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: 18 June 2021 *(update of the initial rapid review of 25 January 2021)*

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

Key findings

- We conducted a review of clinical studies, including those published in preprint format, regarding use of ivermectin with or without other medicines for patients with COVID-19.
- The available randomised controlled trials have considerable heterogeneity with respect to interventions and comparator groups, and many suffer from significant methodological limitations that limit the confidence in any conclusions that can be drawn.
- The current evidence for the use of ivermectin in COVID-19 does not suggest any clear benefits with respect to mortality, clinical improvement, or viral clearance.

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 routinely 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 clinical or virological benefits.
Level of Evidence: RCTs of varying methodological quality with very modest numbers of events in key endpoints
Review indicator: New high quality evidence of a clinically relevant benefit

(Refer to Appendix 5 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 9 June 2021, the International Clinical Trials Registry Platform (ICTRP) lists 68 registered RCTs of ivermectin for the treatment of COVID-19 that are still in progress/ not completed (https://covid-nma.com/dataviz/).

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

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. Wide dissemination of the results of a retrospective cohort study[1] using ivermectin as a repurposed medicine for hospitalised COVID-19 adult patients is being promoted through social media. A rapid evidence summary which was released on 21 December 2020[2] 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 hence this comprehensive evidence review was undertaken and will be updated as required.

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[3].

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.[4] 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.[5, 6]

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[7] 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 publication of additional RCT data, 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), Pan American Health Organization: Institution Repository for Information Sharing (https://iris.paho.org/), the Cochrane COVID-19 Study Register (https://covid-19.cochrane.org/), Clinical.trials.gov registry (https://clinicaltrials.gov/) and the Cochrane living syntheses (https://covid-nma.com/) on 26 May 2021. The search strategy is shown in Appendix 1. Screening of records and data extraction was conducted by two reviewers (TL, JN), with resolution of disagreements through discussion, or, if required, the third reviewer (HD) was consulted. Relevant records were extracted in a narrative table of results (Table 1) and excluded studies were listed with rationale for exclusion (Appendix 3) by one reviewer and checked by a second reviewer reviewers.

We included Randomised controlled trials (RCTs) that were in line with our PICO (Population, Intervention, Comparators, Outcomes) framework (see below), and systematic reviews of RCTS. Phase 1 studies have been excluded, as these studies only investigate safety and dosage. Ideally, larger phase 3 studies that investigate efficacy, effectiveness and safety; and phase 4 post-marketing surveillance studies are preferred for evidence syntheses.

Data from RCTs of day 7 viral clearance with and without ivermectin were pooled to assess publication bias of the RCTs, using STATA version 17 [8] – see appendix 2.

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 or active comparators.

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 and randomised controlled trials. Non-randomised studies, case series and single case reports were excluded. No restrictions were made for language.

RESULTS

Results of the search: A systematic search of the electronic databases produced 266 records of which 15 were duplicates and 107 records were not the required study design. 88 records were incomplete (study in process/study results not reported). Of the remaining 57 records that were screened, 37 records were excluded, 12 records were previously reviewed and 9 additional records were selected for inclusion in the updated evidence synthesis. Three records were re-reviewed, as peer-reviewed publications were now available for these previous preprints. The Cochrane supported COVID-NMA initiative of living systematic reviews of COVID-19 studies provided relevant information for this evidence synthesis (https://covid-nma.com/the-project/ living evidence). As the report was being finalised, an additional RCT was identified on the COVID-NMA platform, and was included in this review.

Excluded studies: Refer to Appendix 3 for a list of the excluded studies and supporting rationale for exclusion.

The excluded meta-analysis by Hill et al.[9] was previously evaluated using AMSTAR 2 tool[10] in the initial rapid review, dated 12 January 2021 (that suggested that the review had several critical flaws and should not be relied on to provide an accurate and comprehensive summary of the available studies). See Appendix 4.

Included studies: 10 additional RCTs were included in the updated analysis (22 RCTs in total):

- 15 compared ivermectin to placebo or standard of care [11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25]
- 3 compared ivermectin + doxycycline to placebo or standard of care[26, 27, 17]
- 1 compared ivermectin to lopinavir/ritonavir [28]
- 1 compared ivermectin + doxycycline to azithromycin + hydroxychloroquine[29]
- 3 compared ivermectin to hydroxychloroquine (including standard of care)[30, 31, 32]

Details of the individual trials are available in table 1.

Effects of the intervention:
The RCTs were heterogeneous with respect to the population (outpatients and/or inpatients, with wide ranges of disease severity included), the intervention (ivermectin alone vs ivermectin + doxycycline) and the control (variously: placebo, standard of care, lopinavir/ritonavir, hydroxychloroquine, or azithromycin + hydroxychloroquine). Additionally, the specific ivermectin intervention varied widely. The course duration ranged from a single day to 10 days, the dosing interval ranged from daily to once every 10 days, the number of doses administered ranged from 1 to 5, and the dosage administered on each occasion varied from 6-12mg to 200-600 mcg/kg (i.e. 14-42 mg for a 70 kg patient). Thus, composite measures of effect, such as meta-analyses, should be treated with caution.

Mortality

Ten RCTs reported on mortality in ivermectin compared to placebo; the absolute number of events was small (31 in total across all 9 trials combined). Kirti et al.[13] compared ivermectin (n=57, given as 12mg daily for 2 consecutive days) with placebo (n=58) among adults with "mild" "moderate" disease (as defined by the Indian Ministry of Health). In-hospital mortality, a secondary outcomes, was reported as 0/57 (0%) in the ivermectin group, compared to 4/58 (6.9%) in the control group; this difference was not statistically significant (95% confidence interval for the risk ratio was 0.01-8.15), and the overall risk of bias in this study was assessed as high. There were potentially important differences in comorbidities between the trial arms, including a higher proportion of cancer, chronic kidney disease and ischaemic heart disease in the placebo group. In addition, all patients received numerous other medications as part of standard of care (including corticosteroids, azithromycin, hydroxychloroquine, heparin and tocilizumab) – making drug interactions hard to determine, and the trial was analysed per protocol rather than intention to treat (thereby excluding 3 patients who received ivermectin, one of whom was lost to follow up).

Beltran-Gonzalez et al. conducted a 3-arm study in patients with moderate COVID-19, comparing ivermectin, hydroxychloroquine and placebo, with 106 patients divided approximately equally into the three arms. There were 5/36 deaths in the ivermectin arm, and 6/37 deaths in the placebo arm, again a non-significant difference (RR 0.29-2.56). The trial had several differences between the pre-registered trial and the final publication that were not accounted for, and was assessed as being at moderate risk of bias owing to weaknesses in the randomisation process and the reporting of the trial outcomes.

Niaee et al.[18] conducted a study of ivermectin in patients with mild to severe COVID-19 in 5 hospitals in Iran; it is currently available as a pre-print only. The trial had 6 arms, 4 of which included ivermectin at various doses and frequencies. 30 patients were enrolled in each arm. Mortality was not a pre-specified outcome but was reported in the preprint. Overall mortality between the 2 arms without ivermectin and the 4 arms with ivermectin was 18.3% vs 3.3% (p~0.001). However, 29% of the patients who were included had a negative RT-PCR test (they were included on the basis of a suggestive lung CT). The proportion of PCR-negative patients differed markedly between the non-ivermectin arms (40%-53.3%) and the ivermectin arms (3.3%-30%), raising the significant possibility that many patients in the non-ivermectin arms may not have had COVID-19 at all. Furthermore, owing to different dosing regimens, it is unlikely that either the patients or the study personnel/carers were blinded.

Okumus et al. compared ivermectin to placebo in severely-ill patients in a small (n=66) single-centre study in Turkey. Standard of care, given to both arms, included drugs such as hydroxychloroquine, favipiravir, and azithromycin. Mortality was reported as a secondary outcome, and occurred in 6/30 in the ivermectin arm, compared to 9/30 in the placebo arm. 6 patients in the treatment arm were excluded after the first dose of ivermectin was given, due to the detection of genetic polymorphisms that might affect ivermectin metabolism. No such testing was done on patients in the control arm however. The follow-up for mortality was inconsistent among patients – it stopped at the date when the trial concluded, which was an average of 60 days after randomisation. The causes of death were not reported. In addition, the trial's randomisation procedure and outcome reporting had significant methodological limitations, and the trial was assessed as being at high risk of bias.

Abd-Elsalam et al.'s trial compared ivermectin to placebo in a multi-centre study in Egypt, with both groups being given drugs as per the Egyptian Ministry of Health's standard of care protocols (these included antibiotics, oseltamivir, and steroids). 164 patients were randomised 1:1 between the two arms. There were again substantial methodological concerns with the trial, but there was no significant difference in mortality (the primary endpoint) between the two arms: 3/82 vs 4/82, p=1.00.

The remainder of the trials of ivermectin vs placebo had either a single death (Shahbaznejad et al, López-Medina) or no deaths in either arms (Ahmed, Mohan, Kroleweicki), and were therefore unable to contribute useful mortality information.

Finally, several trials studied ivermectin in other combinations. Mahmud et al.[20] compared a of ivermectin (12mg daily, n=200) plusdoxycycline (100mg 12-hourly, n=200), each given for 5 days, with placebo. Each arm also received the background standard of care, consisting variably of remdesivir, paracetamol, vitamin D, low-molecular weight heparin, and dexamethasone "if indicated". Mortality was reported as a secondary outcome, and was 0/183 in the ivermectin arm vs

3/180 (1.67%) in the placebo arm. This difference was not statistically significant, p=0.25. The risk of bias in this study was again high. Elgazzar et al.[24] 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. As there was no placebo or standard of care treatment arms, it is not possible to determine whether the difference was due to an ivermectin effect or a hydroxychloroquine effect. In addition, the trial's randomisation procedure was not described, it is unclear whether any blinding occurred, and the outcomes reported in the preprint differ from those in the trial registry. Hashim et al.[21] compared the combination of ivermectin and doxycycline to standard of care in 140 mild to critical patients. Mortality in the two groups was 2.9% vs 8.6% respectively, which was not statistically significant (p=0.14). The study was assessed as being at high risk of bias, due in part to it not being blinded to participants or investigators. The trial methodology was poor in numerous respects, including erratic dosing protocols (patients could receive a 3rd dose of ivermectin "if they needed more time to recover"), a large number of co-administered medications that were not equally balanced across the trial arms, disease severity categories that were not defined (resulting in the possibility that baseline disease severity may have differed substantially between trial arms). Critically-ill patients were not enrolled into the control group, as authors were of the opinion that it was unethical not to give such patients ivermectin and doxycycline. Furthermore, as ivermectin was co-administered with doxycycline, it is unclear which of the two drugs any differences could be attributed to, and whether there were synergistic or antagonistic effects between the two.

Change in clinical status

The included studies varied widely in how they assessed and interpreted clinical outcomes apart from mortality. Most trials measured either the proportion of asymptomatic patients at various defined time points, or measured time to resolution of symptoms.

By far the largest trial of the group was conducted by López-Medina et al., in a study of 400 patients with mild or moderate disease in Columbia. Patients were randomised to ivermectin for 5 days vs placebo. The primary endpoint was changed during the trial from a 2-point worsening on the 8-point WHO ordinal scale to time to resolution of symptoms within a 21-day follow-up period. The median time to resolution was 10 days (IQR 9-13) in the ivermectin group vs 12 days (IQR 9-13) in the placebo group – this was not statistically significant (HR 1.07, 95% CI 0.87-1.32, p=0.53). There was also no statistically or clinically significant difference in the proportion of patients whose symptoms had resolved by day 21.

The other trials reporting change in clinical status are reported in table 1. They were all small, and many were of poor quality, suffering from (amongst other limitations), a lack of adequate blinding, subjective and poorly-defined endpoints, a lack of clarity as to how changes in clinical state were measured, and sometimes an active control arm that had the potential for harm. Overall, there was no clear evidence of any benefit with regards to clinical status. The forest plot of clinical improvement at day 28 is representative (see figure 1):

