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: 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 intervention and comparator groups, and suffer from significant methodological limitations that limit the confidence in any conclusions that can be drawn.
- There is currently insufficient evidence to recommend ivermectin for the treatment of patients with COVID-19. Further evidence is anticipated in the forthcoming weeks and will be incorporated accordingly.

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 for COVID-19, except in the context of a clinical trial.
Rationale: There is insufficient evidence to recommend ivermectin currently. At this time, 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.
Level of Evidence: RCTs of very low methodological quality

Review indicator: New high quality evidence of a clinically relevant benefit

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 14 January 2021, 28 RCTs were still in progress/not completed, 1x phase 2 RCT has been completed, and study results are awaited (NCT04381884); 2x phase 3 RCTs completed, and study results awaited (NCT04391127, NCT04405843) and 1x RCT results are undergoing quality check (NCT04646109).

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 and is not registered in South Africa for human consumption, but may be accessed via S21 application. 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 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.

METHODS

We conducted a 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 14 January 2021. The search strategy is shown in Appendix 1. Screening of records and data extraction was conducted by three reviewers (TL, JN, HD), with resolution of disagreements through discussion, or, if required, the fourth reviewer (AP) was consulted. Relevant records were extracted in a narrative table of results (Table 1) and excluded studies were listed with rationale for exclusion (Appendix 2) by one reviewer and checked by two other 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. However, as the evidence is still maturing, phase 2 studies have been included in this review, until such time as more evidence emerges.

Quality assessment of relevant systematic review(s) were performed independently using the AMSTAR 2 tool for systematic reviews (TL, HD). GRADE[8] quality assessment was not done as the RCTs were too heterogeneous to conduct a meta-analysis.

Meta-analyses are generally conducted if RCTs are sufficiently homogeneous in terms of design, population, interventions, comparators and outcome measures[9]. In an effort to address the controversy around ivermectin's use in COVID-19, data from relevant RCTs were pooled to assess publication bias of the RCTs showing a mortality benefit of ivermectin with/without co-interventions compared to placebo/standard of care or other comparator, using RevMan (Review Manager)[10] – see figure 1, below.

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 205 records of which 11 were duplicates and 163 records were incomplete (study in process/study results not reported). Of the remaining 31 records that were screened, 15 records were excluded and 12 records were selected for inclusion in the evidence synthesis. An additional record from Brazil (in Portuguese) was shared by the review team conducting the prophylaxis review, but was excluded as PICO requirements were not met. The preprint by Hill et al published on the 19 January 2021 was also included in this review, as it is the basis for ivermectin advocacy on many local social media platforms. 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).

Excluded studies: Refer to Appendix 2 for a list of the excluded studies and supporting rationale for exclusion.

One of the excluded studies was a meta-analysis by Hill et al.[11] Evaluating the methodological quality using AMSTAR 2 tool[12] 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.

Evaluating the methodological quality of the Hill et al (2020) systematic review and preliminary meta-analysis – AMSTAR 2 tool (Shea 2017[1])

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

[1] 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.

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.)

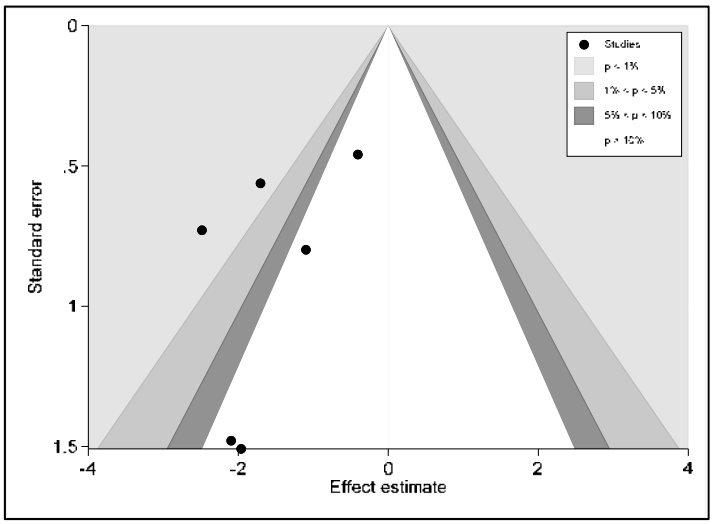

Figure 1: Funnel plot of RCTs included in the meta-analysis by Hill et al.

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 was therefore not included in this review.

Included studies: 12 RCTs were included in the final analysis:

- 7 compared ivermectin to placebo or standard of care [13, 14, 15, 16, 17, 18, 19]
- 3 compared ivermectin + doxycycline to placebo or standard of care[20, 21, 17]
- 1 compared ivermectin to lopinavir/ritonavir [22]
- 1 compared ivermectin + doxycycline to azithromycin + hydroxychloroquine[23]
- 1 compared ivermectin to hydroxychloroquine and to standard of care[24]

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 extreme caution.

Mortality

Five RCTs reported on mortality as a specific outcome; none are yet available as peer-reviewed publications. Kirti et al.[13] compared ivermectin (n=57, given as 12mg daily for 2 consecutive days) with placebo (n=58) among adults with "mild" (no evidence of hypoxia or breathlessness) or "moderate" disease (oxygen saturation 90-94% on room air, respiratory rate of 24-30, and no shock or evidence of life-threatening organ dysfunction). 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. 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, which may have led to an overestimation of the mortality benefit of ivermectin. In addition, the absolute number of events was small (4 across both arms), 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).

Mahmud et al.[20] compared a combination of ivermectin (12mg daily, n=200) and doxycycline (100mg 12-hourly, n=200), each given for 5 days, with placebo. "Mild" and "moderate" cases were enrolled. Each arm also received the background standard of care, consisting variably of paracetamol, vitamin D, low-molecular weight heparin, and dexamethasone "if indicated". Mortality was reported, although it was not a primary outcome of the trial. The mortality in the ivermectin arm was 0/183 vs 3/180 (1.67%) in the placebo arm. This difference was not statistically significant (RR 0.14, 95% CI 0.01-2.75, graded as "very low certainty of evidence"). The risk of bias in this study was again high. 17 patients in the ivermectin group, and 15 patients in the control group, were lost to follow up for reasons that could possibly relate to the outcomes studied. Furthermore, it was not possible to ascertain from the available data whether the two groups differed substantially with respect to co-morbidities, baseline severity, or the drugs that were co-administered.

