was ...similar between groups”). When the results were re-analysed in relation to measured ivermectin levels, there appeared to be a greater proportionate reduction in the viral load for the small subgroup of patients (n=9) with a C_{max} of >160 ng/mL. However, this finding is at substantial risk of bias, due to the 160 ng/mL threshold being chosen in a *post hoc* fashion “based on the observed antiviral response [in the trial’s results]” rather than it being prespecified. In addition, the subgroup’s

size was extremely small (n=9) and this subgroup had a baseline viral load substantially lower than its comparator groups, making valid comparisons across subgroups extremely difficult. The trial was blinded only to assessors (single-blinded), and co-administered medications were not adequately reported.

Podder et al.¹⁰ conducted an open-label randomised control trial at a health facility in Bangladesh. Adult COVID-19 patients were given a single dose of oral ivermectin 0.2 mg/kg, with the endpoints being time to symptom resolution from symptom onset and from study enrolment. Sixty-two patients were enrolled – 30 patients in the control arm and 32 in the intervention arm. There were no statistically significant differences in time to symptom resolution (measured either from symptom onset or study enrolment date), nor rates of PCR positivity at day 10. Significant limitations to this trial included failure to conceal allocation during “randomisation”, missing outcome data and the fact that the study was unblinded.

Results:

There is insufficient data and uncertainty as to whether ivermectin increases or decreases mortality, adverse or serious adverse events, rate of viral clearance or time to clinical recovery; noting the serious risk of bias and very serious imprecision.

Disease progression was only reported in the Argentinian pilot study – there were no significant clinical differences between groups: RR 1.66 (95% CI 0.07 to 38.31) – see Figure 1.

Serious adverse events (SAEs): Similarly only reported in the Argentinian pilot study, with a single serious adverse event (SAE) of hyponatraemia in a patient in the ivermectin group: RR 1.66 (95% CI 0.07 to 38.31) – see Figure 2.

Figure 1: Forest plot of disease progression (Krolewiecki et al, 2020)