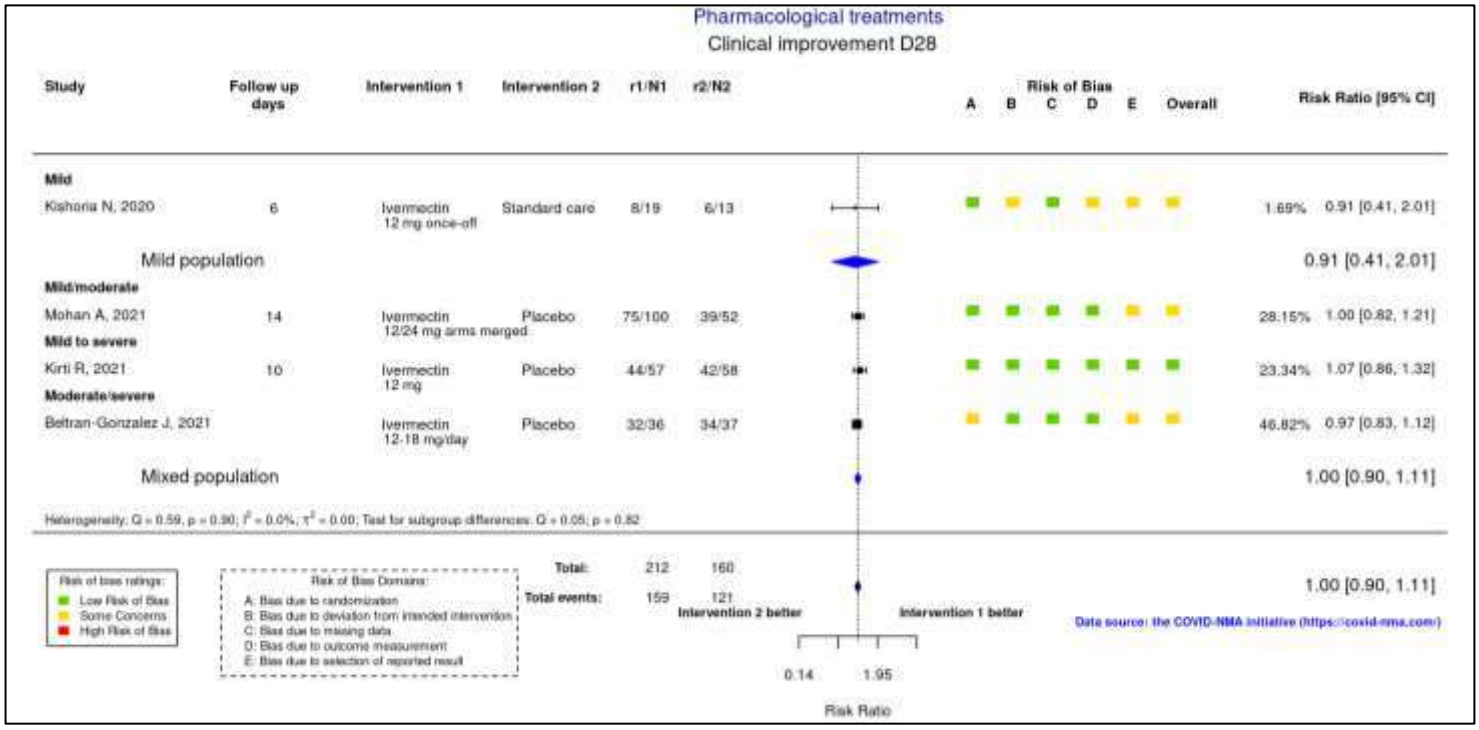


Figure 1: Forest plot comparing ivermectin to placebo/standard of care for clinical improvement at day 28

Changes in viral load

In general, the included RCTs measured changes in viral load either by the proportion of patients with a negative RT-PCR at a particular time point, or by measuring the viral load over time directly. Full details of these trials are available in table 1. Many of these trials again suffered from significant methodological shortcomings. In addition, the assays used in the determination of viral loads and RT-PCR positivity varied substantially across trials, limiting any generalised conclusions.

Eight trials reported the incidence of negative viral RT-PCR at day 7 in studies of ivermectin vs placebo/standard of care; in none of them was there a statistically significant benefit seen with ivermectin administration (see figure 2):

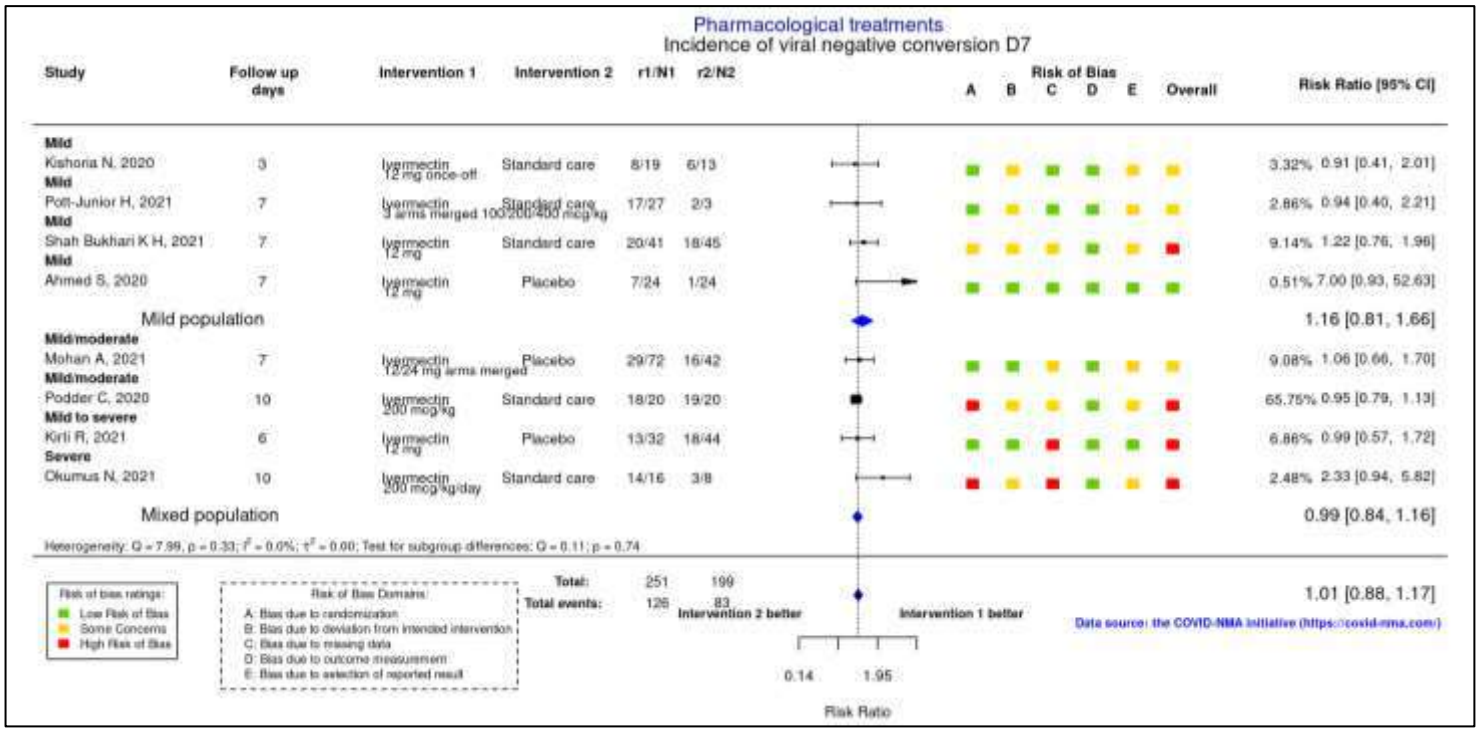


Figure 2: Forest plot comparing ivermectin to placebo/ standard of care for the incidence if viral negative conversion at day 7

Safety

Only a minority of ivermectin RCTs included mention of adverse events. Again, the study by López-Medina provides by far the most data (n=398). The number of patients with ≥1 solicited adverse events was similar between the ivermectin and placebo arms, but adverse events causing treatment discontinuation were more common in the ivermectin arm (7.5% vs 2.5%). Similarly, the number of serious adverse events were numerically higher in the ivermectin arm (9 vs 5). Respiratory failure, acute kidney injury, multiorgan failure and gastrointestinal haemorrhage were all more frequent in the ivermectin arm, though absolute numbers were low.

The studies by Ahmed et al.[17], and Babalola et al.[22] reported no serious adverse events in the trials, although they did not mention less serious adverse events. Chaccour et al.[19] found a similar adverse event rate across trial arms, though there were more patient-days of dizziness and blurred vision in the ivermectin arm. Krolewiecki et al.[16] identified a serious adverse event (hyponatraemia) in 1 patient (3.3%) in the ivermectin arm, and other adverse events possibly/probably related to ivermectin in 9 (30%). The most common adverse event was rash (10%). Mahmud et al.[20] found a serious adverse event (erosive oesophagitis) in 1% of the patients treated with ivermectin + doxycycline, and dyspepsia in 3.8%, though these side-effects are more likely to have been related to doxycycline than to ivermectin. Chowdurry et al.[23] reported possible adverse drug reactions in 32% of patients on the ivermectin + doxycycline arm, including lethargy, nausea and occasional vertigo. It is difficult to clearly separate out ivermectin side effects from doxycycline side effects in studies that combined the two drugs.

CONCLUSION

The current evidence for the use of ivermectin in COVID-19 does not suggest any clear benefits with respect to mortality, clinical improvement, or viral clearance. Many of the trials included have not yet been peer-reviewed. The available 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. These include 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. In addition, trial designs combining ivermectin with doxycycline, or comparing ivermectin to active controls such as azithromycin, hydroxychloroquine and lopinavir/ritonavir, do not allow for ivermectin's effects to be isolated from those of the other drugs (some of which may possibly worsen outcomes and thereby inflate the apparent beneficial effect in the ivermectin arms). The large number of co-administered medications given as background "standard of care" further clouds this issue. 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. Further data from large, well-designed RCTs is needed.

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

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), HD (Infectious diseases, Greys hospital and University of KwaZulu-Natal), AP (Walter Sisulu University) have no interests with regards to ivermectin.

Table 1: Characteristics of included studies

• IVERMECTIN vs PLACEBO/STANDARD OF CARE - 8 RCTs						
Citation	**Study design**	**Population**	**Intervention vs comparator**	**Outcomes**	**Effect sizes**	**Comments**
Kirti R, et al., 2020.[13] Ivermectin as a potential treatment for mild to moderate COVID-19: A double blind randomized placebo-controlled trial. MedRxiv, 9 January 2021 https://www.medrxiv.org/content/10.1101/2021.01.05.21249310v1 Indian Clinical Trials registry: CTRI/2020/08/027225	Parallel, double blind, RCT – single-centre: tertiary care dedicated COVID-19 hospital (India) Study phase not reported, protocol has been requested from investigators Follow-up duration (days): 10 Funding: AIIMS, Patna administration for repeat RT-PCR tests; Ivermectin tablets procured from the learning resource allowance of the PI; Placebo tablets provided by Sun Pharma Pvt. Ltd. Declarations: No conflicts of interest declared.	Sample size: n=115 (ivermectin gp=57; placebo gp=58) Disease severity: Mild (n=88) and moderate (n=24) COVID-19 infected cases; as defined by the Ministry of Health and family welfare guidelines Inclusion criteria: > 18 years admitted with mild to moderate COVID 19 disease (breathlessness and/or hypoxia (saturation 90-94% on room air), respiratory rate ≥ 24/min and no features of severe disease) with no contraindications to ivermectin Male 81 (72.3%) Comorbidities: Hypertension, diabetes, IHD, heart failure, CKD, stroke, COPD, asthma, cancer, other non-specified comorbidities Exclusion criteria: Known allergy/ ADR with ivermectin; unwillingness/unable to provide consent to participate in the study; prior use of ivermectin during the course of this illness; pregnancy and lactation	*Intervention:* • Ivermectin (12mg on day 1; day 2) mcg/kg) *Control:* • Standard care Concomitant medicines: HCQ, steroid, enoxaparin, antibiotics, remdesivir, convalescent plasma, tocilizumab, other medicines	**Primary outcome(s):** A negative RT-PCR report on day 6 **Secondary outcomes:** • Whether or not symptomatic on day 6 • Discharge by day 10# • Admission to ICU • Need for invasive mechanical ventilation • In-hospital mortality *#Discharge criteria: 1) 10 days from the onset of symptoms, 2) Afebrile for three days, 3) Maintaining O_2 saturation >94% without supplemental oxygen for 4 days.*	**Primary outcome(s):** Ivermectin vs standard of care: *A negative RT-PCR report on day 6*: no significant difference between study groups **Secondary outcomes:** Ivermectin vs standard of care: • *Whether or not symptomatic on day 6:* no significant difference between study groups • *Discharge by day 10:* no significant difference between study groups • *Admission to ICU*: no significant difference between study groups • *Need for invasive mechanical ventilation:* no significant difference between study groups • *In-house mortality:* 0.00% (n=0) vs 6.9% (n=4)	• Data extracted and assessed for risk of bias, using the preprint only. The study achieved its stated sample size. • Per protocol analysis (112/115 study participants included in the final analysis). • Baseline demographics reported higher IHD and CKD in the placebo gp (14.0% and 3.6%, respectively) vs ivermectin gp (3.6 % and 1.8%, respectively). • Severe cases not included in the study. • All outcome measures except symptom status on day 6 were objective. • A single repeat RT-PCR was done; thus median time to viral clearance could not be calculated. • Higher doses of ivermectin or ivermectin+doxycycline were not investigated. **Risk of bias assessment: Overall – HIGH RISK** • *Randomisation*: **LOW** to **MODERATE RISK** - Block randomisation. Allocation sequence and concealment – *"allocation table was generated using the Sealed Envelope software. Once a patient had consented to participate in the study, they were allocated an envelope as per the sequence, assigning them to one of the two groups. The person doing the randomisation was not a part of the investigating team. One of these two groups was the intervention group and the other was the placebo group. However, up until the analysis of the data, this information was confined to the pharmacist dispensing the tablets".* ○ Despite randomisation, IHD and CKD was not evenly distributed between groups - higher proportion in the placebo group, which may have overestimated the mortality benefit of ivermectin. • *Deviations from intervention*: **MODERATE RISK** – double-blind study ○ "identical looking placebo tablets" ○ Concomitant administration of HCQ, steroid, enoxaparin, antibiotics, remdesivir, convalescent plasma, tocilizumab, and other medicines reported, generally distributed evenly amongst study groups. Possible confounding effect of concomitant steroids in mild disease, due to mortality harm – "*all patients*

						in the current trial received corticosteroids even though 78.8 % of the patients had only mild disease (table 2). This is because the first dose was prescribed by the doctor on duty in all patients. However, the drug was stopped on the subsequent consultant round in most patients with mild disease". ○ *"..up until the analysis of the data, this information was confined to the pharmacist dispensing the tablets*. Pharmacist dispensed the medicine and ensured blinding. ○ Per protocol analysis • *Attrition:* **HIGH RISK** – 112 of 115 randomised patients were analyzed. ○ Ivermectin gp: 2/58 patients randomized but not included in analysis, as 1 LTFU, 1 excluded from analysis as deviation from study protocol. ○ Placebo gp: 1 patient excluded from analysis as deviation from study protocol. ○ Data available for all or nearly all participants for mortality (D28) and clinical improvement (D28). ○ Data not available for all or nearly participants for viral negative conversion – only 76 patients analyzed for negative viral conversion i.e. 32/57 vs 44/58, and thus risk of bias assessed as high for the outcome: Incidence of viral negative conversion (D7). • .*Measurement of the outcome:* **MODERATE RISK** - Double-blinded study. ○ A conclusive repeat RT-PCR report could not be obtained in 32.1% of the patients. ○ Risk assessed to be low for the outcomes: Mortality (D28). Incidence of viral negative conversion (D7). Clinical improvement (D28). • *Selection of the reported results:* **MODERATE RISK** - The protocol, statistical analysis plan and registry were not available. ○ Risk assessed to be low for the outcomes: incidence of viral negative conversion and clinical improvement – pre-specified outcome measures. ○ Risk assessed to be some concerns for the outcome: mortality (D28), as no timepoint was specified and no information on whether the result was selected from multiple outcome measurements or analyses of the data. Authors conclude that "*Similar but larger studies may be able to give a more definitive answer, especially in relation to the other secondary outcome measures".*
Chachar et al., 2020.[14] Effectiveness of	Open-label; RCT, single centre	Sample size: n=50 (25/study group)	*Intervention:*	**Primary outcome(s):** Clinical response at day 7 –	On follow up at day 7, patients were stratified as asymptomatic and symptomatic:	• Authors stated that, "*our study revealed that after giving Ivermectin, on day 7, 64% patients were*