Niaee et al.[18] conducted a study of ivermectin in patients with mild to severe COVID-19 in 5 hospitals in Iran. 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. This necessarily casts into doubt whether the mortality differences seen can be attributed to ivermectin.

Elgazzar et al.[24] studied the effect of ivermectin and 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.

Finally, 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.

In addition to the above trials, mortality could be indirectly inferred from the studies by Chaccar[14], Chaccour[19], Babalola[22], and Krolewicki[16]. No deaths were seen in either the control or the intervention arms of these studies.

Change in clinical status

The included studies varied widely in how they assessed and interpreted clinical outcomes apart from mortality.

Several studies measured the proportion of asymptomatic patients at defined time points. Ravikirti et al.[13], Chachar et al.[14], and Ahmed et al.[17] all found no statistically significant differences in this regard between trial arms on days 6, 7 and 7 respectively. By contrast, Mahmud et al.'s[20] study had a higher proportion of patients with early (7 days) and late (12 days) clinical improvement in the ivermectin + doxycycline arm compared to placebo.

Other studies measured the time to resolution of symptoms. Podder et al.[15] and Chowdurry et al.[23] found approximately a 1 day shorter duration of symptoms in the ivermectin arm, though in neither case was this was statistically significant. Patients in the ivermectin arm of Chaccour's[19] small study had numerically fewer patient-days of symptoms than the placebo group, but no test of statistical significance was performed. Hashim et al.'s[21] study showed a shorter time to recovery in the ivermectin + doxycycline arm, although how "time to recovery" was defined or measured is not mentioned in the preprint.

Finally, several trials assessed "improvement" more generically. Elgazzar et al.[24] reported that the ivermectin arm of their trial showed improvement in "prognosis" in a higher number of cases compared to the hydroxychloroquine arm. However, no test of statistical significance was performed, and how the improvement in "prognosis" was defined or measured was not stated. Hashim et al[21] found no significant difference in the rate of progression to severe disease; disease severity was not defined. Naiee[18] found a statistically significant decrease in hospitalisation length in the trial arms containing ivermectin compared to the non-ivermectin arms, though the absolute difference was small, the groups were potentially imbalanced with respect to true COVID-19 cases, and it is not clear that the analysis was adjusted for differential mortality rates. Kirti et al.[13] found no significant differences in rates of admission to ICU or the need for mechanical ventilation.

Further details on the trials are available in table 1. The trials were of poor quality overall, suffering from, amongst other limitations, a lack of blinding, subjective and poorly-defined endpoints, a lack of clarity as to how changes in clinical state were measured, and often an active control arm that had the potential for harm.

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.

Kirti et al.[13] found no significant differences in the proportion of negative RT-PCR results on day 6. Similarly, a study by the Chaccour et al.[19] showed no significant differences in the same by day 7, and Podder et al.'s[15] trial showed no significant differences after 10 days from the initial RT-PCR. Ahmed et al.'s[17] small trial paradoxically found a higher proportion of viral clearance at 7 and 14 days in the ivermectin arm, but not in the ivermectin + doxycycline arm (in both cases compared to placebo). Mahmud et al.[20] found a lower proportion of patients with a positive RT-PCR on day 14 in the ivermectin + doxycycline group.

Kroeliecki et al.[16] found no significant difference in viral loads between the intervention and control arms at day 5. Likewise, Chaccour et al.'s[19] study found comparable viral loads at days 4,7, 14, and 21 between ivermectin and placebo groups. Chowdurry' et al.[23] found no significant difference in time to negative PCR in the ivermectin + doxycycline group compared to the hydroxychloroquine + azithromycin group.

Further details of these trials are available in table 1. Again, the trials were of poor quality overall, and sample sizes were generally very small, limiting the strength of any conclusions. In addition, the assays used in the determination of viral loads and RT-PCR positivity varied substantially across trials, limiting any generalised conclusions. A positive PCR also does not necessarily denote viable virus or infectivity, especially at later time points after an acute infection.

Safety

Only a minority of ivermectin RCTs included mention of adverse events. 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.

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.

CONCLUSION

The current evidence base for the use of ivermectin in COVID-19 remains poor. The vast majority of the trials included have not been peer-reviewed. The available RCTs generally 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 of 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 urgently needed. We anticipate that further data will be forthcoming in the coming weeks, and this review will be updated accordingly.

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**
Ravikirti et al.[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	*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*: **HIGH RISK -** Block randomisation. Allocation sequence and concealment – *"allocation table was generated using the Sealed Envelope software".* o 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:* **HIGH RISK –** double-blind study o 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"..* o *"..up until the analysis of the data, this information was confined to the pharmacist dispensing the tablets*. Pharmacist dispensed the medicine and ensured blinding. o Per protocol analysis • *Attrition:* **MODERATE RISK** – 112 of 115 randomised patients were analyzed.