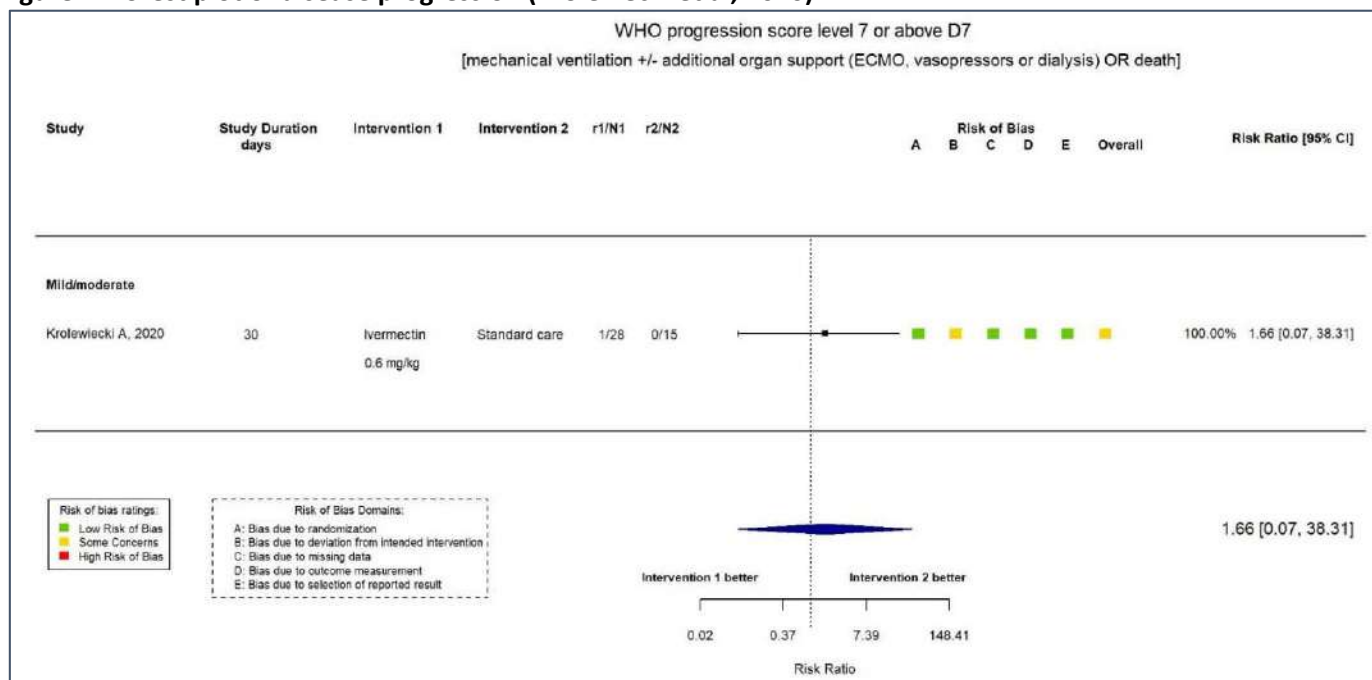
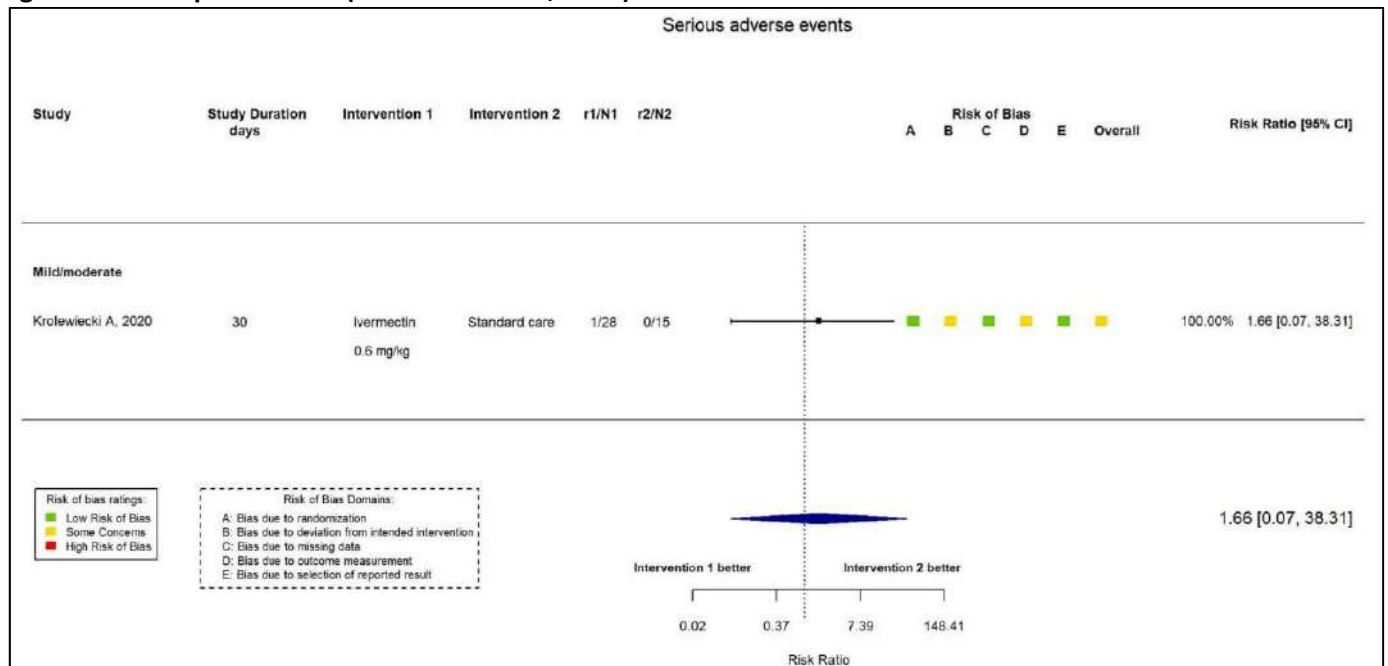