Ivermectin in SARS-CoV-2/COVID-19 Patients, International journal of sciences, https://www.ijsciences.com/pub/article/2378 Clinical trial registration: NCT04739410	(Fatima Memorial Hospital, Lahore, Pakistan - patients reporting to COVID-19 clinics and outpatient department) Study phase has not been reported Follow-up duration (days): 7 Funding: not reported Declarations: No conflicts of interests declared	Disease severity: mild Inclusion criteria: 18-75 years, RT-PCR confirmed COVID-19 disease, mild disease, can take oral medication and able to adhere to medicine regimen, Mean age: 40.60 ± 17, Males = 31 (62%). Comorbidities: *(case/ intervention gp vs control gp)* -Diabetes mellitus, 11(22%) vs 9(18%); -Hypertension: 7(14%) vs 6(12%); -Obesity: 2(%4) vs 4 (8%). -Cardiovascular disease: 2(4%) vs 2(4%); -Active smokers: 9(18%) vs 6(12%) in control group. Exclusion Criteria: Known severe allergy to Ivermectin; pregnancy, breastfeeding, severe symptoms (likely attributed to cytokine release storm), malignant diseases, CKD, liver cirrhosis (Child class B or C)	• Ivermectin 12mg stat and then 12 mg 12 hours later followed by 12mg 24 hours later. • Conventional symptomatic treatment • Duration: 2 days *Control:* • Conventional symptomatic treatment *Conventional symptomatic treatment:* • Not described/ reported	○ symptom improvement (clinical parameters included fever, cough, sore throat, headache, shortness of breath, lethargy, and fatigue ○ side effects	○ Case/intervention gp: 16/25 (64%) symptomatic ○ Control gp: 15/25 (60%) symptomatic Study didn't show any statistical significant difference between case and control group. **Primary outcome(s):** Ivermectin vs control: ○ Cough was observed more in case group: 24 (48%) 18(36%) (p= 0.049). ○ Fever, myalgias and dyspnea similar in both groups (p= 1.000). ○ Diarrhea more common in control group: 4(8%) vs 17(34 %) (p=0.0001) ○ Vomiting more common in control group: 6(12%) 14(28 %) (p= 0.042) respectively). ○ Loss of taste more common in case group: 15(30%) vs 5(10%) (p= 0.009 ○ Anosmia more common in case group: 15(30%) vs 5(10%) (p=0.0009)	*symptom free (recovery)";* however this is **relative to the control group** that showed a recovery rate of 60%. The small difference was not statistically significant in this small study (n=50). • Sampling technique was convenient sampling as per the inclusion and exclusion criteria. • Control group participants' were older than the case group statistically. • Baseline demographics differed between study groups: diabetes mellitus, hypertension and active smoking more common in the case/intervention compared to the control group. **Risk of bias assessment: Overall – HIGH RISK** • *Randomisation*: **HIGH RISK –** "*Quote: "Patients were allocated randomly to the groups by computer generated number"……."there was randomization but non-blinded and there was no concealment".* Allocation sequence random, but allocation not concealed. • *Deviations from intervention:* **LOW RISK –** Open label study ○ Administration of co-interventions of interest was reported and balanced between arms No participant cross-over. ○ Data were analyzed using ITT analysis. • *Attrition:* **LOW RISK** – all 50 randomised patients were analyzed – ITT analysis. Data available for (>) 95% of population. Risk assessed as low for the outcomes: clinical improvement and adverse events. • *Measurement of the outcome:* **MODERATE RISK -** Assessors were unblinded. ○ Viral negative conversion is an observer-reported outcome not involving judgement. ○ Clinical improvement (defined as becoming asymptomatic), require clinical judgement and could be affected by knowledge of intervention receipt. Also, adverse events and serious adverse events may contain both clinically- and laboratory-detected events. All these outcomes can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic. • *Selection of the reported results:* **MODERATE RISK -** ○ The protocol, statistical analysis plan and registry were available. ○ Results for viral negative conversion, adverse events and serious adverse events were obtained via contact with authors. – risk assessed as low for these

						outcomes as probably analyzed as pre-specified and not selected from multiple outcome measurements. ○ Risk assessed to be some concerns for the outcomes: clinical improvement D28/ symptom improvement (fever, cough, sore throat, headache, shortness of breath, lethargy, and fatigue), as was not reported in the protocol and the registry and likely not a pre-specified outcome. Authors concluded that, *"….we need to conduct more randomized controlled trials across our country involving major tertiary care health care facilities with larger sample size to assess its efficacy for validating the use of Ivermectin against SARS-CoV-2".*
Podder et al., 2020.[15] Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study. IMC Journal of Medical Science, 3 September 2020 http://www.imcjms.com/registration/journal_abstract/353 Not registered on a clinical trial register	RCT, unblinded, Single center (Bangladesh) Study phase not reported Follow-up duration (days): 10 Funding: No specific funding (Self-financed) Declarations: No conflicts declared	Sample size: n = 62 (ivermectin gp: n=32; control gp n= 30) Disease severity: Mild (n=50) and moderate (n=12) COVID-19 infected cases Patient characteristics: Consecutive RT-PCR positive eligible mild to moderate COVID-19 cases; >18 years; 44 males Inclusion criteria: Exclusion criteria: Known allergy to Ivermectin, pregnancy, lactation, patients on other antimicrobials (besides doxycycline, oral) or HCQ	*Intervention:* • Ivermectin (200 mcg/kg) • Co-Intervention: Standard care • Duration : 1 day *Control:* • Standard care *Standard care:* Symptomatic treatment - antipyretics, cough suppressants, and doxycycline (100 mg cap 12 hrly x 7days) for possible community-acquired pneumonia as part of the local working protocol.	**Primary outcome(s):** 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 day 10.	**Primary outcome(s):** Ivermectin vs standard of care: • *Time needed for resolution of all symptoms and the negative result of repeat RT-PCR on day 10:* Mean ±SD (days) - 6.33±4.23 vs 5.31±2.48; p>0.05 • *Recovery time from the onset of initial symptoms:* Mean ±SD (days) - 11.50±5.32 vs 10.09±3.24; p>0.05	• Published article used for data extraction and risk of bias assessment as no study registry, protocol or analysis plan was available. The study achieved its stated sample size. • No a priori sample size calculation 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 assessment: Overall – HIGH RISK** • *Randomisation:* **HIGH RISK -** Quasi-randomisation. A consecutive odd-even allocation suggests probably no allocation concealment. • *Deviations from intervention:* **MODERATE RISK –** open-label, unblinded study. ○ Concomitant administration of medicines such as antivirals, anticoagulants, biologics and corticosteroids not reported. ○ Intention-to-treat analysis • *Attrition:* **MODERATE** to **HIGH RISK** – 62 of 82 randomised patients were analyzed; 40 patients analyzed for outcome of interest. Data unavailable for >5% of population. ○ 18/82 patients randomized but not included because of prior symptom duration. ○ 2/82 patients randomized not included because of insufficient data.

						○ Only 20 patients in each arm tested for viral negative conversion with no information on how they were selected. ○ Risk assessed to be moderate to high for the outcome: Incidence of viral negative conversion. • *Measurement of the outcome:* **LOW RISK** - Unblinded study. ○ Risk assessed to be low for the outcome: Incidence of viral negative conversion; an observer-reported outcome not involving judgement • *Selection of the reported results:* **MODERATE RISK** - The protocol, statistical analysis plan and registry were not available. ○ Unsure whether trial was analyzed as pre-specified or whether results were selected from multiple outcome measurements or analyses of the data. ○ Risk assessed to be some concerns for the outcome: Incidence of viral negative conversion. Authors conclude that "*Larger trials will be needed to confirm these preliminary findings*".
Krolewiecki et al., 2020.[16] Antiviral Effect of High-Dose Ivermectin in Adults with COVID-19: A Pilot Randomised, Controlled, Open Label, Multicentre Trial. SSRN, 11 November 2020 10.2139/ssrn.3714649 Clinical trial registration: NCT04381884	RCT, unblinded Multicenter (Argentina) Follow-up duration (days): 30 Funding: Agencia Nacional de Promoción de la Investigación, el Desarrollo Tecnológico y la Innovación, Argentina and Laboratorio ELEA/Phoenix, Argentina (The sponsors of the study participated in study design, but had no role in primary data collection, data analysis, data	Sample size: n = 45 Disease severity: Mild (n=42); Moderate (n=3) COVID-19 infected cases Patient characteristics: Mean age : 40.9 years; 25 males (56%) Inclusion criteria: 18-69 years; RT-PCR confirmed infection; Hospitalised with disease stages 3 to 5 from the WHO 8-Category ordinal scale of clinical status; Not requiring ICU admission; COVID-19 symptoms onset ≤5 days from enrollment; No concomitant HCQ, CQ, LPV, azithromycin (also not permitted during the first week of the trial); Patients of child-bearing age (unless on contraceptive up to	*Intervention:* • Ivermectin (0.6mg/kg) daily • Co-Intervention: Standard care • Duration : 5 days *Control:* • Standard care • Duration : 5 days *Standard of care:* Not reported	**Primary outcome(s):** The reduction in SARS-cov-2 viral load in respiratory secretions between baseline vs day-5. **Secondary outcome(s):** • Clinical evolution at day-7. • Relationship between ivermectin plasma concentrations and the primary outcome. • Frequency and severity of adverse events in each group.	**Primary outcome(s):** Ivermectin vs control: • *The reduction in SARS-cov-2 viral load in respiratory secretions between baseline vs day-5:* No difference between groups but a significant difference in reduction was found in patients with higher median plasma ivermectin levels (72% IQR 59 to 77) vs untreated controls (42% IQR 31 to 73) (p=0·004). **Secondary outcome(s):** • *Relationship between ivermectin plasma concentrations and the primary outcome:* The mean ivermectin plasma concentration levels showed a positive correlation with viral decay rate (r: 0·47, p=0·02). • *Adverse events:* were reported in 5 (33%) patients in the controls and 13 (43%) in the IVM treated group, without a relationship between IVM plasma levels and adverse events. Ivermectin shown to have a concentration dependent antiviral activity against SARS-CoV-2.	• Pre-print publication (not peer-reviewed) and trial registry was used in data extraction and assessment of risk of bias, as study protocol and statistical analysis plan unavailable. The study achieved its stated sample size. • No substantive differences between pre-print and the registry regarding study procedures, population, treatments or outcomes. • Standard care not described. • Reporting of adverse events experienced is incomplete **Risk of bias assessment: Overall – MODERATE RISK** • *Randomisation*: **LOW RISK** - Allocation sequence and allocation sequence concealment adequately reported. • *Deviations from intervention:* **MODERATE RISK** – Study participants and investigators were not blinded to the treatment arm; but only outcome assessors (virology staff) were blinded to the treatment group "*by receiving the samples labeled with randomization code and visit number.*" ○ No participant crossover; but no information was provided on co-interventions e.g. antivirals, corticosteroids, biologics. • *Attrition:* **LOW RISK** – 32 of 45 randomised patients were analyzed for WHO score 7 and above; all 45

	interpretation, writing of the report, or the decision to submit for publication) <u>Declarations:</u> AK reports grants from Laboratorio Elea/Phoenix. MAT, MDG and ES are employees of Laboratorios Elea/Phoenix. SG is a moember of the Board of Directors of Laboratorio Elea/Phoenix.	30 days after last study drug administration;				patients analyzed for, adverse events and serious adverse events. ○ Risk assessed to be low for the outcomes: WHO score 7 and above; adverse events and SAEs. • *<u>Measurement of the outcome:</u>* **MODERATE RISK** - Blinded Outcome assessors not blinded for outcomes of interest. ○ Risk assessed to be low for the outcomes: WHO score 7 and above. ○ Risk assessed to be some concerns for the outcomes: Adverse events; SAEs. • *<u>Selection of the reported results</u>:* **LOW RISK** - Pre specified in the registry, but neither the protocol nor the statistical analysis plan available. ○ Risk assessed to be low for the outcomes: WHO score 7 and above; adverse events and SAEs. • Authors conclude that "*… adding ivermectin to usual care in the management of mild to moderate COVID-19 patients did not show any benefit. However, since the sample size was small, future multicenter studies with a larger sample size could be conducted to confirm the outcome".*
Ahmed S et al., 2020.[17] 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 <u>Funding:</u> Beximco Pharmaceutical Limited, Bangladesh – supplier of ivermectin 12 mg tablets <u>Declarations:</u> Authors reported no conflicts of interest to declare.	<u>Sample size:</u> n = 72 randomised (n=24/group: ivermectin +doxycycline vs control vs ivermectin) <u>Disease severity:</u> Mild <u>Inclusion criteria</u>: 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]; <u>Patient characteristics:</u> Mean age: 42 years; 46% male; Duration of illness before assessment was an average of 3.83 days.	*<u>Intervention:</u>* • Ivermectin+doxycycline (12 mg/100 mg) daily • Co-Intervention: Standard care • Duration : 5 days *<u>Control 1</u>:* • Placebo • Co-Intervention: Standard care • Duration : 5 days *<u>Control 2:</u>* • Ivermectin (12 mg) daily • Co-Intervention: Standard care	**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):** <u>Ivermectin+doxycycline vs placebo</u> • *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	• 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** • *<u>Randomisation</u>*: **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*