		participate in the study; prior use of ivermectin during the course of this illness; pregnancy and lactation				o Ivermectin gp: 2/58 patients randomized but not included in analysis, as 1 LTFU, 1 excluded from analysis as deviation from study protocol. o Ivermectin gp: 1 patient excluded from analysis as deviation from study protocol. o Risk assessed to be some concerns for the outcome: In-house mortality. • *Measurement of the outcome:* **HIGH RISK** - Double-blinded study. o A conclusive repeat RT-PCR report could not be obtained in 32.1% of the patients. • *Selection of the reported results:* **MODERATE RISK** - The protocol, statistical analysis plan and registry were not available. o Risk assessed to be some concerns for the outcome: Incidence of viral negative conversion. 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.[14] Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients, International journal of sciences, https://www.ijsciences.com/pub/article/2378 Not registered on a clinical trial registry	Open-label; RCT, single centre (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	Sample size: n=50 (25/study group) 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.	*Intervention:* • 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	**Primary outcome(s):** Clinical response at day 7 – o symptom improvement (clinical parameters included fever, cough, sore throat, headache, shortness of breath, lethargy, and fatigue o side effects	On follow up at day 7, patients were stratified as asymptomatic and symptomatic: o Case/intervention gp: 16/25 (64%) symptomatic o 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: o Cough was observed more in case group: 24 (48%) 18(36%) (p= 0.049). o Fever, myalgias and dyspnea similar in both groups (p= 1.000). o Diarrhea more common in control group: 4(8%) vs 17(34 %) (p=0.0001) o Vomiting more common in control group: 6(12%) 14(28 %) (p= 0.042) respectively). o Loss of taste more common in case group: 15(30%) vs 5(10%) (p= 0.009 o Anosmia more common in case group: 15(30%) vs 5(10%) (p=0.0009)	• Data extracted only from the publication, as protocol and registry trial information not available – attempted to contact the corresponding author, but no contact details provided. The study achieved its stated sample size. • Authors stated that, "*our study revealed that after giving Ivermectin, on day 7, 64% patients were 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. • Only symptomatic patients were analysed according to predefined clinical paramaters. Asymptomatic patients were not analysed (perhaps using RT-PCR). **Risk of bias assessment: Overall – HIGH RISK** • *Randomisation:* **MODERATE RISK** - " *Quote: "Patients were allocated randomly to the groups by computer generated number."* • *Comment: Allocation sequence random. No information on allocation concealment.* • *Deviations from intervention:* **MODERATE** to **HIGH RISK** – Open label study

		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)				o Details of conventional symptomatic treatment or co-interventions not reported. o No participant cross-over. o Data were analyzed using intention-to-treat analysis. • *Attrition:* **LOW RISK** – all randomised patients were analyzed. Data available for (>) 95% of population. Risk assessed as low for the outcomes: clinical improvement and adverse events. • *Measurement of the outcome:* **HIGH RISK** - Unblinded study. o Risk assessed to be high for determining symptom improvement, as these are subjective measures (fever, cough, sore throat, headache, shortness of breath, lethargy, and fatigue) which were not well defined in the report – and the study protocol was not accessible. • *Selection of the reported results*: **HIGH RISK** – o The protocol, statistical analysis plan and registry were not available. No information on whether the trial was analyzed as pre-specified. o Asymptomatic patients were not analysed. o Risk assessed to be high for the outcome: symptom improvement (fever, cough, sore throat, headache, shortness of breath, lethargy, and fatigue). 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.[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:	*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	**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.

		Exclusion criteria: Known allergy to Ivermectin, pregnancy, lactation, patients on other antimicrobials (besides doxycycline, oral) or HCQ	the local working protocol.			o Concomitant administration of medicines such as antivirals, anticoagulants, biologics and corticosteroids not reported. o Intention-to-treat analysis • *Attrition:* **HIGH RISK** – 62 of 82 randomised patients were analyzed; 40 patients analyzed for outcome of interest. Data unavailable for >5% of population. o 18/82 patients randomized but not included because of prior symptom duration. o 2/82 patients randomized not included because of insufficient data. o Only 20 patients in each arm tested for viral negative conversion with no information on how they were selected. o Risk assessed to be high for the outcome: Incidence of viral negative conversion. • *Measurement of the outcome:* **LOW RISK** - Unblinded study. o 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. o 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.[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	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;	*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	• 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. • Pre-specified sample size was achieved. • 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.*"

	had no role in primary data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication) Declarations: 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.	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 30 days after last study drug administration;			relationship between IVM plasma levels and adverse events. Ivermectin shown to have a concentration dependent antiviral activity against SARS-CoV-2.	o 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 patients analyzed for, adverse events and serious adverse events. o Risk assessed to be low for the outcomes: WHO score 7 and above; adverse events and SAEs. • *Measurement of the outcome:* **MODERATE RISK** - Blinded Outcome assessors not blinded for outcomes of interest. o Risk assessed to be low for the outcomes: WHO score 7 and above. o Risk assessed to be some concerns for the outcomes: Adverse events; SAEs. • *Selection of the reported results:* **LOW RISK** - Pre specified in the registry, but neither the protocol nor the statistical analysis plan available. o 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.[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	RCT, double-blinded, single center (Bangladesh) Phase of study not reported Follow-up duration (days): 14 Funding: Beximco Pharmaceutical Limited, Bangladesh – supplier of ivermectin 12 mg tablets Declarations: Authors reported no conflicts of	Sample size: n = 72 randomised (n=24/group: ivermectin +doxycycline vs control vs ivermectin) Disease severity: Mild Inclusion criteria: 18-65 years; admitted to hospital ≤ 7 days [with either fever (>37.5C); cough or sore throat; and diagnosed positive for SARS-CoV-2 by rRT-PCR]; Patient characteristics: Mean age: 42 years; 46% male;	*Intervention:* • Ivermectin+doxycycline (12 mg/100 mg) daily • Co-Intervention: Standard care • Duration : 5 days *Control 1:* • Placebo • Co-Intervention: Standard care • Duration : 5 days *Control 2:* • Ivermectin (12 mg) daily • Co-Intervention: Standard care • Duration: 5 days	**Primary outcome(s):** Time required for virological clearance (a negative rRT-PCR result on nasopharyngeal swab); remission of fever (>37.5°C) and cough within 7 days	**Primary outcome(s):** Ivermectin+doxycycline vs placebo • *The mean duration to viral clearance:* o Ivermectin+doxycycline: 11.5 days (95% CI 9.8 to 13.2 days); p=0.27 o Placebo: 12.7 days (95% CI 11.3 to 14.2 days); no p-value reported o Ivermectin: 9.7 days (95% CI 7.8 to 11.8 days); p=0.02 • *Viral clearance at 7 days:* o Ivermectin vs placebo: HR = 4.1, 95% CI 1.1 to 14.7; p = 0.03 o Ivermectin+doxycycline vs placebo: HR 2.3, 95% CI 0.6 to 9.0; p=0.22 • *Viral clearance at 14 days:* o Ivermectin vs placebo: HR = 4.1, 95% CI 1.1 to 14.7; p=0.03 o Ivermectin+doxycycline vs placebo: HR 1.7, 95% CI 0.8 to 4.0; p=0.19	• Only the published article was used in data extraction and assessment of risk of bias. No study protocol, statistical analysis plan or trial 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). • Mortality, reported as a study outcome in the methods, was not clearly reported. **Risk of bias assessment: Overall – MODERATE RISK** • *Randomisation*: **MODERATE RISK** - Allocation sequence and allocation sequence concealment not reported. "*randomized, double-blind, placebo-controlled trial* ".