Figure 2: Forest plot of SAEs (Krolewecki et al, 2020)



• **Ivermectin + doxycycline vs Standard care/Placebo**

A living review¹¹ of one single centre blinded phase 3 trial in Bangladesh (n=400)¹² where adult study participants with mild to moderate COVID-19 were randomised to either single dose ivermectin (12mg) with 5 days of 100 mg doxycycline 12 hourly or placebo and followed up over 30 days to determine the effect of ivermectin with doxycycline on clinical improvement at day 7 and day 14. Standard of care was administered as indicated to all patients (i.e. paracetamol, vitamin D, oxygen, low molecular weight heparin and dexamethasone). The study results were posted on the clinicaltrials.gov registry and have not been published yet in peer-reviewed format. The risk of bias of the study is high due to missing outcome data (only data from 363/400 participants were analysed due to 21% loss to follow-up). In addition, the effects of ivermectin cannot be disentangled from those due to doxycycline and dexamethasone, since patients were randomised to both or neither, and all apparently received the corticosteroid. Furthermore, the additive effects of the numerous additional drugs given as standard of care cannot be assessed, nor is it possible to ascertain whether the administration of drugs differed across the two arms.

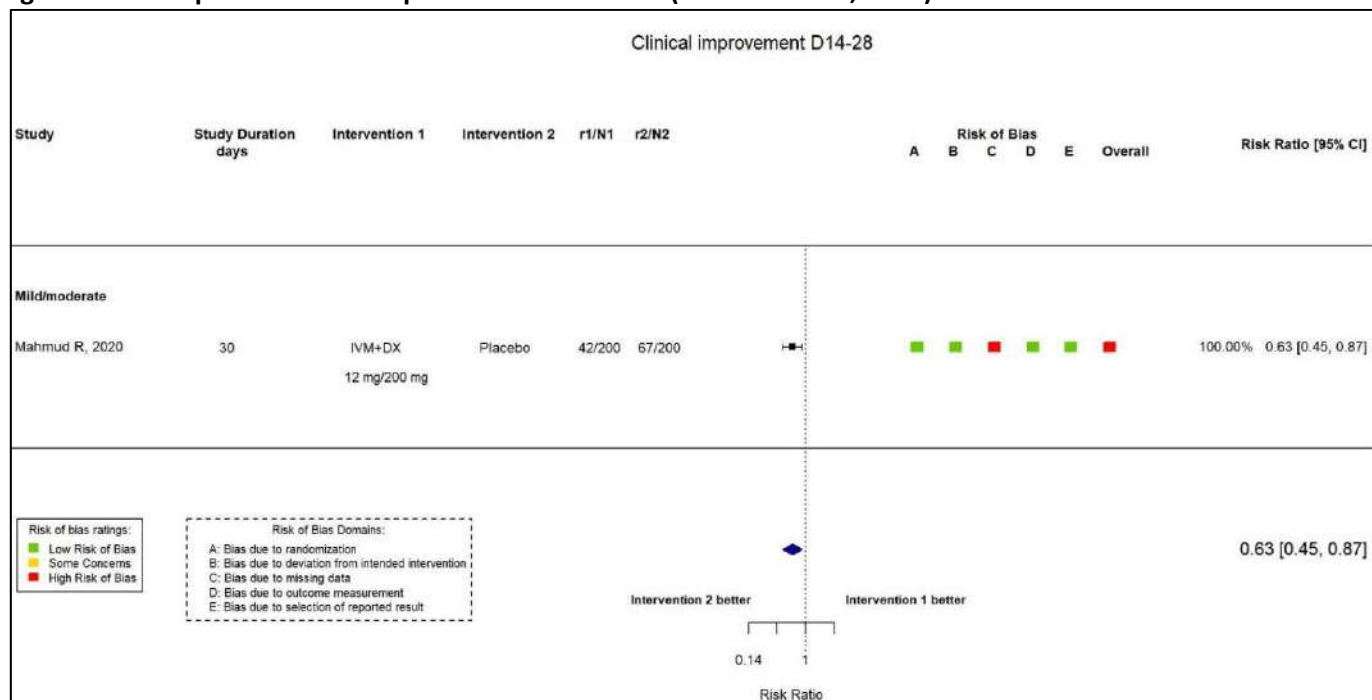
Results:

Primary outcomes (ivermectin + doxycycline vs placebo):

- Clinical improvement at D7: RR 1.39 (95% CI 1.12 to 1.71)
- Clinical improvement at D14-28: RR 0.63 (95% CI 0.45 to 0.87) – see figure 4.

There is insufficient data and high uncertainty whether ivermectin has a beneficial effect on the disease course over usual care in mild to moderate COVID-19 cases.

Figure 4: Forest plot of clinical improvement at D14-28 (Mahmud et al, 2020)



• **Ivermectin + doxycycline vs azithromycin + hydroxychloroquine**

A living review¹³ of one single centre RCT in Bangladesh (n=125)¹⁴ to determine time to negative PCR and time to full symptomatic recovery of 200mcg single dose ivermectin with doxycycline 100mg 12 hourly for 10 days (n=63) compared to azithromycin (500 mg daily for 5 days) with hydroxychloroquine (400mg daily for 10 days), (n=62) amongst adult patients with confirmed mild COVID-19. Patients were followed up for 35 days. Medication for symptomatic treatment for fever, headache, cough, myalgia, administered as required (but details not reported). High risk of bias was evident, due to probable lack of allocation concealment (relying on an odd-even randomisation methodology in a consecutive fashion in a 1:1 ratio) and the study being unblinded, resulting in possible selection and reporting bias. Most importantly, the effects of ivermectin are impossible to assess from this trial design. Any superiority due to the ivermectin + doxycycline arm could be due to ivermectin, or doxycycline, or a combination of the two, or due to deleterious effects from azithromycin or hydroxychloroquine or a combination of the two.

Results:

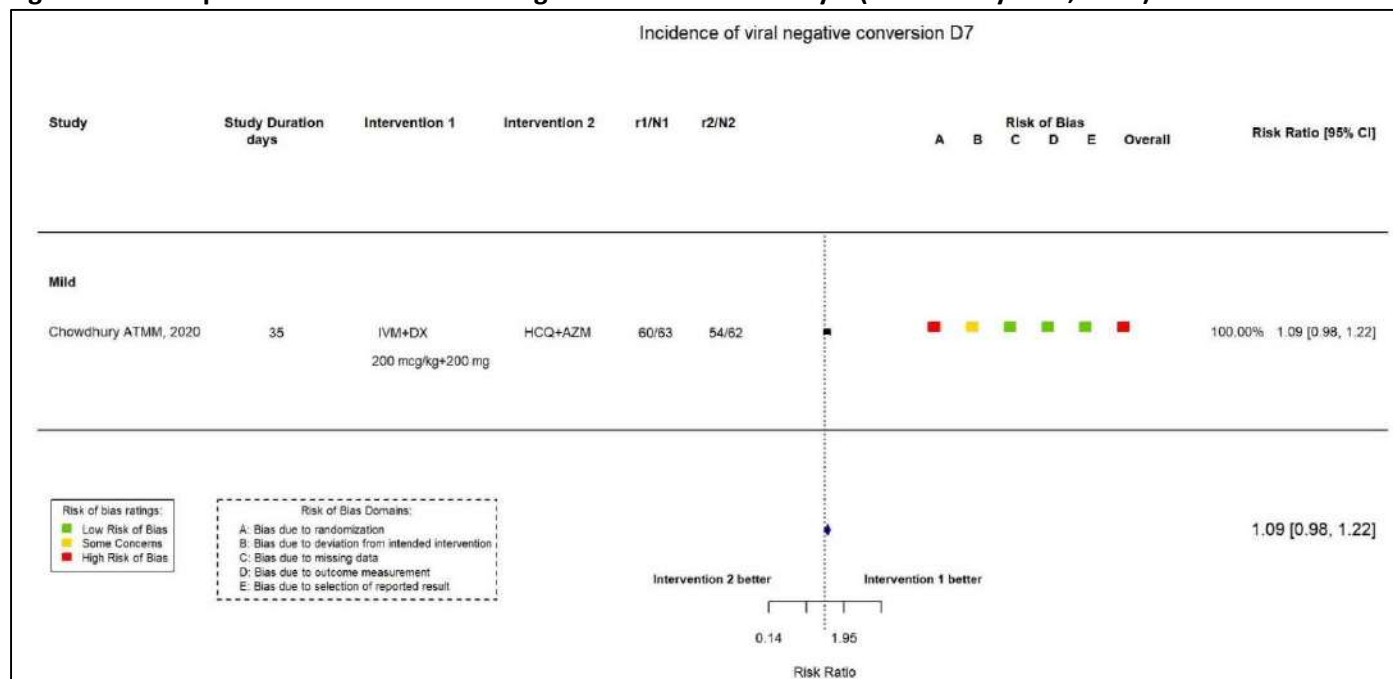
Ivermectin + doxycycline group vs azithromycin + hydroxychloroquine groups:

- Time to negative PCR for SARS-CoV-2: Mean of 8.93 days (100%) vs 6.99 days (96.36%); p=0.0231.
- Time to symptomatic recovery: Mean of 5.93days vs mean of 9.33days; p=0.071.

(See figure 5, below)

The Ivermectin + doxycycline combination showed a trend toward superiority over the azithromycin + hydroxychloroquine combined treatment for the difference in time to becoming symptom-free and the difference in time to negative PCR, but this was not statistically significant. However, additional limitations include the small sample size, and confounders such as severity of disease, unknown comorbidity.

Figure 5: Forest plot of incidence of viral negative conversion at day 7 (Chowdhury et al, 2020)



Ongoing clinical trials:

As of 21 December 2020, 37 clinical trials investigating the role of ivermectin (as various dosage forms) for the treatment and prophylactic management of COVID-19 are registered on <https://clinicaltrials.gov/> - studies [NCT04668469](#), [NCT04646109](#), [NCT04591600](#), [NCT04446104](#), [NCT04422561](#), [NCT04391127](#), [NCT04390022](#) and [NCT04343092](#) have been completed, but study results have yet to be published.

CONCLUSION:

There is limited evidence for the repurposing of ivermectin for the treatment of COVID-19 – two small early phase RCTs of ivermectin vs placebo constitute the bulk of the available evidence. Each had significant methodological shortcomings, but despite this, no clear benefit to ivermectin was seen with respect to viral load reduction or improvement in clinical outcomes. The effective concentrations and the relevance of *in vitro* concentrations against SARS Cov-2 needs to be determined and if this concentration is likely achieved *in vivo* with few adverse events.

The evidence does not support the use of ivermectin as an antiviral agent, except in a clinical trial setting.

Reviewer(s): Ms TD Leong, Dr J Nel, Dr H Dawood.

Declaration of interests: TDL (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), HD (Department of Internal Medicine, Infectious Diseases Unit, Grey's Hospital, University of KwaZulu-Natal), have no interests to declare in respect of ivermectin for COVID-19.