			• Duration: 5 days *<u>Standard of care:</u>* Not reported		*Severe adverse drug events:* None recorded in the study.	*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".* • *<u>Blinding:</u>* **LOW RISK** - Blinded study, "*randomized, double-blind, placebo-controlled trial".* • *<u>Attrition:</u>* **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. • *<u>Measurement of the outcome:</u>* **LOW RISK** - Blinded outcome assessor (risk assessed as low for the outcomes: Time to viral negative conversion; serious adverse events • *<u>Selection of the reported results</u>:* **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".*
Niaee et al., 2020.[18] Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center	RCT, double-blind, placebo-controlled, multi-center (5 hospitals, Velayat, Bu Ali,	<u>Sample size</u>: n = 180 (n=30 per arm) <u>Disease severity:</u> Mild = 25	6 gps – 4 intervention gps and 2 control gps <u>Intervention gps:</u>	**Primary outcome(s):** The primary outcomes reported in the preprint differs from the clinical trial registry:	**Primary outcome(s):** ***Mortality rate (not pre-specified in trial registry or preprint) :*** *<u>Intervention:</u>*	• Preprint and trial registry information was used for data extraction and assessment of risk of bias. Study protocol, and statistical analysis plan not available.

clinical trial. Research Square, 2020 https://www.researchsquare.com/article/rs-109670/v1 Iranian Registry of Clinical Trials IRCT20200408046987N1) https://en.irct.ir/trial/47012 Ethics: medical ethics committee of Qazvin University of Medical Sciences (registration ID IR.QUMS.REC.1399.017	Taleghani, Razi, and Sina) in Qazvin and Khuzestan provinces of Iran) Phase 2/3 study: *"Dose-Finding study of Ivermectin treatment on patients infected with Covid-19"* Follow up duration (days): 45 Funding: The research deputy of Qazvin University of Medical Sciences and Science and Technology Park, Qazvin, Iran. Declarations: No conflicts of interest declared	Moderate = 131 Severe = 22 (more severe cases in ivermectin gps) Patient characteristics: Median age: 56 years [IQR 45-67] 90 (50%) male Inclusion criteria: Age >18 years; clinical symptoms of suggestive of COVID-19 pneumonia: cough (with or without sputum), fever, pleuritic chest pain or dyspnea; mild to severe COVID-19 disease confirmed by chest CT scan findings compatible with COVID-19 or positive RT-PCR. Exclusion criteria: Severe immuno- suppression (e.g., on immunesuppressants, HIV positive), pregnant women, chronic kidney disease, malignancy, and indications that the patients unlikely to follow study protocol.	**Gp 1**: Ivermectin 200 mcg/kg as a single dose on D1 **Gp 2**: Ivermectin 200 mcg/kg as a single dose on D1, D2, D5 **Gp 3**: Ivermectin 400 mcg/kg as a single dose on D1, D2, D5 **Gp 4**: Ivermectin 400 mcg/kg as a single dose on D1, followed by ivermectin 200 mcg/kg as a single dose on D2, D5 Control gps: **Gp 1**: Placebo as a single dose on D1 + SoC **Gp 2**: Only SoC *Standard care (SoC):* All patients received: • HCQ 200mg/kg 12 hrly, • heparin prophylaxis, • supplemental oxygen *SoC as per theIranian guideline of hospitalized COVID-19 patients' management (v5)*	*Primary outcome in preprint* Clinical recovery within 45 days of enrolment (Clinical recovery defined as normal fever, respiratory rate, and oxygen saturation (>94) without oxygen therapy sustained for 24h) *Primary outcome(s) in trial registry* • Chest CT scan • Hospitalization time • CBC and CRP	• Gp 1: IVM 200mcg/kg stat: 0/30; 0% • Gp 2: IVM 200mcg/kg x3d: 3/30; 10% • Gp 3: IVM 400mcg/kg stat:0/30; 0% • Gp 4: IVM 400mcg/kg stat, 200mcg/kg x 2days: 1/30; 3.3% *Control:* • Gp 1: Placebo with SoC: 6/30; 20% • Gp 2: SoC: 5/30; 16.7% ***Length of hospitalisation stay – days:*** *Intervention* • Gp 1: IVM 200mcg/kg stat: 6 (5 to 7) days • Gp 2: IVM 200mcg/kg x3d: 8 (6 to 9) days • Gp 3: IVM 400mcg/kg stat: 5 (4 to 7) days • Gp 4: IVM 400mcg/kg stat, 7 (6 to 10) days *Control:* • Gp 1: Placebo with SoC: 8 (6 to 11) days • Gp 2: SoC: 7 (7 to 9) days *p=0.006* ***Duration of low oxygen sats - days:*** *Intervention:* • Gp 1: IVM 200mcg/kg stat: 2 (1 to 2) days • Gp 2: IVM 200mcg/kg x3d: 3 (2 to 5) days • Gp 3: IVM 400mcg/kg stat: 2 (1 to 4) days • Gp 4: IVM 400mcg/kg stat, 200mcg/kg x 2days: 5 (3 to 6) days *Control:* • Gp 1: Placebo with SoC: 4 (2 to 6) days • Gp 2: SoC: 3 (2 to 5) days *p=0.025*	• Dose-finding study that achieved its stated sample size. Registered as a phase 3 study in the trial registry, but reported as a phase 2/3 study in the preprint. • The primary outcomes reported in the preprint differs from the clinical trial registry. • Changes during the study included, "*During the process the criteria for discharge was changed over the course of study";* details not reported. • Mortality rate was not a pre-specified outcome for data analysis. • Baseline comorbidities of patients in the study groups not reported. • Underpowered study • Cases counted as COVID-19 if either SARS-CoV-2 PCR positive or suggestive findings on CT scan (i.e. may not all have been true cases). • Unclear if hospitalisation duration excluded or adjusted for cases who died. **Risk of bias assessment: Overall – MODERATE to HIGH RISK** • *Randomization:* **MODERATE RISK** - "*Randomization according to the severity of the disease was as follows: mild, moderate, and severe. The transposed block randomization sequence, including stratification, was prepared by a statistician not involved in the trial using Random Allocation Software. Pharmacia generated the randomization list and provided the list to the central randomization service"; "randomized after calling the central randomization telephone number and receiving randomization information and confirmation. Each patient received the unique patient numbers that were to be used on all study medication containers, case report forms, and to identify all specimens".* ○ Allocation sequence and concealment appears adequately reported. ○ However, the diagnosis of COVID-19 was made either with PCR or compatible lung CT, but there were striking discrepancies in PCR positivity rates at baseline (47% in placebo, 60% in SOC, and 97% in Arm/Gp 3.) With the small sample sizes (30 patients per arm) these differences may have arisen by chance, but do raise concerns about the adequacy of randomisation, even though this was well described. • *Deviations from intervention:* Blinding (participants, clinicians, outcome assessors): **MODERATE RISK** ○ Registry states the following are blinded: Participant; Care provider; Outcome assessor; Data

						analyser: but 2 groups received a single dose, 2 groups received 3 doses, and the standard care group did not receive any doses. Therefore, it is unlikely that patients or personnel/carers were blind to treatment group. ○ No indication of patient cross-over. ○ No information on other co-interventions such as steroids, antivirals, biologicals not reported. ○ ITT analysis • *Attrition:* 180 patients randomized; 180 patients analyzed. Data available for all participants.: **LOW RISK** • *Measurement of the outcome:* **LOW RISK** – trial registry states that outcome assessor; data analyser are blinded, but no details in the preprint. Mortality is an observer-reported outcome not involving judgement. Risk assessed to be low for the outcome • *Selection of the reported results:* **MODERATE RISK -** The trial registry and preprint was available - protocol and statistical analysis plan were not available. ○ Primary outcomes differ between trial registry and preprint and mortality has not been included as a pre-specified outcome (though relevant). ○ Results were not selected from multiple outcome measurements or analyses of the data. Authors comments, "*Ongoing studies with larger sample sizes, using strategies to enhance the antiviral potency of ivermectin and its combination with other antivirals or higher-dose regimens, and focus on severe COVID-19 cases are recommended*"
Chaccour et al.[19] The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with mild COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial. EClinicalMedicine. 2021 Feb;32:100720. https://pubmed.ncbi.nlm.nih.gov/33495752/ Clinical trial registration: NCT04390022	RCT, double-blinded, single centre (Spain) Phase 2 study Follow-up duration (days): 30 Funding: Mixed - ISGlobal; University of Navarra. Unitaid; Spanish Ministry of Science and Innovation; Generalitat de Catalunya;	Sample size: n=24 (12/study gp) Disease severity: Mild: n=24 Patient characteristics: n=24 Mean age : not reported 12 (50%) males Inclusion criteria: Diagnosed with COVID-19 in emergency room with a positive SARS-CoV-2 PCR ; 18 to 59 years; child-bearing women on reliable contraceptive; patient	*Intervention:* • Ivermectin, 400 mcg/kg as a single dose • Duration : 1 day *Control:* • Placebo tablet (not matched to ivermectin; but administered by staff not involved in the clinical care. • Duration : 1 day	**Primary outcome(s):** Proportion of patients with a positive SARS-CoV-2 PCR from a nasopharyngeal swab at day 7 post-treatment – reported in trial registry **Secondary outcome(s):** • Viral load at days 4, 7, 14 and 21 post treatment; • Proportion of patients with symptoms (particularly fever and cough) at days 4, 7, 14 and 21 post treatment. • Proportion of patients progressing to severe disease/death.	**Primary outcome(s):** Ivermectin vs placebo *Proportion of patients with detectable SARS-CoV-2 RNA by PCR from nasopharyngeal swab at day 7 post-treatment – reported in preprint:* ○ 1/6 in the ivermectin (one previously positive sample reportedly was lost) vs 1/7 in the placebo group effectively replicated Vero cell culture – no difference between gps. **Secondary outcome(s):** • *Viral load at days 4, 7, 14 and 21 post treatment:* Genes E and N had comparable results at all-time points. ○ Target gene E: 11 (91%) vs 12(100%); RR 0.92, 95% CI: 0.77 to 1.09, p = 1.0. ○ Target gene N: 12 (100%) in both gps	• Small pilot study showed no difference between ivermectin and placebo groups for the primary outcome of reducing positivity of viral cultures; or other important effects such as reduction in inflammatory markers or duration of disease. • Pre-print with supplementary appendices, the study registry, protocol and data analysis plan used in data extraction and risk of bias assessment - no substantive differences between the pre-print article and the trial registry, study protocol and statistical analysis plan in population, procedures, interventions or outcomes. The study achieved its stated sample size (n=24). • Placebo tablets did not match ivermectin in appearance, "*therefore, in order for the clinical team to remain blinded, treatment was administered under direct supervision by a nurse not participating in patient´s care*".

	Idipharma SL (placebo donation) <u>Declarations:</u> No conflicts of interest declared	compliance including home follow up during isolation). <u>Exclusion Criteria:</u> Known ivermectin allergy or Stromectol® hypersensitivity: COVID-19 pneumonia; fever/ cough for > 48 hours; positive IgG against SARS-CoV-2 by rapid test; <18 or >60 years; co-morbidities including COPD, immunosuppression, diabetes, hypertension, obesity, acute/ chronic renal failure, history of coronary disease or cerebrovascular disease, current neoplasm or other comorbidity as determined by study investigator; recent travel history to endemic countries; CYP 3A4 or P-gp inhibitor drug use.	*<u>Concomitant medicines:</u>* Not reported	• Proportion of patients with seroconversion at day 21 post-treatment. • Proportion of ADRs.	○ No difference between gps ○ Authors state that for the primary outcome, "*…quantifcation of the viral load presented is intrinsically limited by heterogeneity in the samples, even if all were obtained by the same clinicians, standardization against a human epithelial cell gene would be required to ensure the viral loads are truly comparable".* • *Symptoms (particularly fever & cough)*: ○ Patients in the ivermectin gp reported fewer patient-days of any symptoms vs placebo gp (171 vs 255 patient-days). ○ Hyposmia/anosmia:76 vs 158 patient-days ○ Cough: 68 vs 97 patient-days • *Progression to severe disease/death:* No patient in either group progressed to severe disease/death. • *Seroconversion at day 21 post-treatment:* All patients in both groups seroconverted by day 21 post treatment. Median of IgG titers lower in ivermectin gp: Index 4.7; IQR (3.5 to 8.9) vs 7.5; IQR (4.2 to 9.3) • *ADRs*: 15 types of ADRs (7 vs 8) experienced by 10 patients (5 vs 5) - dizziness (7 vs 1) and blurred vision (24 vs 1), with 1 patient evaluated with undiagnosed presbyopia; no SAEs. • *Other:* There were no major differences between study gps regarding the evolution of vital signs, inflammatory markers (CRP, procalcitonin, ferritin and IL-6, d-dimer) and other of laboratory parameters (RBC,Hb, platelets, WBC, lymphocytes, neutrophils) of patients.	• There was slow recruitment due to a sharp reduction in local transmission for 10 weeks after the lockdown of March-April 2020. • Study protocol was amended on September 2nd to extend the inclusion criteria from 48 to a maximum of 72 hours of cough or fever." • Baseline demographics show a heterogeneous sample of patients in terms of symptoms (reduction in symptoms being the most important study finding); i.e. less cough and anosmia at baseline in the placebo arm; more fever in the placebo arm and a difference between groups in the time of onset for symptoms. • ITT analysis of small study (n=24). **Risk of bias assessment: Overall – MODERATE RISK** • *Randomisation*: **MODERATE RISK - "***The randomization sequence was computer-generated by the trial statistician using blocks of four to ensure balance. Allocation was made by the attending investigator using opaque envelopes."* ○ Allocation sequence random, but allocation sequence concealment unclear – query as to whether the envelopes were sealed or sequentially-numbered; blinding is also not perfect; single center; block of four) • *Deviations from intervention:* **MODERATE RISK -** double-blind study ○ Placebo tablet not matched to ivermectin in appearance*; "therefore, in order for the clinical team to remain blinded, treatment was administered under direct supervision by a nurse not participating in patient's care."* ○ Study clinical team blinded, but the blinding of participants is uncertain. ○ No information on co-interventions of interest: antivirals, biologics and corticosteroids. ○ ITT analysis. • *Attrition:* **LOW RISK** – All randomised and analyzed (n=24) ○ Data available for 100% of study population. ○ Risk assessed to be low for the outcomes: Mortality, incidence of viral negative conversion, WHO score 7 and above, adverse event, SAEs. • *Measurement of the outcome:* **MODERATE RISK -** Blinded outcome assessor (risk assessed as low for the outcomes: Mortality, incidence of viral negative conversion, WHO score ≥7, adverse event, SAEs).