	interest to declare.	Duration of illness before assessment was an average of 3.83 days.	*Standard of care:* Not reported		• *Clinical symptoms of fever, cough, and sore throat at day 7:* Comparable among the three groups *Severe adverse drug events:* None recorded in the study.	• *Blinding:* **LOW RISK** - Blinded study, "*randomized, double-blind, placebo-controlled trial".* • *Attrition:* **MODERATE RISK** – 68 of 72 randomised patients were analyzed. o 1 patient from each of the ivermectin+doxycycline and placebo arms and 2 from the 5-day ivermectin arm withdrew their consent. o Risk assessed as low for the outcomes: Time to viral negative conversion; serious adverse events. • *Measurement of the outcome:* **LOW RISK** - Blinded outcome assessor (risk assessed as low for the outcomes: Time to viral negative conversion; serious adverse events • *Selection of the reported results*: **MODERATE RISK** - The trial registry, protocol and statistical analysis plan were not available. o Unclear whether the result was selected from multiple outcome measurements or analyses of the data and if the trial was analyzed as pre-specified. 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[18]. Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center 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	RCT, double-blind, placebo-controlled, multi-center (5 hospitals, Velayat, Bu Ali, 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	Sample size: n = 180 (n=30 per arm) Disease severity: Mild = 25 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	6 gps – 4 intervention gps and 2 control gps Intervention gps: **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:	**Primary outcome(s):** The primary outcomes reported in the preprint differs from the clinical trial registry: *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	**Primary outcome(s):** ***Mortality rate (not pre-specified in trial registry or preprint) :*** *Intervention:* • 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*	• Preprint and trial registry information was used for data extraction and assessment of risk of bias. Study protocol, and statistical analysis plan not available. • 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 – HIGH RISK** • *Randomization:* **MODERATE RISK** - "*Randomization according to the severity of the disease was as follows:*

	Medical Sciences and Science and Technology Park, Qazvin, Iran. Declarations: No conflicts of interest declared	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: 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)*		***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*	*mild, moderate, and severe. The transposed block randomization sequence, including stratifcation, 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"*. o Allocation sequence and concealment appears adequately reported. o 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): **UNCLEAR RISK** o Registry states the following are blinded: Participant; Care provider; Outcome assessor; Data analyser: but details not provided in preprint o Other co-interventions such as steroids, antivirals, biologicals not reported. • *Attrition:* % attrition not reported, appears that all were included in the analysis: **LOW RISK** • *Measurement of the outcome:* **UNCLEAR RISK** – trial registry states that outcome assessor; data analyser are blinded, but no details in the preprint • *Selection of the reported results:* **HIGH 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). 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-	RCT, double-blinded, single centre (Spain) Phase 2 study	Sample size: n=24 (12/study gp) Disease severity: Mild: n=24	*Intervention:* • Ivermectin, 400 mcg/kg as a single dose • 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	**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:*	• Small pilot study showed no difference between ivermectin and placebo gps for the primary outcome of reducing positivity of viral cultures; or other important effects such as reduction in inflammatory markers or duration of disease.

19: a pilot, double-blind, placebo-controlled, randomized clinical trial. Red Square, December, 2020 https://dx.doi.org/10.13140/RG.2.2.22193.81767/3 NCT04390022	Follow-up duration (days): 30 Funding: Mixed - ISGlobal; University of Navarra. Unitaid; Spanish Ministry of Science and Innovation; Generalitat de Catalunya; Idipharma SL (placebo donation) Declarations: No conflicts of interest declared	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 compliance including home follow up during isolation). Exclusion Criteria: 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.	*Control:* • Placebo tablet (not matched to ivermectin; but administered by staff not involved in the clinical care. • Duration : 1 day *Concomitant medicines:* Not reported	**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. • Proportion of patients with seroconversion at day 21 post-treatment. • Proportion of ADRs.	o 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. o Target gene E: 11 (91%) vs 12(100%); RR 0.92, 95% CI: 0.77 to 1.09, p = 1.0. o Target gene N: 12 (100%) in both gps o No difference between gps o 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)*: o Patients in the ivermectin gp reported fewer patient-days of any symptoms vs placebo gp (171 vs 255 patient-days). o Hyposmia/anosmia:76 vs 158 patient-days o 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	• 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".* • 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."* o 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 o 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."* o Study clinical team blinded, but the blinding of participants is uncertain. o No information on co-interventions of interest: antivirals, biologics and corticosteroids. o ITT analysis. • *Attrition:* **LOW RISK** – All randomised and analyzed (n=24)

					IL-6, d-dimer) and other of laboratory parameters (RBC,Hb, platelets, WBC, lymphocytes, neutrophils) of patients.	o Data available for 100% of study population. o 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). o 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.*