Table 1: Characteristics of completed RCTs included in the living review

i) Ivermectin vs placebo/standard of care

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
Podder et al, 2020 (Study not registered on trial registries)	RCT (single center in Bangladesh) Follow up: 10 days	Adult patients ≥ 18 years of age with confirmed mild to moderate COVID-19 (n=62) Mild: n=50; Moderate: n=12 Patients taking other antimicrobials or hydroxychloroquine were excluded Mean age : not reported 44 males NB: No a priori sample size determination was reported	Ivermectin (200 mcg/kg) as a single dose (n=32) vs placebo (n=30) Co-Intervention: Standard care that included symptomatic (antipyretics, cough suppressants, and capsule doxycycline (100 mg every 12 hours for seven days) to treat possible community-acquired pneumonia)	Time needed for resolution of fever, cough, shortness of breath and finally, full recovery from all symptoms and the negative result of repeat RT-PCR on D10.	<u>Ivermectin vs placebo:</u> <ul style="list-style-type: none"> • Total recovery time from the onset of symptoms to complete resolution of symptoms: 10.09 ± 3.236 days vs 11.50 ± 5.32 days (95% CI -0.860 to 3.627, p>0.05) • The mean recovery time after enrolment: 5.31 ± 2.48 days, vs 6.33 ± 4.23 days (95% CI – 0.766 to 2.808, p> 0.05). • Results of negative repeat RT- PCR at D10: 90% vs intervention 95%, p>0.05). 	<ul style="list-style-type: none"> • Preprint • ITT analysis; but > 5% missing outcome data • Only the published article was used in data extraction and risk of bias assessment as no study registry, protocol or analysis plan was available. No a priori sample size determination was reported. Patients were allocated to treatment groups using a quasi-randomisation method, based on odd and even registration numbers in a consecutive fashion. After allocation, a sizeable proportion of patients was not included in the analysis due to the prior duration of symptoms and it is unclear whether this was a post hoc decision. • Risk of bias assessed as HIGH: <ul style="list-style-type: none"> ○ Randomisation: Quasi-randomization. A consecutive odd-even allocation suggests probably no allocation concealment: HIGH ○ Deviations from intervention: Unblinded, open-label study; co-administered medicines not adequately reported - MODERATE ○ Missing outcome data: Data unavailable for >5% of study population.– HIGH ○ Measurement of the outcome: LOW ○ Selection of the reported results: The protocol, statistical analysis plan and registry were not available. Risk assessed to be some concerns for the outcome: Incidence of viral negative conversion.: MODERATE
Krolewiecki et al, 2020 NCT04381884	RCT (multi-center in Argentina) Follow up: 35 days	Hospitalised stage 3 to 5 COVID-19 ≥ 18 years, not requiring ICU admission with symptom onset ≤5 days at recruitment (No concomitant hydroxychloroquine, chloroquine, lopinavir and azithromycin; except after the 1 st week of the study); contraceptives were permitted, as required. n=45	Ivermectin 0.6 mg/kg (n=30) vs placebo (n=15) Co-Intervention: All patients in both groups received standard of care for 5 days Mean age : 40.9 years 25 males	<ul style="list-style-type: none"> • Viral load reduction in respiratory secretions at day-5. • Adverse events and serious adverse events 	<ul style="list-style-type: none"> • <i>Viral load reduction</i>: no difference in between groups with no other significant clinical differences between groups: RR 1.66 (95% CI 0.07 to 38.31) – see figure 1. • <i>Serious adverse events (SAEs)</i>: a single serious adverse event (SAE) of hyponatraemia in a patient in the ivermectin group: RR 1.66 (95% CI 0.07 to 38.31) – see figure 2. 	<ul style="list-style-type: none"> • Preprint • No information is provided on what is included in standard care. There is little information on what adverse events were experienced. • Subgroups of ivermectin levels were decided post hoc after observing the viral load data, rather than being prespecified. • Risk of bias assessed as MODERATE <ul style="list-style-type: none"> ○ Randomisation: LOW ○ Deviations from intervention: Single-blinded study; Co-administered medicines not adequately reported - MODERATE ○ Missing outcome data: LOW

		<p><i>Exclusions:</i> Immunomodulators within 30 days of recruitment; pregnancy, breast feeding; poorly controlled comorbidities; allergies to ivermectin</p>	<p>Mild: n=42; Moderate: n=3</p>			<ul style="list-style-type: none"> ○ Measurement of the outcome: Unblinded study for outcomes of interest - MODERATE ○ Selection of the reported results: LOW
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ii) Ivermectin + doxycycline vs Standard care/placebo