						○ Symptoms (reduction of symptoms being the most important finding in this study): patients reported symptoms through an online questionnaire. • *Selection of the reported results:* **LOW RISK** - The trial registry, protocol and statistical analysis plan were available. Data analyses pre-specified (risk assessed as low for the outcomes: Mortality, incidence of viral negative conversion, WHO score 7 and above, adverse event, SAEs). Authors concluded that, "*The positive signal found in this pilot warrants the conduction of larger trials using ivermectin for the early treatment of COVID-19*", and that the study was "*designed to explore a potential signal for the use of ivermectin in COVID-19, not to provide definitive evidence on the subject, hence its small sample size.*
Mohan et al., 2021. Ivermectin in mild and moderate COVID-19 (RIVETCOV): a randomized, placebo-controlled trial. Red Square, 2 February 2021. https://www.researchsquare.com/article/rs-191648/v1 Clinical trial registration: CTRI/2020/06/026001	RCT, blinded, single centre (India) Phase 2/3 study Follow-up duration (days): 28 Funding: Mixed (Department of Science and Technology, Government of India; WindLas BioTech Ltd. Haryana (drug contribution)) Declarations: No conflicts of interest declared	Sample size: n=152 (n_1=49/ n_2=52/ n_3=51) Disease severity: Mild: n= 115 Moderate: n=10 Severe: n=0 Critical: n=0 Patient characteristics: n=24 Mean age : 35.3 years 111 (73%) males Inclusion criteria: ≥18 years; diagnosed COVID-19 positive (based on a positive result on either SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) or the rapid antigen test);non-severe COVID-19 (i.e. room air saturation (SpO2) >90%, no hypote Exclusion Criteria: Informed consent not given; pregnant or lactating; known hypersensitivity to ivermectin; chronic kidney disease with creatinine clearance <30 mL/min; elevated transaminase levels (>5 x upper limit of normal)	Intervention: 1) Ivermectin 12 mg 2) Ivermectin 24 mg Control: Placebo Concomitant medicines: Not reported	**Primary outcome(s):** *In the report*: Reduction of viral load and conversion to negativity of nasopharyngeal/oropharyngeal RT-PCR on day 5 after intervention	**Primary outcome(s):** Ivermectin 24mg vs 12mg vs placebo • *Negative RT-PCR at D5:* ○ 19/40 (47.5%) vs 14/40 (35.0%) vs 14/45 (31.1%); p = 0.30 , ns • *Decline of viral load at D5((log10 viral copies/mL), mean (SD):* ○ 3.05 (2.29%) vs 3.04 (2.05%) vs 3.08 (1.98%); p=0.999, ns No serious adverse events reported.	• Pre-print article, the study registry and supplementary materials were used in data extraction and risk of bias assessment. • Unclear what the target sample size was and if it was achieved. • Outcomes were not reported in the study registry, so it is unclear if these were reported at the correct follow-up point. • Modified ITT analysis – only 125 of 157 randomized participants were analyzed. **Risk of bias assessment: Overall – MODERATE RISK** • *Randomisation*: **LOW RISK** - "*A variable block randomization stratifed based on disease severity (mild or moderate illness) was done using a centralized telephone-based system"; "Sequentially numbered, sealed, opaque envelopes*" ○ Random allocation sequence random that was sufficiently concealed. • *Deviations from intervention:* **MODERATE RISK** - double-blind study ○ Blinded study (participants and personnel/carers). ○ Participants were analyzed according to their randomized groups for the outcome. ○ 5 participants (unclear distribution/proportion between arms) excluded from the analysis of safety outcomes post-randomization due to withdrawn consent. This method was considered appropriate to estimate the effect of assignment to intervention. ○ A further 20 vs 7 participants were excluded from the analysis of clinical improvement and viral negative conversion outcome post-randomization due to non-positive PCR result on day of enrolment (exclusion

						criteria). This method was considered appropriate to estimate the effect of assignment to intervention.
						• *Attrition:* **MODERATE RISK**
						  ○ 157 patients randomized;
						  ○ 152 patients analyzed for adverse events, WHO score 7 and above, mortality;
						  ○ 125 patients analyzed for clinical improvement;
						  ○ 114 patients analyzed for viral negative conversion at D7.
						• *Measurement of the outcome:* **LOW RISK** - Blinded outcome assessor.
						  ○ Measurement or ascertainment of outcome probably does not differ between groups.
						• *Selection of the reported results:* **MODERATE RISK** - The trial registry was available.
						  ○ No outcomes were pre-specified
						  ○ No information on whether the result was selected from multiple outcome measurements or analyses of the data.
						  ○ Risk assessed to be some concerns for outcomes: mortality (D28); incidence of viral negative conversion (D7); clinical improvement (D28); WHO score 7 and above (D28); adverse events; serious adverse events.

Shah Bukhari et al., 2021. Efficacy of Ivermectin in COVID-19 Patients with Mild to Moderate Disease. MedRxiv, 5 February 2021. https://www.medrxiv.org/content/10.1101/2021.02.02.21250840v1 Clinical trial registration: NCT04392713	RCT, unblinded, single centre (Pakistan) Phase: not reported Follow-up duration (days): 28 Funding: Not reported/ unclear Declarations: No conflicts of interest declared	Sample size: n=100 (n1=50/n2=50) Disease severity: Mild: n= 100 Patient characteristics: Mean age: 40.6 years 73 (73%) males Inclusion criteria: 15-65 years; any gender; COVID-19 RT-PCR positive; Mild (fever <38oC quelled without treatment with or without cough, no dyspnea, no gasping, no chronic disease, no imaging findings of pneumonia) to moderate (fever, respiratory symptoms, imaging findings of pneumonia) disease; study consent provided; able to take oral medication Exclusion Criteria: Pregnant; severe symptoms likely due to cytokine release syndrome; uncontrolled co-morbidities; malignant diseases; diabetes mellitus; chronic kidney disease; cirrhosis liver with CPT class B or C; immunocompromised; history of ivermectin allergy; patients taking CYP 3A4 inhibitors or inducers; supplemental oxygen required (equivalent to FiO2 ≥50% in moderate severity patients).	Intervention: Ivermectin 12 mg, once-off dose on admission Control Standard care: oral vitamin C 500mg once daily, oral vitamin D3 200,000 IU once weekly, and oral paracetamol 500 mg as required. Concomitant medicines: Not reported	**Primary outcome(s):** *In the report*: Viral clearance (measured as the days to achieve RT-PCR negativity following ivermectin administration)	**Primary outcome(s):** Ivermectin vs SOC: • *Negative RT-PCR at 72 hours:* ○ 17/50 (34%) vs 2/50 (8%) , p=0.001 • *Negative RT-PCR at D7:* ○ 20/50 (40%) vs 18/50 (36%); p=0.001 • *Negative RT-PCR at D14:* ○ 4/50 (8%) vs 25/50 (50%); p=0.001 No adverse reactions or derangements in laboratory parameters were reported.	• Pre-print article and the study registry were used in data extraction and risk of bias assessment. **However, the trial was registered retrospectively while the trial was ongoing.** • There are some differences between the pre-print article and the trial protocol in exclusion criteria relating to comorbidities. Standard care was different between the registry (chloroquine) and the report (vitamin C, paracetamol). The primary outcome timepoints differ between the registry and the pre-print article. • The secondary outcome in the registry (need for ventilation) was not reported in the pre-print article. The target sample size specified in the registry was achieved. • Gender distribution between study arms differed by about 10%. • Small study. **Risk of bias assessment: Overall – HIGH RISK** • *Randomisation*: MODERATE RISK - *"The patients were randomized in a 1:1 ratio via a lottery method."* ○ Allocation sequence random, but allocation sequence concealment unclear. • *Deviations from intervention:* MODERATE RISK - unblinded study ○ No information on co-interventions of interest: antivirals, biologics and corticosteroids. ○ Modified ITT analysis (using available cases). • *Attrition:* MODERATE RISK – 86/100 patients analyzed with >5% missing data ○ Study participants left against medical advice before D14 ○ Risk assessed to be some concerns for the outcome: Incidence of viral negative conversion (D7). • *Measurement of the outcome:* LOW RISK - Unblinded study, but risk assessed to be low for the outcome: Incidence of viral negative conversion (D7). • *Selection of the reported results:* MODERATE RISK – The trial registry was only available. ○ The timepoints at which viral conversion is reported differ from the registry, and thus not analyzed as prespecified.
Lopez-Medina et al., 2021. Effect of Ivermectin on Time to Resolution of Symptoms Among Adults	RCT, blinded, single centre (Columbia)	Sample size: n=476 (n_1=238/n_2=238) Disease severity:	Intervention: Ivermectin 300 mcg/kg/day orally for 5 days	**Primary outcome(s):** *In the report* Time from randomization to complete resolution of	**Primary outcome(s):** Ivermectin vs placebo • *Time to resolution of symptoms – median no. of days (IQR):*	• Published article, tstudy protocol, statistical analysis plan and trial registry were used in data extraction and assessment of risk of bias.

With Mild COVID-19. JAMA, 4 March 2021 https://jamanetwork.com/journals/jama/fullarticle/2777389 Clinical trial registration: NCT04405843	Phase 3 study Follow-up duration (days): 21 Funding: Mixed (Centro de Estudios en Infectologia Pediatrica; Tecnoquimicas (drug and placebo donation)) Declarations: Conflicts declared included grant/professional fees from Sanofi Pasteur, GlaxoSmithKline, Janssen, Merck Sharp & Dohme and Gilead.	Mild: n= Moderate: n= Patient characteristics: Mean age: 40.6 years 167 (35%) males Inclusion criteria: > 18 years; RT-PCR confirmed COVID-19; onset of symptoms within the previous 7 day; "mild" disease, (home- or hospital- based with no supplemental oxygen as high-flow or invasive [note: this would be categorised as mild or moderate in most studies]) Exclusion Criteria: History of liver disease or liver impairment (liver function results >1.5 times normal level; allergy to ivermectin; participant in another trial evaluating COVID-19 therapeutics; COVID-19; asymptomatic patients; had severe pneumonia; previous use of ivermectin within the last 5 days; concomitant warfarin, erdafitinib, or quinidine	Control: Placebo Concomitant medicines: Not reported, but the use of other treatments outside of clinical trials was allowed	symptoms within the 21-day follow-up period	○ 10 (9-13) vs 12 (9-13); ARR = -2 (-3 to 3); HR = 1.09 (0.90 to 1.32) • *Symptoms resolved at 21 days. No. (%)* ○ 232 (84.4%) vs 156 (78.%); ARR = 5.57 (-1.56 to 12.71); HR = 1.45 (0.81 to 2.32)	• Difference(s) between protocol and publication -the original primary outcome measure (worsening by 2 points in an 8-point ordinal scale) was changed to resolution of symptoms during the trial due to low incidence of the original outcome, resulting an unattainable sample size. This change was identified before the interim analysis and approved by the data and safety monitoring board. • For two weeks both arms received ivermectin due to a labeling error, including 38 in the control group; all patients recruited during this period (n=75) were not included in primary analyses extracted here, but were included in sensitivity and as-treated analysis. • As treated population varied marginally between study groups – less elderly ≥65 years (3.7%), males (4.2%), history of BCG vaccination (2%), smokers (2%), home-based participants with limited activity/home oxygen (4.3%), concomitant glucocorticoids (3.5%) and concomitant anticoagulants (3.2%) in intervention group compared to placebo arm. • Small study. **Risk of bias assessment: Overall – MODERATE RISK** • *Randomisation*: **LOW RISK** – Random allocation sequence random, sufficiently concealed. • *Deviations from intervention:* **MODERATE RISK** – blinded study - participants and personnel/carers ○ Due to a labelling error, 38 participants randomized to placebo were given the study drug. All participants randomized during this time period (n=75) were excluded from the primary analysis. Study authors present as-treated results in supplementary files, considered inappropriate to estimate the effect of assignment to intervention for the primary outcome – time to clinical improvement. • *Attrition:* **LOW** to **MODERATE RISK** – 476/398 patients analyzed due to protocol deviation (labelling error – see above). As-treated analysis. • *Measurement of the outcome:* **LOW RISK** - Blinded study (outcome assessor). • *Selection of the reported results:* **MODERATE RISK** ○ Primary outcome (time to clinical improvement) not pre-specified (added as an outcome at a later date), ○ Other outcomes (mortality (D28), WHO score 7 and above (D28), adverse events, serious adverse events): Outcome data acquired from contact with authors, and assessed to be low as results were probably not selected from multiple outcome