• **IVERMECTIN + DOXYCYCLINE vs PLACEBO/STANDARD OF CARE – 3 RCTs**						
Citation	**Study design**	**Population**	**Intervention vs comparator**	**Outcomes**	**Effect sizes**	**Comments**
Mahmud et al,[20] Dhaka Medical College. Clinical Trial of Ivermectin Plus Doxycycline for the Treatment of Confirmed Covid-19 Infection, Clinical Trials Registry, NCT04523831 http://clinicaltrials.gov/show/NCT04523831 Ethics: ERC-DMC/ECC/2020/ 117	RCT, double-blinded, single center (Bangladesh) Phase 3 study Follow-up duration (days): 30 Funding/ agreements: *"Principal Investigators are not employed by the organization sponsoring the study.*	Sample size: n = 400 randomised (200/ group) Disease severity: Mild and moderate COVID-19 infected cases; Patient characteristics: Mean age: 39.6 years; 235 males (59%) Inclusion criteria: ≥18 years; PCR-confirmed COVID-19 infection within 3 days from enrollment;	*Intervention:* • Ivermectin+Doxycycline (12 mg/100 mg) daily • Co-Intervention: Standard care • Duration : 5 days *Control:* • Placebo • Co-Intervention: Standard care • Duration : 5 days *Standard of care:* Paracetamol, vitamin D, oxygen if indicated, low molecular weight heparin,	**Primary outcome(s):** • Number of patients with early clinical improvement at 7 days (defined by WHO and Bangladesh local guideline) • Number of participants with late clinical recovery at 12 days **Secondary outcome(s):** • Number of patients having clinical deterioration at 1 month • Number of patients remaining persistently positive for RT-PCR of Covid-19 **Other reported outcome(s):** • All-cause mortality • SAEs	**Primary outcome(s):** Ivermectin+Doxycycline vs placebo • *Number of patients with early clinical improvement at 7 days*: 111/183 (60.7%) vs 80/180 (44.4%); p<0.03 • *Number of participants with late clinical recovery at 12 day:* 42/183 (23.0%) vs 67/180 (37.2%); p<0.004 **Secondary outcome(s):** Ivermectin+Doxycycline vs placebo • *Number of patients having clinical deterioration at 1 month:* 16/183 (8.7%) vs 32/180 (17.8%); p<0.013 • *Number of patients remaining persistently positive for RT-PCR of Covid-19 at day 14:* 14/183 (7.7%) vs 36/180 (20.0%), p<0.001 **Other reported outcome(s):** Ivermectin+Doxycycline vs placebo	• No published report, data collected from the online trial registry, protocol and statistical analysis plan. • Target sample size specified in the registry and protocol was achieved. • No deviation between the trial registration and protocol in the intervention and control treatments or in the outcomes. • Registry states that the study uses an ITT analysis, but denominators for SAEs/withdrawal due to AEs and mortality do not seem to include the participants with these outcomes. **Risk of bias assessment: Overall – 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.

	There is an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed."		dexamethasone if indicated.	• Adverse events	• *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%)	• *Attrition:* **HIGH RISK** - 400 randomised/363 analyzed o 15 participants lost to follow-up in the intervention and 17 participants in the control arm. o 3 participants that died in the control group and 2 in the intervention group due to adverse events, were also excluded. o 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:* **LOW RISK** - The trial registry, protocol and statistical analysis plan were available. Data analyses and presented as pre-specified (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).
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 https://www.medrxiv.org/content/10.1101/2020.10.26.20219345v1 NCT04591600	RCT , parallel, single-blinded (outcome assessors), single-center (Alkarkh and Alforat hospitals in Baghdad, Iran) Phase 1/2 study Follow-up duration: 8 weeks Funding: Alkarkh Health Directorate-Baghdad Declarations: No conflicts of interest declared	Sample size: n=140 (70/study gp – ivermectin+ doxycycline and standard care gps); hospital outpatients and inpatients Disease severity: *(defined as per WHO criteria)* Mild-moderate:96 (48 vs 48) Severe: 33 (11vs 22) Critical: 11 (11 vs 0) Patient characteristics: Mean age: 48.7±8.6 years 73 male s (52%) Inclusion criteria: 16-86 years, COVID-19 patients at any stage of this disease (diagnosed by clinical, radiological and laboratory PCR testing)	*Intervention:* • Ivermectin 200mcg/kg, oral daily • Duration: 2-3 days **PLUS** • Doxycycline 100mg, oral 12 hrly • Duration: 5-10 days **PLUS** • Standard therapy *Control:* • Standard therapy *Standard therapy:* Acetaminophen 500mg as needed, vitamin C 1000mg 12 hrly, zinc 75-125 mg daily, vitamin D3 5000IU daily, azithromycin 250mg daily (5 days), oxygen/ C-pap as needed, dexamethasone 6 mg	**Primary outcome(s):** o Mortality rate o Progression of the disease **Secondary outcome(s):** o Time to recovery	**Primary outcome(s):** Ivermectin+ doxycycline vs standard care *Mortality rate (%):* • Total: 2/70 (2.85%) vs 6/70 (8.57); p=0.14; OR 0.31; p=0.16 • Mild-moderate: 0/48 (0%) vs 0/48 (0%); p=1 • Severe: 0/11 (0%) vs 6/22 (27.27%); p= 0.052; OR 0.11; p=0.14 • Critical: 2/11 (18.2%) vs n/a *Rate of progression of disease (%):* • Total: 3/70 (4.28%) vs 7/70 (10%); p=0.19; OR 0.4; p=0.2 • Mild-moderate: 0/48 (0%) vs 0/48 (0%); p=1 • Severe: 1/11 (9%) vs 7/22 (31.81%); p=0.15; OR 0.21; p=0.17 • Critical: 2/11 (18.2%) vs n/a **Secondary outcome(s):** Ivermectin+ doxycycline vs standard care *Mean time to recovery (days):* • Total: 10.61± 5.3 vs 17.9±6.8; p<0.0001	• Data extracted from preprint and online trial registry. Protocol and statistical analysis plan not available • Target sample size specified in the registry and protocol was achieved. • Standard therapy administered to both groups included azithromycin • Baseline comorbidities of patients not provided for; to determine confounding. **Risk of bias assessment: Overall – HIGH RISK** • *Randomisation*: **HIGH RISK** – Allocation sequence concealment and allocation concealment unlikely and study gps were "*age-and sex-matched"* – *"COVID-19 patients were randomly allocated to one of the study groups depending on a simple method. Patients recruited at dates with odd number were allocated to Ivermectin-Doxycycline group while other patients were allocated to the control group".* • *Deviations from intervention*: **HIGH RISK** – Single blinded study (outcome assessors and not participants and investigators). • *Attrition:* **LOW RISK** - 140 randomised/140 analyzed • *Measurement of the outcome:* **UNCLEAR RISK** - Blinded outcome assessor, but) - protocol and statistical plan not available for further review..