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
<p>Muhammed et al, 2020 NCT04523831</p>	<p>RCT (single center in Bangladesh)</p>	<p>Adult patients ≥18 years, with confirmed COVID-19 (mild-moderate); n =400</p> <p>Mean age : 39.6 235 males</p>	<p>Ivermectin+doxycycline (n=200) vs Placebo (n=200)</p> <p>Standard of care was administered as indicated to all patients (i.e. paracetamol, vitamin D, oxygen, low molecular weight heparin and dexamethasone)</p>	<p><u>Primary outcomes</u></p> <ul style="list-style-type: none"> • number of participants with early clinical recovery at d7 • number of participants with late clinical recovery at d14 	<p><u>Primary outcomes (ivermectin + doxycycline vs placebo):</u></p> <ul style="list-style-type: none"> • Clinical improvement at D7: 111/200 vs 80/200; RR 1.39 (95% CI 1.12 to 1.71) – see figure 3. • Clinical improvement at D14-28: 42/200 vs 67/200 RR 0.63 (95% CI 0.45 to 0.87) – see figure 4. 	<ul style="list-style-type: none"> • Study results, protocol and statistical analysis posted on clinical trial registry – not published in peer-review format yet. • Can't disentangle effects of ivermectin from those of doxycycline. • Multiple drugs given as standard of care to both arms – unclear if unequally distributed across arms. • Double-blinded RCT • ITT analysis • Study underpowered to detect a mortality benefit • Risk of bias assessed as HIGH: <ul style="list-style-type: none"> ○ Randomisation: LOW ○ Deviations from intervention: LOW ○ Missing outcome data: 21% of participants randomized not included in analysis – HIGH ○ Measurement of the outcome: LOW ○ Selection of the reported results: LOW

i) Ivermectin + doxycycline vs azithromycin + hydroxychloroquine

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
<p>Chowdhury et al, 2020 NCT04434144</p>	<p>RCT (single center in Bangladesh)</p> <p>Follow up: 35 days</p>	<p>Adult patients ≥16 years, with mild COVID-19 disease; mean age: 33.8 years (n=125)</p> <p>90 males</p>	<p>Ivermectin + doxycycline (n=63) vs azithromycin + hydroxychloroquine (n=62)</p> <p><i>Concomitant medicines:</i> Symptomatic treatment for fever, headache, cough, myalgia, administered</p>	<ul style="list-style-type: none"> • Time to negative PCR for SARS-CoV-2. • Time to symptomatic recovery. 	<p>Ivermectin + doxycycline group vs azithromycin + hydroxychloroquine groups:</p> <ul style="list-style-type: none"> • Time to negative PCR for SARS-CoV-2: Mean of 8.93 days (100%) vs 6.99 days (96.36%); p=0.231 • Time to symptomatic recovery: Mean of 5.93days vs mean of 9.33days, p=0.071 	<ul style="list-style-type: none"> • Preprint • Cannot assess effects of ivermectin alone – any benefits to ivermectin/doxycycline arm may be due to ivermectin, or doxycycline, or due to adverse outcomes from azithromycin or hydroxychloroquine arms. • Patient comorbidities not reported. • 95% confidence intervals not reported, statistical significance provided by p-values. • Unblinded, small single centre study • Patient relevant clinical outcomes (e.g. mortality, disease progression etc) not reported.

			as required (but details not reported)			<ul style="list-style-type: none"> • Risk of bias assessed as HIGH: <ul style="list-style-type: none"> ○ Randomisation: Allocation concealment probably not concealed - HIGH ○ Deviations from intervention: Unblinded, details of concomitant medication not reported: MODERATE ○ Missing outcome data: LOW ○ Measurement of the outcome: Unblinded - MODERATE ○ Selection of the reported results: LOW
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