						measurements or analyses of the data, and analyzed as pre-specified. Authors concluded that, *"Among adults with mild COVID-19, a 5-day course of ivermectin, compared with placebo, did not significantly improve the time to resolution of symptoms. The findings do not support the use of ivermectin for treatment of mild COVID-19, although larger trials may be needed to understand the effects of ivermectin on other clinically relevant outcomes".*
Okumus et al., 2021. Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients. BMC Infectious Diseases, 4 May 2021. https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-021-06104-9 Clinical trial registration: NCT04646109	RCT, single-blinded, multi-centre (Turkey) Phase 3 study Follow-up duration (days): 90 Funding: Public/non profit (Afyonkarahisar Health Science University) Declarations: None	Sample size: n=66 (n_1=36/n_2=30) Disease severity: Severe=58 Critical=2 Patient characteristics: Mean age: 61.8 years 40 (61%) males Inclusion criteria: Hospitalised patients with a pre-diagnosis of "severe COVID-19 pneumonia" and thereafter, COVID-19 diagnosed - confirmed microbiologically with PCR positivity in respiratory tract samples; Severe COVID-19 pneumonia with at least one of following criteria: 1) Tachypnea ≥ 30/minute; SpO2 level < 90% in room air; PaO2/FiO2 <300 in oxygen receiving patient; or 2) Radiological finding for COVID-19 in lung tomography (bilateral lobular, peripherally located, diffuse patchy ground glass opacities); or 3) Mechanical ventilation requirement; or 4) Acute organ dysfunction findings; patients with SOFA >2 Exclusion Criteria: <18 years; pregnant;	Intervention: Ivermectin 200 mcg/kg enterally once daily x 5 days. (36–50kg: 9mg; 51–65kg: 12mg, 66–79kg: 15mg; > 80 kg: 200 mcg/kg) + SOC (n_1=36) Control: SOC (n_2=30) SOC: COVID-19 (SARS CoV-2 Infection) guide, Turkish Ministry of Health: hydroxychloroquine (2x400mg followed by 2x200mg, po, 5 days), favipiravir (2x1600mg followed by 2x600mg, po, total 5 days) and azithromycin (500mg followed by 250mg/day, po, total 5 days) Concomitant medicines: Not reported.	**Primary outcome(s):** *In the report* Clinical responses and drug side effects obtained in patients on the 5th day (17 outcomes were registered in the clinical registry).	**Primary outcome(s):** Ivermectin vs control: • *Clinical improvement at D5:* ○ 14/30 (46.7%) vs 11/30 (36.7%) ▪ *SpO2:* 93.52 ± 4.36 vs 93.00 ± 3.25, p=0.14 ▪ *PaO2/FiO2 ratio:* 178.94 ± 98.21 vs 180.13 ± 95.43, p=0.68 **Other outcomes:** • *Mortality at ± 60 days:* ○ 6/30 (20%) vs 9/30 (30%), p=0.37 • *Negative RT-PCR at D10:* ○ 14/16 (87.5%) vs 3/8 (37.5%), p=0.01 – not all study participants were tested	• Pre-print, published article, study registry (including outcome data) and protocol were used in data extraction and risk of bias assessment. • The study was registered retrospectively but the protocol was dated prospectively. • The trial used a quasi-randomized design. • Small study **Risk of bias assessment: Overall – HIGH RISK** • *Randomisation*: **HIGH RISK** – *"Starting from the first patient included in the study, patients with odd numbers were grouped as the study group, and patients with even numbers as the control group"* – random allocation sequence but allocation sequence not concealed. • *Deviations from intervention:* **HIGH RISK** – single-blinded study (unclear if participants or personnel/carers were blinded) ○ Antivirals administered as part of SOC, but no information on biologics and corticosteroids. ○ Per protocol analysis – 6 patients removed from ivermectin arm after receiving 1st dose for pharmacogenetic reasons; these patients were not included in the analysis. Similar testing was not done on the placebo arms. • *Attrition:* **HIGH RISK** – 60/66 patients analyzed for mortality and safety, but 24/66 analyzed for negative viral conversion. ○ Reasons for missing data: gene mutation putting participant at risk of serious adverse events (n=6 in intervention group); no reasons reported for the remaining 14 vs 22 participants missing - Risk assessed as high for the outcome: Incidence of viral negative conversion (D7). • *Measurement of the outcome:* **MODERATE RISK** - Unclear blinding (outcome assessor). ○ Mortality follow-up duration inconsistent ("until study completed, average 3 months"), unclear if patients followed up after discharge, and cause of death not recorded (COVID vs non-COVID).

		active breast feeding; concurrent autoimmune disease; chronic liver or kidney disease; immunosuppression; SNP mutation in MDR-1/ABCB1 gene and/or haplotypes and mutations of the CYP3A4 gene; known ivermectin allergy				• *Selection of the reported results:* **MODERATE RISK** ○ No information on whether the result for viral negative conversion was selected from multiple outcome measurements or analyses of the data.
Beltran-Gonzalez et al., 2021. 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".
Kishoria et al., 2021. Ivermectin as adjuvant to hydroxycholoroquine in patients resistant to standard treatment for Sars-Cov-2: Results of an open-label randomized clinical study. Wordlwide Journals - Paripex - Indian journal of research, August 2020 https://c19ivermectin.com/kishoria.html Not registered on a clinical trial register	RCT, unblinded, single centre (India) Phase 3 study Follow-up duration (days): 6 Funding: Not reported/unclear Declarations: Not reported	Sample size: n=32 (n_1=19/ n_2=13) Disease severity: Mild: n=32 Patient characteristics: Mean age: 38.5 years 23 (72%) males Inclusion criteria: ≥18 years; positive test after completion of standard care treatment for SARS-CoV-2 confirmed by RT-PCR; mild/ asymptomatic; no comorbidities rendering high-risk patients; informed consent obtained. Exclusion Criteria: Allergy or hypersensitivity to ivermectin; respiratory distress; immunosuppressants (including systemic corticosteroids) in the last 30 days; HIV-positive with CD4<300 cell/ L; pregnant or lactating; malabsorption syndromes affecting proper ivermectin absorption; autoimmune disease and/or decompensated chronic diseases; uncontrolled, diseases including renal impairment, hepatic impairment, symptomatic CHF, unstable chest angina or heart arrhythmia; study participant in any other study in previous 30 days; concomitant enzyme inducers (such as carbamazepine) that could affect the effectiveness of the drug and those receiving CYP3A4 substrates (such as statins) due to the risk of increased toxicity.	Intervention: Ivermectin 12mg single dose (n_1=19), in addition to standard of care. Control: SOC (n_2=13) *SOC:* HCQ 400 mg twice daily, paracetamol 500mg as needed, vitamin C twice a day, plenty of water with caloric diet intake. Temperature and spO2 monitoring, good oral hygiene. Concomitant medicines: Not reported.	**Primary outcome(s):** *In the report* Negative throat swab report for SARS-CoV-2 conducted by RT-PCR after 48 hours of day one of research therapy. (However if patient was tested positive on the then the test was repeated again after 48 hours.	**Primary outcome(s):** Ivermectin vs SOC: • *Negative RT-PCR at D3* ○ 8 (42.2%) vs 6 (46.2%), p=0.820 Other outcomes: • *Discharged from hospital at end of study (n):* ○ 8 (42.2%) vs 6 (46.2%) - no significant difference	• Only the published article was used in data extraction and assessment of the risk of bias. No trial registry, study protocol or statistical analysis plan was available. • The sample included in this hospital-based study was small due to change in guidelines during the study in which asymptomatic patients and patients with mild symptoms were recommended to be home isolated and not hospitalized. • Safety outcomes such as adverse events or death are not reported. • Small study. • Patients included "after completion of standard care treatment" – unclear if this implies several days of standard care prior to randomisation. **Risk of bias assessment: Overall – MODERATE RISK** • *Randomisation*: **LOW RISK** - *"The randomization list was generated by a computerized system by a unit independent of the study team. The randomization codes was kept in sealed sequentially numbered opaque envelopes"* – random allocation sequence that was adequately concealed. • *Deviations from intervention:* **MODERATE RISK –** unblinded, open-label study ○ No information on co-interventions - biologics, antivirals and corticosteroids. ○ ITT analysis • *Attrition:* **LOW RISK –** 32/32 patients analyzed. • *Measurement of the outcome:* **MODERATE RISK** - unblinded study (outcome assessor). ○ Clinical improvement D28 (defined as discharge) requires clinical judgement and could be affected by knowledge of intervention receipt. • *Selection of the reported results:* **MODERATE RISK** ○ No information on whether the result was selected from multiple outcome measurements or analyses of the data. ○ No information on whether the trial was analyzed as pre-specified. Authors concluded that, *"In summary, this open label randomized study of patients with COVID-19 found that the use of a regimen containing hydroxychloroquine and ivermectin was associated with no evidence of benefit in comparison to hydroxychloroquine alone. However, it was observed that ivermectin was well tolerated with no serious drug related adverse event thus a large sample sized*

						randomized clinical trial may be initiated to further investigate its efficacy as anti-viral agent inCOVID-19".
Shahbaznejad et al., 2021. Effects of Ivermectin in Patients With COVID-19: A Multicenter, Double-Blind, Randomized, Controlled Clinical Trial. Clinical Therapeutics (article in press), accepted for publication April 2021 https://www.clinicaltherapeutics.com/action/showPdf?pii=S0149-2918%2821%2900201-0 Clinical trial registration: IRCT20111224008507N3	RCT, double-blinded, multi-centre (Iran) Phase 3 study Follow-up duration (days):7 Funding: No specific funding (Mazandaran University of Medical Sciences) Declarations: None	Sample size: n=73 (n_1=35/ n_2=38) Disease severity: Moderate: unknown Severe: unknown Critical: n=3 Patient characteristics: Mean age: 46.4 years 36 (49%) males Inclusion criteria: Hospitalized patients (age >5 years, weight >15 kg) with any of the following: a positive result of COVID-19 RT-PCR; or clinical complaints of COVID-19 with a history of contact with a COVID-19 patient; or abnormalities in chest CT scan compatible with COVID-19 (ground-glass opacity, halo sign, reversed halo sign, and patchy infiltration). Exclusion Criteria: History of chronic liver and/or renal disease; concomitant warfarin, angiotensin-converting enzyme inhibitors, or angiotensin II receptor antagonists; acquired immunodeficiency; pregnant women and lactating mothers.	Intervention: Ivermectin 0.2 mg/kg orally once-off (weight-based doses, i.e. 15-24 kg: 3 mg; 25-30 kg: 6 mg; 36-50 kg: 9 mg; 51-80 kg: 12 mg; >80 kg: 0.2 mg/kg) - (n_1=35) Control: SOC (n_2=38) *SOC:* As per national protocols of Iran at the time of this study (HCQ and/or LPV/r). All participants received appropriate antibiotics and/or supplementary oxygen as indicated. Concomitant medicines: Not reported.	**Primary outcome(s):** *In the report* Clinical improvement after baseline defined as resolving patients' baseline status on persistent and continuous cough (coughing >1 hour, or ≥3 coughing episodes in 24 hours that interferes with daily life and ability to work) and tachypnea in addition to increasing oxygen saturation >94%. (Described in the register as: clinical symptoms including fever, chills, sore throat, cough, shortness of breath, decreased appetite, abdominal pain, dizziness, insomnia, itching, joint pain, joint swelling, headache, nausea, vomiting, diarrhea, malaise, conjunctivitis, tachycardia, wheezing, rhonchus, retraction, hypotension, rash, other symptoms; respiratory rate and O2 saturation-The first, second, third, fourth, fifth, sixth, seventh day).	**Primary outcome(s):** Ivermectin vs SOC: • *Clinical improvement from baseline:* ○ Mean duration of symptoms: 4.2 (0.3%) vs 5.2 (0.3%) days, p=0.023. ○ Mean duration of dyspnea: 2.4 (1.7%) vs 3.7 (2.1%) days, p=0.02. ○ Persistent cough: 3.1 (1.8%) vs 4.8 (2.0%), p <0.001. Other outcomes: • *Mean length of hospital stay:* ○ 6.9 (3.1%) vs 8.3 (3.3%) days, p =0.01. • *Supplemental oxygen:* ○ 10 (28.6%) vs 9 (26.5%), p=0.84 • *Invasive mechanical ventilation:* ○ 2 (6%) vs 1 (3%) • *Mortality:* ○ 1 (3%) vs 0 (0%) ○ 78-year-old critically ill woman with a history of diabetes mellitus, and heart failure died within 24 hours No adverse reactions or derangements in laboratory parameters were reported.	• The published report (pre-proof) and the retrospective registry was used in data extraction and assessment of the risk of bias. The protocol or statistical analysis plan was not available. • The study achieved the target sample size specified in the trial registry (n=60). • There is no change from the trial registration in the intervention and control treatments. • Study is double-blinded (registry). • Some outcomes from the report are not mentioned in the registry (e.g. adverse events, mortality). • Small study. • Diagnostic criteria for "COVID-19" were very broad – did not require a positive COVID-19 test – clinical or radiological evidence sufficient. **Risk of bias assessment: Overall – MODERATE RISK** • *Randomisation*: **LOW RISK** - random allocation sequence that was adequately concealed. • *Deviations from intervention:* **MODERATE RISK –** blinded to personnel/carers. Package of oral pills given to each group containing standard of care drugs with or without ivermectin. However, no placebo given to those in control group. • *Attrition:* **MODERATE RISK –** 69/73 patients analyzed. ○ Reasons: 4 withdrawals from the study, all participants were allocated to the control group receiving standard of care (no further details provided). ○ Risk assessed to be some concerns for the outcomes: Mortality (D28). • *Measurement of the outcome:* **LOW RISK** - blinded study (outcome assessor). • *Selection of the reported results:* **LOW RISK** ○ Primary outcome was pre-specified, but mortality outcome was not pre-specified in the registry; but considered appropriate.
Abd-Elsalam et al, 2021. Clinical study evaluating the efficacy of ivermectin in COVID-19 treatment: A randomized controlled study. J Med Virol. 2021 Jun 2. https://pubmed.ncbi.nlm.nih.gov/34076901/	RCT, unblinded, multi-centre (Egypt) Phase 2/3 study Follow-up duration (days):30	Sample size: n=164 (n_1=82/ n_2=82) Disease severity: Unclear Patient characteristics: Mean age: 40.9 years 82 (50%) males	Intervention: Ivermectin 12 mg per day orally for 3 days Control: SOC (n_2=38)	**Primary outcome(s):** *In the report* All-cause mortality within 1 month after randomization	**Primary outcome(s):** Ivermectin vs SOC: • *All-cause mortality (n):* ○ 3 (3.7%) vs 4 (4.9)%, p=1.00 Other outcomes: • *Length of hospital stay:* ○ 8.82 ± 4.94 days vs 10.97 ± 5.28 days, p = 0.085	• The published article and the trial registry was used in data extraction and risk of bias assessment. Neither protocol nor statistical analysis plan was available. • The trial was first registered during the conduct of the study. • There were substantial changes to methods during and after the conduct of the study from the initial trial registration to the final registration and report: sample size was reduced; intervention and control treatments