		Exclusion criteria: Allergy to ivermectin or to doxycycline	daily or methylprednisolone 40mg 12 hrly as needed, mechanical ventilation as needed		• 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	• *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 ivm + placebo0					

• **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 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	*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	**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	**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	• 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: o 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

		participate in the study, and were either asymptomatic or had mild/moderate symptoms <u>Exclusion criteria:</u> COVID 19 negative patients, patients who had COVID pneumonia or requiring ventilator therapy, renal failure, thromboembolic complications, or unconscious by reduced Glasgow Coma Scale	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.	• 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)	o Platelet count increase was inversely correlated to days to negative PCR (r = -0.52, p = 0.005). No SAEs reported.	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 –** o 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). o Preprint: No information on randomization procedure. • *Deviations from intervention*: **MODERATE RISK –** o 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"* o 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."* o Conflicting information between the preprint and protocol regarding the control/ placebo. o Despite beinga 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. o No participant cross-over. o Only co-administration of corticosteroids were reported (balanced between groups); but there was no information on administration of other co-interventions. o 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. o Mortality was not an outcome pre-specified in the protocol or registry but should be reported even if not planned. o Time to viral negative conversion was pre-specified as reported. o Results were not selected from multiple outcome measurements or analyses of the data. o Trial analyzed as pre-specified.

• **IVERMECTIN vs HYDROXYCHLOROQUINE – 1 RCT**						
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 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:	*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	**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. • 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).

		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, 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	Duration: 9 days *Standard care: Egyptian MOH protocol*[2]*:* azithromycin 500mg daily x5days, paracetamol 500mg as needed, 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)			• 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. • Heterogeneous patient sample: o *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. o *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[25] 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*: **UNCLEAR RISK** – details of randomisation is unclear, "… *distributed over 6 groups …The study was conducted on 600 subjects; 400 patients and 200 health care and household contacts that were divided into 6 groups".* However, the trial registry describes, *"A block randomization method was used to randomize the study participants into two groups that result in equal sample sizes. This method was used to ensure a balance in sample size across groups over time and keep the numbers of participants in each group similar at all times*". Generally, RCT study reports provide flowcharts describing the enrolment process for randomization and the excluded study participants. Allocation sequence concealment and allocation concealment unclear.

[2] 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

		Exclusion criteria: 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				• *Deviations from intervention*: **UNCLEAR RISK** – details not provided. Entry in the trial registry as a double-blinded study, but preprint provides no information. • *Attrition:* **UNCLEAR RISK** – details not reported, particularly regarding ADRs, which is a study outcome. • *Measurement of the outcome:* **UNCLEAR RISK** - Unclear blinding; no information on blinding of outcome assessor; but risk assessed to be some concern for clinical improvement and serious ADRs; but low for the outcomes: Mortality, time to viral negative conversion. Statistical plan not available. • *Selection of the reported results:* **HIGH RISK** – The primary and secondary outcomes differ in the preprint and trial registry – protocol not available. o More detailed information provided in trial registry regarding clinical and laboratory improvements vs preprint. Mortality rate (reported in preprint), reduction of recovery time and hospital stay days (not reported in preprint) included as primary outcomes in trial registry, but not preprint.

• **IVERMECTIN+DOXYCYCLINE vs HYDROXYCHLOROQUINE+AZITHROMYCIN – 1 RCT**						
Citation	**Study design**	**Population**	**Intervention vs Comparator**	**Outcomes**	**Effect sizes**	**Comments**
Chowdurry et al. [23] A comparative study on Ivermectin- Doxycycline and Hydroxychloroquine-	RCT, single centre (health complex in Bangladesh; though registered	Sample size: n=125 (ivermectin+ doxycyline gp: n=63;	*Intervention:* • Ivermectin + doxycycline (200 mcg/kg/100 mg)	**Primary outcome(s):** A negative PCR and resolution of symptoms.	**Primary outcome(s):** Ivermectin+doxycycline group vs HCQ+azithromycin:	• Study registered as an observational single center study, retrospectively after enrollment was already completed (NCT04434144). However, the methodology describes a RCT.

Azithromycin therapy on COVID19 patients 14 July 2020 https://www.researchsquare.com/article/rs-38896/v1 NCT04434144	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 <u>Funding:</u> reported as not applicable <u>Declarations:</u> No conflicts of interests declared	HCQ+azithromycin gp n=62) Enrolled patients treated as outpatients. <u>Disease severity:</u> Mild <u>Characteristics of participants:</u> Mean age: 33.8 years 90 males <u>Inclusion criteria:</u> SARS-CoV-2 infection diagnosed by RT PCR with/without symptom(s) at a health complex; ≥95% oxygen saturation (pulse oximeter measurement); normal or near-normal chest radiograph in patients with respiratory symptoms <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	• Co-Intervention: Standard care • Duration : Once-off+10 day <u>*Control:*</u> • HCQ + azithromycin (200 mg/500 mg) • Duration: 10 days+5 days <u>*Standard of care:*</u> Not reported and symptomatic treatment for fever, headache, cough, myalgia, etc provided to all, details not provided.	Adverse events.	• *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:* o Possible ADRs: 31.67% vs 46.43% o Ivermectin + doxycycline gp: lethargy in 14(23.3%), nausea in 11(18.3%), and occasional vertigo in 7(11.66%) o HCQ+azithromycin gp: 13(23.21%) mild blurring of vision and headache; 22(39.2%) increased lethargy and dizziness, 10(17.85%) occasional palpitation, and 9(16.07%) nausea and vomiting.	• Study information including study results are available as pre-print format and in the trial registry. • Outcomes not registered in the registry were reported in the article. • There is no change from the trial registration in the intervention and control treatments. • Results submitted to ClinicalTrials.gov by the sponsor or investigator is not posted, pending quality control review for apparent errors, deficiencies, or inconsistencies (results returned to investigator 19 August 2020). • Baseline comorbidities of patients not provided for; to determine confounding. • New signals of harm[26] associated with chloroquine-azithromycin in the control group may have contributed to the apparent benefit of ivermectin. • New signals of harm associated with chloroquine-azithromycin in the control group may have contributed to the apparent benefit of ivermectin. **Risk of bias assessment: Overall – HIGH RISK** • *Randomisation*: **HIGH RISK** – Allocation of study participants probably not concealed as "*Randomization was done using an odd-even methodology applied to registration numbers, in a consecutive fashion in a 1:1 ratio, by the hospital registration office".* • *Deviations from intervention*: **MODERATE RISK** - Unblinded study. o No participant cross-over. o No information reported on co-interventions (i.e. antivirals, corticosteroids, biologics). o Patients analyzed according to intervention assignment. • *Attrition:* **LOW RISK** – 116/ 125 patients analyzed. o 7% missing data - 5%(3/63) in ivermectin + doxycycline arm; 10%(6/62) in HCQ + azithromycin arm, due to LTFU. o Risk assessed to be low for the outcomes: Incidence of viral negative conversion, adverse events. • *Measurement of the outcome:* **MODERATE RISK** - Unblinded study. o Risk assessed to be low for the outcome: Incidence of viral negative conversion, an observer-reported outcome not involving judgement. o 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. o Reported outcomes in the preprint were aligned with the trial registry. o Trial probably analyzed as pre-specified. o 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

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: 14 January 2021
Results: 148 total articles

- 7 broad syntheses
- 9 systematic reviews - 1 duplicate excluded, 8 records screened and **all systematic reviews excluded**
- 132 RCTs - only 19 RCTs reporting data of which 5 records were duplicates; 14 records screened, 2 excluded, **12 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 18 December 2020, 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: 14 January 2021
Results: 12 records retrieved; 11 excluded as study results not reported; 1 RCT screened which is a duplicate record retrieved from the L·OVE for COVID-19 search.
- 0 studies included in evidence synthesis.

Clinical.trials.gov registry
Search strategy: "ivermectin and COVID-19"
Search date: 14 January 2021
Results: 44 records retrieved; 5 duplicates removed; 5 prophylaxis RCTs excluded; 29 RCTs excluded as study underway/not completed of which 1 is a non-RCT; 1 non-RCT excluded; 1 phase 2 RCT completed, but study results awaited (NCT04381884); 2 phase 3 RCTs completed, but study results awaited (NCT04391127, NCT04405843), 1 RCT's study results undergoing QC (NCT04646109)
– 0 studies included for 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: Excluded studies

Study	Reason for exclusion
1. Rahman et al. Comparison of Viral Clearance between Ivermectin with Doxycycline and Hydroxychloroquine with Azithromycin in COVID-19 Patients Journal of Bangladesh online, 2021 https://link.springer.com/article/10.1007/s15010-020-01522-4	• Details of randomisation is unclear and unsure if this is truly a RCT, *"… prospective comparative study conducted at Combined Military Hospital Dhaka. Total 400 Covid-19 PCR positive patients were included in this study. Among them 200 cases received ivermectin 18 mg first day and Doxycycline 100 mg twice daily for 05 days comprising Group A and the rest 200 patients were given hydroxychloroquine 800 mg on first day then 400mg daily";* trial investigator contacted for more information. • Register number not reported in the paper; thus cannot verify report against study protocol to determine a priori research questions; trial investigator contacted for more information. • There is unclear risk of bias as randomisation, allocation concealment and blinding are incompletely reported, decreasing confidence in the results. • New signals of harm associated with chloroquine-azithromycin in the control group may have contributed to the apparent benefit of ivermectin. • Cardiac monitoring not performed in this study – cardiac side-effects of both azithromycin and chloroquine (e.g. QT prolongation, etc). • Authors conclude that, *"further control study is required to know more about the effects of ivermectin and doxycycline on covid -19 patient".*
2. Zagazig University. Prophylactic Ivermectin in COVID-19 Contacts Clinical Trials Registry, NCT04422561 https://clinicaltrials.gov/ct2/show/NCT04422561 NCT04422561	Study investigating ivermectin for prophylaxis of Covid-19 (see the separate rapid review for ivermectin as prophylaxis treatment)
3. 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. 11 January 2021; https://onlinelibrary.wiley.com/doi/epdf/10.1111/fcp.12644	Systematic review of preclinical studies – *in vitro* and in vivo animal studies.
4. Stefanie Kalfas, Kumar Visvanathan, Kim Chan, John Drago. The therapeutic potential of ivermectin for covid-19: a review of mechanisms and evidence. medRxiv. 4 December 2020; https://dx.doi.org/10.1101/2020.11.30.20236570	RCTs were not appraised for methodological quality in the systematic review.
5. Marra LP, Oliveira Jr HA, Medeiros FC, Brito GV, Matuoka JY, Parreira PCL, Bagattini AM, Pachito DV, Riera R. 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	Systematic review in Portuguese, but cannot access article through link, oxford brazil EBM Alliance webpage or via google search; attempting to source this article
6. Kim MS, An MH, Kim WJ, Hwang TH. Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: A systematic review and network meta-analysis. PLoS medicine. 30 December 2020;17(12):e1003501. https://dx.doi.org/10.1371/journal.pmed.1003501	SR and NMA – submitted for publication 1 July 2020 – many more RCTs have been completed since then. Only 2 observational studies of ivermectin was included in this analysis.
7. 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	More updated version of living review available (18 Dec 2020); *"The use of medications such as ivermectin, antivirals, and immunomodulators, among others, should be done in the context of patient consented, randomized clinical trials that evaluate their safety and efficacy"*
8. 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	More updated version of living review available (18 Dec 2020); *"Currently, as to ivermectin, we found 1 in vitro study and 4 weak observational studies that were largely confounded (nonrandomized), and lacked the methodological rigor to allow much confidence in the results. They were pre-print and non-peer reviewed and were judged to be of high risk of bias and very low quality of evidence. The researchers concluded in large part that the findings could be considered hypothesis testing and urged the conduct of large sample sized RCTs to assess any clinical benefit".*
9. 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/10665.2/52719	More updated version of living review available (18 Dec 2020); *"The drugs currently under review are: meplazumab, ivermectin, siltuximab, danoprevir, tocilizumab (IL-6), favipiravir, darunavir, nelfinavir, remdesivir, interferon-alpha, chloroquine or hydroxychloroquine, convalescent plasma, heparin, corticosteroids, IVIG, sarilumab, umifenovir (arbidol), lopinavir/ritonavir, and α-Lipoic acid".*
10. 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	Pooled estimates from a mixture of observational and randomised controlled studies suggest significant benefits. However, there are methodological limitations and overall, the small number of events results in very low certainty of the evidence. The early data may be