Clinical trial registration: NCT04403555	Funding: Not reported/ unclear Declarations: None	Inclusion criteria: Hospitalised adult patients, 20 to 65 years; mild to moderate COVID-19 infection confirmed by pharyngeal swab PCR Exclusion Criteria: Allergy or contraindication to study drugs; pregnant and lactating mothers; patients with cardiac problems	*SOC:* Egyptian MOH national protocols at the time of this study: paracetamol , oxygen, fluids, empiric antibiotic, oseltamivir if needed, invasive mechanical ventilation with hydrocortisone for severe cases if PaO_2 <60 mm Hg, O_2 sats <90% despite oxygen or noninvasive ventilation, progressive hypercapnia, respiratory acidosis (pH < 7.3), and progressive or refractory septic shock Concomitant medicines: Not reported.		• *Invasive mechanical ventilation:* ○ 3 (3.7%) vs 3 (3.7%), p=1.00	changed from ivermectin+doxycycline vs chloroquine to ivermectin vs standard care; ivermectin dosage was changed; primary outcome changed from resolved viral infection to mortality, and additional outcomes were added after the study had been completed. **Risk of bias assessment: Overall – MODERATE RISK** • *Randomisation*: **LOW RISK** - random allocation sequence that was adequately concealed. • *Deviations from intervention:* **MODERATE RISK –** Unblinded study (participants and personnel/carers); ITT analysis. • *Attrition:* **LOW RISK –** 164/164 patients analyzed. • *Measurement of the outcome:* **LOW RISK -** unblinded study (outcome assessor), but mortality is an observer-reported outcome not involving judgement. Risk assessed to be low for the outcome: Mortality (D28). • *Selection of the reported results:* **MODERATE RISK** ○ Trial registry was retrospective, and substantial changes were made to outcomes, follow up and interventions both during and after the conduct of the study. ○ Outcome not pre-specified: Primary outcome changed from negative viral conversion at 6 months to improvement or mortality at 1 month during the conduct of the study. The outcomes reported in the article were specified after study completion

• **IVERMECTIN + DOXYCYCLINE vs PLACEBO/STANDARD OF CARE – 4 RCTs**						
Citation	**Study design**	**Population**	**Intervention vs comparator**	**Outcomes**	**Effect sizes**	**Comments**
Mahmud et al,[20] 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	RCT, double-blinded, single center (Bangladesh) Phase 3 study Follow-up duration (days): 30	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;	*Intervention:* • Ivermectin+Doxycycline (12 mg/100 mg) daily • Co-Intervention: Standard care • Duration : 5 days	**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	**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	• 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

Clinical trial registration: NCT04523831	Funding/ agreements: No specific funding (No specific grant) Declarations: None	235 males (59%) Inclusion criteria: ≥18 years; PCR-confirmed COVID-19 infection within 3 days from enrollment;	*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.	**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	**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%)	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). • *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.[21] Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq. MedRxiv, 27 October 2020	RCT , parallel, single-blinded (outcome assessors), single-center (Alkarkh and Alforat hospitals in Baghdad, Iran)	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)	*Intervention:* • Ivermectin 200mcg/kg, oral daily • Duration: 2-3 days **PLUS**	**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	• 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.

https://www.medrxiv.org/content/10.1101/2020.10.26.20219345v1 NCT04591600	Phase 1/2 study Follow-up duration: 8 weeks Funding: Alkarkh Health Directorate-Baghdad Declarations: No conflicts of interest declared	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	• 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, mechanical ventilation as needed		• 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	**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*".
Ahmed S et al.[17] 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 Not registered on a clinical trial register	See study characteristics above (section ivermectin vs placebo)					

- **IVERMECTIN vs LIPONAVIR/RITONAVIR – 1 RCT**

Citation	Study design	Population	Intervention vs Comparator	Outcomes	Effect sizes	Comments
Babalola et al,[22] 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	RCT, parallel, double-blinded, dose-response, single-center (Lagos University Teaching Hospital, Nigeria) Phase 3 study Follow-up duration: 14 days Funding: Rachel Eye Center, Lagos University Teaching Hospital Declarations: No conflicts of interest reported	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) 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	*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 *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.	**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) – *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)	**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) 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.	• 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 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.[24] 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 Clinical trial registration: NCT04668469	RCT, double-blind, multicenter (Benha and Kafrelsheikh University Hospitals, Egypt) Study phase: Reported as not applicable in trial registry Follow up duration: 14 days Funding: No funding/support Declarations: The authors declare no competing interest.	Sample size: n=600 (Six gps, n= 100/study gp) **Note:** n = 400 in treatment gps (also 200 in 2 prevention gps not reported here) Disease severity: Mild/moderate: 200 Severe: 200 Characteristics of participants: Mean age: ranges from 33 to 79 years 281(70%) males Comorbidities *(Gp1=IVM:Gp2=HCQ:Gp3=IVM:Gp=-HCQ):* Diabetes: 15%:14%:18%:21%; Hypertension: 11%:12%:14%:18%; Ischaemic heart disease (IHD):2%:6%:5%:12%; Bronchial asthma: 5%:6%:14%:12% Inclusion criteria: Age 14-80 years; COVID-19 infected patients, diagnosed with at least one positive nasopharyngeal/ oropharyngeal swab rt-PCR result . • *Mild cases:* Mild symptoms such as anosmia, loss of taste, fever or respiratory tract symptoms,	*Intervention(s):* (4 gps for treatment of COVID-19) ***Mild/moderate*** • **Gp 1**: Ivermectin 400 mcg/kg to a max of 4x6mg tabs daily Duration: 4 days • **Gp 2:** HCQ (400 mg 12hrly x 1day, then 200mg 12hrly x5days Duration: 6 days ***Severe*** • **Gp 3**: Ivermectin 400 mcg/kg to a max of 4x6mg tabs daily Duration: 4 days • **Gp 4**: HCQ (400 mg 12hrly x 1day, then 200mg 12hrly x5days Duration: 9 days *Standard care: Egyptian MOH protocol*[1]*:* azithromycin 500mg daily x5days, paracetamol 500mg as needed,	**Primary outcome(s):** • Clinical, laboratory investigations improvement and/or; • 2 consecutive negative PCR tests taken at least 48 hours apart. • Mortality rate • Hospital stay days • Reduction of recovery time **Secondary outcomes:** *preprint* • Adverse events requiring stoppage of treatment and management of any side effects accordingly	**Primary outcome(s):** Ivermectin (Gps 1,3) vs HCQ (Gps 2,4) *Mortality rate:* • *Mild/Moderate disease:* 0/100 vs 4/100 • *Severe disease:* 2/100 vs 20/100 *Prognosis – improved:* • *Mild/Moderate disease:* 99/100 vs 74/100 • *Severe disease:* 94/100 vs 50/100 *Prognosis – progressed:* • *Mild/Moderate disease:* 1/100 vs 22/100 • *Severe disease:* 4/100 vs 30/100 **Secondary outcome(s):** *Adverse events: "The reported incidence and type of adverse events were generally comparable between ivermectin (24%) and placebo (35%) and didn't increase with dose".*	• Data extracted from the preprint and trial registry. Protocol and statistical analysis plan not available. **The trial was registered after the study was completed.** • Conflicting information between preprint and trial registry regarding: o *Standard care*: trial registry also includes steroids as needed o *Outcomes:* improvement of laboratory investigations and 2 consecutive negative PCR tests taken at least 48 hours apart reported as secondary outcomes in trial registry, but as primary outcomes in preprint. • Definition for severe and critical cases (latter excluded from study) may overlap in terms of respiratory support. • Concerns that exclusion criteria was applied during the trial, as eligibility/exclusion criteria included, "*Treatment was terminated at any time by a multidisciplinary team if a serious side effect occurred, which was attributed to the medications used"* – may be a language issue. • Details of clinical failures are not clearly reported (i.e. loss to follow-up, whether cross-over of study participants occurred, whether an ITT or per protocol analysis – all unclear), "*….Any patient demonstrates worsening of symptoms; radiological progression with virologically persistence within at least 7 days of the therapeutic evaluation period of the study after exclusion of cytokine storm was considered as a clinical failure and was shifted to the other management".* • The report lacks a sample size calculation and power statement (n=400 for treatment; n=200 for prophylaxis). • The statistical analysis software is described, but the following statement is unclear, "*…After the calculation of each of the test statistics, the corresponding distribution tables were counseled to get the "P"(probability value)".* • Tabulated laboratory results for respective study groups are not clearly described, as reported as both "at one week" and "after one week". • There is unclear risk of bias (see below) - as randomisation, allocation concealment and blinding are incompletely reported, decreasing confidence in the results.

[1] Ghazy, R.M., Almaghraby, A., Shaaban, R. et al. A systematic review and meta-analysis on chloroquine and hydroxychloroquine as monotherapy or combined with azithromycin in COVID-19 treatment. Sci Rep 10, 22139 (2020). https://doi.org/10.1038/s41598-020-77748-x

		gastrointestinal symptoms, etc. with clear chest imaging. • *Moderate cases:* Symptoms such as fever, respiratory tract symptoms, gastrointestinal symptoms, etc. with pneumonia manifestations from chest imaging. • *Severe cases:* confirmed COVID-19 with any of: 1. Respiratory rate > 30/min. 2. Blood oxygen saturation < 93%. 3. PaO2/FiO2 <200 4. Lung infiltrates >50% or rapid progression within 24-48 hours. 5. Need for respiratory support e.g. high flow oxygen, noninvasive/ invasive mechanical <u>Exclusion criteria:</u> Pregnancy, lactation, critical cases (respiratory failure requiring mechanical ventilation), patients in shock, other organ failure requiring ICU management, contra-indications to HCQ (QTc > 500 m/sec, myasthenia gravis, porphyria, retinal pathology, epilepsy, G6PD deficiency, allergy to 4-aminoquinolone, chronic heart, kidney or liver disease, arrhythmias, any patient with worsening of symptoms/ radiological progression with virologically persistence within at least 7 days of the therapeutic evaluation period of the study after exclusion of cytokine storm, treatment was terminated at any time by a multidisciplinary team if a serious ADR occurred	vitamin C 1gm oral daily, Zinc 50mg oral daily, lactoferrin 100mg sachets 12hrly, acetylcysteine 200mg 8hrly, prophylactic/ therapeutic anticoagulation if D-dimer >1000) and systemic steroid if needed (reported in registry but not preprint)			• Heterogeneous patient sample: ○ *Baseline comorbid IHD* – Gp I (IVM)=2%, Gp 2 (HCQ)=6%, Gp 3(IVM)=12%, Gp 4(HCQ)=18%; with statistically significant prevalence of ischemic heart disease as severity increase (p=0.03) – mortality may have been attributed to underlying IHD in the HCQ groups. ○ *Baseline clinical symptoms*: "*Clinically there was a highly statistically significant difference between groups regarding fatigue, dyspnea, and respiratory failure (p-value <0.001), as most of group III & IV, showed fatigue and dyspnea (86%, 88% and 86%, 88%, respectively), compared to (36%, 38% and 54%, 52%, respectively), in group I & II. Respiratory failure had been detected in 38% and 40% in group III& IV respectively while no patients in group I& II developed respiratory failure".* • New signals of harm[33] associated with chloroquine-azithromycin in the control group may have contributed to the apparent benefit of ivermectin. • This study was updated with data from contact with authors on 12 April 2021 by the COVID.nma team. • Overall the study was not clearly reported. **Risk of bias assessment: Overall - MODERATE to HIGH RISK** • *Randomisation*: **LOW RISK** – "*A block randomization method was used to randomize the study participants into two groups that result in equal sample size. This method was used to ensure a balance in sample size across groups over the time and keep the number of participants in each group similar at all times." In the protocol "The main investigator with the statistician had the randomization code, which was hidden from both the patients and treating doctors*" – random allocation sequence that was sufficiently concealed. • *Deviations from intervention*: **MODERATE RISK** – *"double blind randomized controlled clinical trial"* – but details not provided and it is unclear how carers were blinded as the frequency and duration of the treatments were different between groups • *Attrition:* **LOW RISK** – 200/200 patents analyzed. • *Measurement of the outcome:* **MODERATE RISK** - Unclear blinding of outcome assessor. ○ Mortality is an observer-reported outcome not involving judgement, thus risk assessed as low for this outcome. ○ Adverse events and serious adverse events that may contain both clinically- and laboratory-detected events, can be influenced by knowledge of the intervention

						assignment, but is not likely in the context of the pandemic. Thus, risk assessed to be some concerns for the outcomes: Adverse events. Serious adverse events. • *Selection of the reported results:* **MODERATE RISK – registration occurred after the study was completed.** ○ No information on whether the results were selected from multiple outcome measurements or analyses of the data, or whether the trial was analyzed as pre-specified.
Beltran-Gonzalez et al., 2021. 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	See study characteristics above (section ivermectin vs placebo)					
Galan L et al, 2021. 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	*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.