	meta-analysis. J Pharm Pharm Sci. 23 November 2020;23:462-469. https://dx.doi.org/10.18433/jpps31457	considered hypothesis generating and further research is needed to confirm or discard the findings.
11.	Pan American Health Organization. Ongoing Living Update of COVID-19 Therapeutic Options: Summary of Evidence. Rapid Review, 18 December 2020. Pan American Health Organization. 2020; https://iris.paho.org/handle/10665.2/52719	Most current version of the living review is dated the 18 December 2020, which was excluded as a number of study results have been published subsequently (in either peer reviewed or preprint format).
12.	Gorial F, University of Baghdad et al. Effectiveness of Ivermectin as add-on Therapy in COVID-19 Management, 4 November 2020. https://www.clinicaltrials.gov/ct2/show/NCT04343092 NCT04343092	Exclude, as although completed and study results have been posted; it is a non-randomised study
13.	National University Hospital, Singapore. A Preventive Treatment for Migrant Workers at High-risk of COVID-19, 19 October 2020. https://clinicaltrials.gov/ct2/show/NCT04446104 NCT04446104	Exclude: completed phase 3 prevention of COVID-19 study (see the separate rapid review for ivermectin as prophylaxis treatment)
14.	Okumu N, Afyonkarahisar Health Sciences University. Ivermectin for Severe COVID-19 Management, 27 November 2020. https://www.clinicaltrials.gov/ct2/show/NCT04646109 NCT04646109	Exclude, as although completed, study results undergoing QC: *"Results information has been submitted to ClinicalTrials.gov by the sponsor or investigator, but is not yet publicly available (or "posted") on ClinicalTrials.gov. The submitted information may not be available if it is pending Quality Control (QC) Review by the National Library of Medicine (NLM) or if issues identified during QC review are being addressed or corrected by the sponsor or investigator. NLM's limited QC review assesses for apparent errors, deficiencies, or inconsistencies. NLM staff do not verify the scientific validity or relevance of the submitted information".*
15.	de los Angeles et al, Ministry of Public Health, Argentina. Prophylaxis Covid-19 in Healthcare Agents by Intensive Treatment With Ivermectin and Iota-carrageenan (Ivercar-Tuc), 11 January 2021. https://www.clinicaltrials.gov/ct2/show/NCT04701710 NCT04701710	Exclude, as although completed; it is a phase 1/2 study to prevent COVID-19 (see the separate rapid review for ivermectin as prophylaxis treatment)
16.	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	Excluded due to critical flaws as per AMSTAR evaluation. See text for details.

Note: 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. However, as the evidence is still maturing, phase 2 studies have been included in this review, until such time as more evidence emerges.

Appendix 3: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High: [ ] Moderate: [ ] Low: [ ] Very low: [x] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Very low certainty evidence based on small sample sizes and low event rates, methodological issues with the reports available *(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.
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes: [ ] No: [X] Uncertain: [ ]	Ivermectin is not SAHPRA registered and requires to be accessed through section 21 approval.
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [ ] Uncertain: [X]	**Price of medicines/ treatment course :** **Medicine** | **Tender Price** | **SEP** Currently not SAHPRA registered for human consumption | n/a | n/a
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: [ ] Major: [X] Uncertain: [ ] **Is the intervention acceptable to key stakeholders?** Yes: [X] No: [ ] Uncertain: [ ]	There is no local survey data to determine stakeholder acceptability. However, interest groups support use of ivermectin based on anecdotal data. Some compounding is being done locally, which is also legally questionable. To date, a small number of patients have been given s21 approval to import the registered oral solid dosage (marketed as Stromectol® by Merck)
EQUITY	**Would there be an impact on health inequity?** Yes: [X] No: [ ] Uncertain: [ ]	Access is currently only available through S21, as currently there is no SAHPRA registered product available for human use in South Africa.

Version control:

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.

REFERENCES:

[1] Cepelowicz Rajter J, Sherman M, Fatteh N, et al. ICON (ivermectin in COVID nineteen) study: use of ivermectin is associated with lower mortality in hospitalized patients with COVID19. medRxiv. 2020. https://www.medrxiv.org/content/10.1101/2020.06.06.20124461v2

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

[3] South African Medicines Formulary, 2016 edition.

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

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

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

[7] Cepelowicz Rajter J, Sherman M, Fatteh N, *et al.* ICON (ivermectin in COVID nineteen) study: use of ivermectin is associated with lower mortality in hospitalized patients with COVID19. medRxiv. 2020. Available at: https://www.medrxiv.org/content/10.1101/2020.06.06.20124461v2

[8] Guyatt GH, Oxman AD, *et al*; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008 Apr 26;336(7650):924-6. https://pubmed.ncbi.nlm.nih.gov/18436948/

[viii] 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

[9] South African National Department of Health. NEMLC Subcommittee for COVID-19 Therapeutics. Protocol template for rapid reviews of COVID-19 v1.0, 31 May 2020. http://www.health.gov.za/covid-19-rapid-reviews/

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

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

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

[13] Ravikirti, Roy R, Pattadar C *et al*. 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

[14] Chaccar AZK, Khan KA, Asif M et al. Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients, International journal of sciences. September; 9(09):31-35 https://www.ijsciences.com/pub/article/2378

[15] Podder CS, Chowdhury N, Sina MI *et al*. 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; 14(2): 002 http://www.imcjms.com/registration/journal_abstract/353

[16] Krolewiecki A, Lifschitz A, Moragas M *et al*. 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

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

[18] Niaee MS, Gheibi N, Namdar P et al. Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial. Research Square, 2020. https://www.researchsquare.com/article/rs-109670/v1

[19] Chaccour C, Casellas A, Blanco-Di Matteo A *et al*. 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. Red Square, December, 2020. https://dx.doi.org/10.13140/RG.2.2.22193.81767/3

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

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

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

[23] Chowdurry ATMM, Shahbaz M, Karim MR *et al*. A comparative study on Ivermectin- Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients 14 Research Square, July 2020. https://www.researchsquare.com/article/rs-38896/v1

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

[25] Juurlink DN. Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of SARS-CoV-2 infection. CMAJ. 2020 Apr 27;192(17):E450-E453. doi: 10.1503/cmaj.200528. Epub 2020 Apr 8. Erratum in: CMAJ. 2020 May 25;192(21):E590. https://pubmed.ncbi.nlm.nih.gov/32269021/