		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.				○ 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*".

• **IVERMECTIN+DOXYCYCLINE vs HYDROXYCHLOROQUINE+AZITHROMYCIN – 1 RCT**						
Citation	**Study design**	**Population**	**Intervention vs Comparator**	**Outcomes**	**Effect sizes**	**Comments**
Chowdhury et al. [23] 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:	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	*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,	**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	• 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*

	None	in patients with respiratory symptoms <u>Exclusion criteria:</u> Unstable comorbid conditions (bronchial asthma, COPD, ischemic heart disease, uncontrolled diabetes mellitus, advanced renal and hepatic disease, carcinoma); hospitalised and Immuno-compromised patients	details not provided.		palpitation, and 9(16.07%) nausea and vomiting.	*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. ○ 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".*

Appendix 1: Search strategy

Updated Search performed on 26 May 2021

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: "prevention or treatment and ivermectin and COVID-19"
Search date: 26 May 2021
Results: 265 total articles

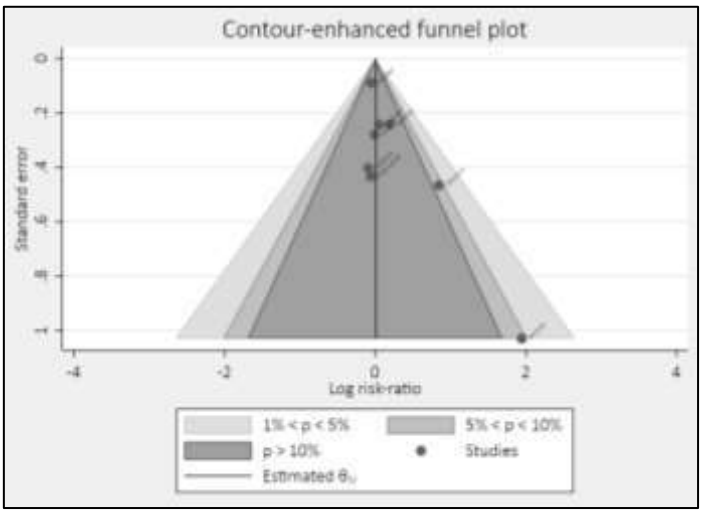
- 6 broad syntheses
- 25 systematic reviews - 2 duplicates excluded, 23 records screened and **all systematic reviews excluded**
- 234 studies - 139 reported as RCTs of which 51 RCTs reported data: 12 records were duplicates, 1 record was a non-RCT, 3 were news releases and 2 presentations of RCT data; 33 records screened: 14 excluded, 11 records previously reviewed, **9 additional records of RCTs reviewed for evidence synthesis**

Pan American Health Organization: Institution Repository for Information Sharing. https://iris.paho.org/
Most current version of the living review is dated the 6 May 2021, which was excluded as a number of study results have been published subsequently (in either peer reviewed or preprint format).

Cochrane COVID-19 Study register
Search strategy: "ivermectin and COVID-19"
Search date: 15 January 2021 to 26 May 2021
Results: 1 records retrieved which was a duplicate record retrieved from the L·OVE for COVID-19 search
- 0 studies included in evidence synthesis.

Cochrane living syntheses
https://covid-nma.com/
COVID-NMA is an international research initiative supported by the WHO and Cochrane. Provides a living mapping of COVID-19 trials available through interactive data visualizations and conducts living evidence synthesis on preventive interventions, treatments and vaccines for COVID-19. Living review protocol: https://zenodo.org/record/4018607#.YAq8HegzbIU

Appendix 2: Funnel plot of RCTs comparing ivermectin vs placebo/ standard of care for viral clearance at day 7.



The funnel plot suggests missing small negative trials, but such plots are less useful when there are so few absolute numbers of events in small trials.

Appendix 3: Excluded studies

Study	Reason for exclusion
1. Bryant et al. Ivermectin for Prevention and Treatment of COVID-19 Infection: a Systematic Review and Meta-analysis, 18 March 2021. https://www.researchsquare.com/article/rs-317485/v1	Preprint, currently under review and later RCTs have been published.
2. 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/	Review of ivermectin as prophylaxis.
3. Taher M et al. Drugs intervention study in COVID-19 management. Drug Metab Pers Ther. 2021 Apr 5, https://pubmed.ncbi.nlm.nih.gov/33818031/	Analysis included studies up to December 2020. Later RCTs have been published.
4. Alex Castaneda-Sabogal et al. Outcomes of Ivermectin in the treatment of COVID-19: a systematic review and meta-analysis, MedRxiv, January 2021. https://www.medrxiv.org/content/10.1101/2021.01.26.21250420v1	Preprint, currently under review and later RCTs have been published.
5. Kow CS et al. The association between the use of ivermectin and mortality in patients with COVID-19: a meta-analysis. Pharmacol Rep. 2021 Mar 29:1–7. https://pubmed.ncbi.nlm.nih.gov/33779964/	Analysis included studies up to 28 February2021. Later RCTs have been published.
6. Hill A, Abdulamir A, Ahmed S, et al. Meta-analysis of randomised trials of ivermectin to treat SARS-CoV-2 infection. Preprint. https://www.researchsquare.com/article/rs-148845/v1	Previously excluded – see the previous ivermectin rapid review report, dated 25 January 2021.
7. Kory P et al. Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19. American Journal of Therapeutics. 2021;28(3). https://dx.doi.org/10.1097/MJT.0000000000001377	Review and analysis included a mix of RCTs and observational studies. Later RCTs have been published.
8. Kinobe RT, Owens L. A systematic review of experimental evidence for antiviral effects of ivermectin and an in-silico analysis of ivermectin's possible mode of action against SARS-CoV-2. Fundamental & clinical pharmacology. 2021;35(2):260-276. https://pubmed.ncbi.nlm.nih.gov/33427370/	Review of "in vitro" and "in vivo" studies.
9. 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 Apr 16:1–10. https://pubmed.ncbi.nlm.nih.gov/33864232/	Analysis included studies up to 28 February 2021. Mix of RCTs and observational studies.
10. Rodríguez-Gutiérrez R et al. Ivermectin in the Prophylaxis and Treatment of Patients with SARS-CoV-2: A Living Systematic Review and Meta-Analysis. SSRN, March 2021. https://dx.doi.org/10.2139/ssrn.3802499	Preprint, currently under review and later RCTs have been published
11. Alexander et al. Early Multidrug Outpatient Treatment of SARS-CoV-2 Infection (COVID-19) and Reduced Mortality Among Nursing Home Residents. medRxiv. 1 February 2021. https://dx.doi.org/10.1101/2021.01.28.21250706	Preprint, currently under review and later RCTs have been published
12. 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 - Evidence-based Medicine Consultancy Ltd. January 2021. http://dx.doi.org/10.13140/RG.2.2.27751.88486	Manuscript not peer-reviewed (only published on researchgate), and later RCTs have been published.
13. Comisión Nacional de Evaluación de Tecnologías de Salud. Ivermectin for the treatment of patients with COVID-19 y expuestos al SARS-CoV-2 (May 7, 2021). 2021. https://docs.bvsalud.org/biblioref/2021/05/1222803/informe-covid-19-n14-ivermectina.pdf	Spanish HTA (Argentina) and later RCTs have been published.
14. 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.
15. 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.
16. 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.
17. Pan American Health Organization. Ongoing Living Update of Potential COVID-19 Therapeutics: Summary of Rapid Systematic Reviews, 16 June 2020. Pan American Health Organization. 2020; https://iris.paho.org/handle/10665.2/52294	Previously excluded – see the previous ivermectin rapid review report, dated 25 January 2021.
18. Padhy B.M., Meher B.R., Mohanty R.R., Das S.. Therapeutic potential of ivermectin as add on treatment in COVID 19: A systematic review and meta-analysis. J Pharm Pharm Sci. 23 November 2020;23:462-469. https://dx.doi.org/10.18433/jpps31457	Previously excluded – see the previous ivermectin rapid review report, dated 25 January 2021.

19. Gonçalves . Therapeutic potential of ivermectin for COVID-19. Authorea. May 26, 2020. https://doi.org/10.22541/au.159050476.60928563	Preprint, currently under review and later RCTs have been published.
20. Pan American Health Organization. Ongoing Living Update of Potential COVID-19 Therapeutics: summary of rapid systematic reviews. Pan American Health Organization. 13 July 2020:91-91. https://iris.paho.org/handle/10665.2/52481	Previously excluded – see the previous ivermectin rapid review report, dated 25 January 2021.
21. Pan American Health Organization. Ongoing Living Update of Potential COVID-19 Therapeutics: summary of rapid systematic reviews. Rapid Review, 23 May 2020. Pan American Health Organization. 2020. https://iris.paho.org/handle/10665.2/52193	Only "*in vitro*" and observational studies were reviewed for ivermectin.
22. de Agassiz Almeida Vasques M et al. Abordagem profilática da nitazoxanida e ivermectina na COVID-19: Sumário de Evidências: Nitazoxanide and Ivermectin COVID-19 prophylaxis approach: Evidence summary. 2020;31. https://academic.microsoft.com/paper/3091272409/reference	Review of ivermectin as prophylaxis for COVID-19.
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36. Chahla RE et al. Cluster Randomised Trials - Ivermectin Repurposing For COVID-19 Treatment Of Outpatients With Mild Disease In Primary Health Care Centers, Research Square, 6 May 2021. https://www.researchsquare.com/article/rs-495945/v1 NCT04784481	Phase 1 / 2 open label cluster RCT.

Appendix 4: Evaluating the methodological quality of the Hill et al (2020) systematic review and preliminary meta-analysis – AMSTAR 2 tool (Shea 2017[2])

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.)

[2] 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.

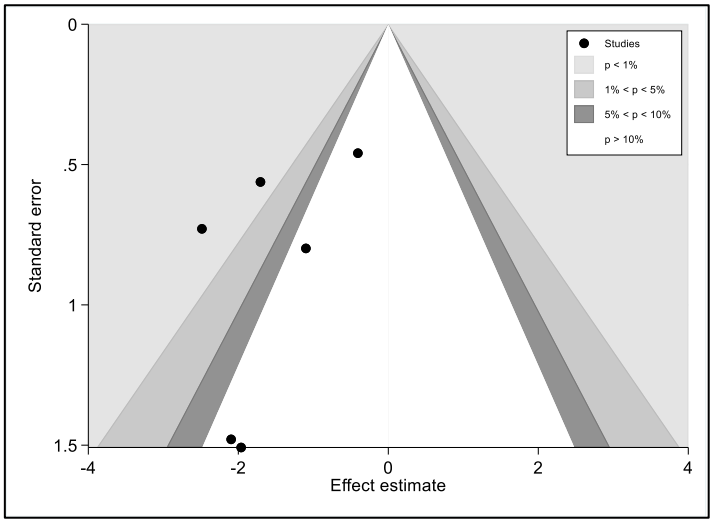

Figure 1: Funnel plot of RCTs included in the meta-analysis by Hill et al.

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.

Appendix 5: 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 *(possible publication bias if negative studies are not being shared in reports yet).*
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. In addition, it is difficult to clearly separate out ivermectin side effects from doxycycline side effects in studies that combined the two drugs.
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.
FEASABILITY	**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 equity?** Yes: X No: ☐ Uncertain: ☐	Access is currently only available through section 21 or as a compounded product.

Appendix 6: 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.

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APPRAISAL OF THE SYSTEMATIC REVIEW BY BYRANT *et al*. ON USE OF IVERMECTIN FOR TREATMENT AND PREVENTION OF COVID-19

Date: 2 July 2021

Background:

An updated NEMLC COVID-19 rapid review of ivermectin (18 June 2021) for the management of COVID-19[1] was published on the National Department of Health website in June 2021. A meta-analysis and systematic review of randomised controlled trials (RCTs) for ivermectin by Byrant *et al.* had been published in the American Journal of Therapeutics on 17 June 2021[2]. This study was not included in the rapid review, and thus an appraisal of this review follows:

Overview:

Rosenthal[3] 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 AMSTAR[4] 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[5] 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

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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.
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[6].

[6] 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.

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.

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

Declaration of interests: AP (Walter Sisulu University); TK (Cochrane South Africa, South African Medical Research Council; Division of Clinical Pharmacology, Stellenbosch University; South African GRADE Network); JN (Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand); HD (Infectious diseases, Greys hospital and University of KwaZulu-Natal); TL (National Department of Health, Affordable Medicines Directorate, Essential Drugs Programme) and MR (Better Health Programme, South Africa) have no interests with regards to ivermectin.

Appendix A: Evaluating the methodological quality of the Bryant et al (2021) systematic review and meta-analysis – AMSTAR 2 tool (Shea 2017[4])

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.