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Ivermectin for preventing and treating COVID-19 (Review)

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[Intervention Review]

Ivermectin for preventing and treating COVID-19

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ABSTRACT

Background

Ivermectin, an antiparasitic agent used to treat parasitic infestations, inhibits the replication of viruses in vitro. The molecular hypothesis of ivermectin's antiviral mode of action suggests an inhibitory effect on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication in the early stages of infection. Currently, evidence on efficacy and safety of ivermectin for prevention of SARS-CoV-2 infection and COVID-19 treatment is conflicting.

Objectives

To assess the efficacy and safety of ivermectin compared to no treatment, standard of care, placebo, or any other proven intervention for people with COVID-19 receiving treatment as inpatients or outpatients, and for prevention of an infection with SARS-CoV-2 (postexposure prophylaxis).

Search methods

We searched the Cochrane COVID-19 Study Register, Web of Science (Emerging Citation Index and Science Citation Index), medRxiv, and Research Square, identifying completed and ongoing studies without language restrictions to 26 May 2021.

Selection criteria

We included randomized controlled trials (RCTs) comparing ivermectin to no treatment, standard of care, placebo, or another proven intervention for treatment of people with confirmed COVID-19 diagnosis, irrespective of disease severity, treated in inpatient or outpatient settings, and for prevention of SARS-CoV-2 infection.

Co-interventions had to be the same in both study arms.

We excluded studies comparing ivermectin to other pharmacological interventions with unproven efficacy.

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Data collection and analysis

We assessed RCTs for bias, using the Cochrane risk of bias 2 tool. The primary analysis excluded studies with high risk of bias. We used GRADE to rate the certainty of evidence for the following outcomes 1. to treat inpatients with moderate-to-severe COVID-19: mortality, clinical worsening or improvement, adverse events, quality of life, duration of hospitalization, and viral clearance; 2. to treat outpatients with mild COVID-19: mortality, clinical worsening or improvement, admission to hospital, adverse events, quality of life, and viral clearance; (3) to prevent SARS-CoV-2 infection: SARS-CoV-2 infection, development of COVID-19 symptoms, adverse events, mortality, admission to hospital, and quality of life.

Main results

We found 14 studies with 1678 participants investigating ivermectin compared to no treatment, placebo, or standard of care. No study compared ivermectin to an intervention with proven efficacy. There were nine studies treating participants with moderate COVID-19 in inpatient settings and four treating mild COVID-19 cases in outpatient settings. One study investigated ivermectin for prevention of SARS-CoV-2 infection. Eight studies had an open-label design, six were double-blind and placebo-controlled. Of the 41 study results contributed by included studies, about one third were at overall high risk of bias.

Ivermectin doses and treatment duration varied among included studies.

We identified 31 ongoing and 18 studies awaiting classification until publication of results or clarification of inconsistencies.

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

We are uncertain whether ivermectin compared to placebo or standard of care reduces or increases mortality (risk ratio (RR) 0.60, 95% confidence interval (CI) 0.14 to 2.51; 2 studies, 185 participants; very low-certainty evidence) and clinical worsening up to day 28 assessed as need for invasive mechanical ventilation (IMV) (RR 0.55, 95% CI 0.11 to 2.59; 2 studies, 185 participants; very low-certainty evidence) or need for supplemental oxygen (0 participants required supplemental oxygen; 1 study, 45 participants; very low-certainty evidence), adverse events within 28 days (RR 1.21, 95% CI 0.50 to 2.97; 1 study, 152 participants; very low-certainty evidence), and viral clearance at day seven (RR 1.82, 95% CI 0.51 to 6.48; 2 studies, 159 participants; very low-certainty evidence). Ivermectin may have little or no effect compared to placebo or standard of care on clinical improvement up to 28 days (RR 1.03, 95% CI 0.78 to 1.35; 1 study; 73 participants; low-certainty evidence) and duration of hospitalization (mean difference (MD) −0.10 days, 95% CI −2.43 to 2.23; 1 study; 45 participants; low-certainty evidence). No study reported quality of life up to 28 days.

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

We are uncertain whether ivermectin compared to placebo or standard of care reduces or increases mortality up to 28 days (RR 0.33, 95% CI 0.01 to 8.05; 2 studies, 422 participants; very low-certainty evidence) and clinical worsening up to 14 days assessed as need for IMV (RR 2.97, 95% CI 0.12 to 72.47; 1 study, 398 participants; very low-certainty evidence) or non-IMV or high flow oxygen requirement (0 participants required non-IMV or high flow; 1 study, 398 participants; very low-certainty evidence). We are uncertain whether ivermectin compared to placebo reduces or increases viral clearance at seven days (RR 3.00, 95% CI 0.13 to 67.06; 1 study, 24 participants; low-certainty evidence). Ivermectin may have little or no effect compared to placebo or standard of care on the number of participants with symptoms resolved up to 14 days (RR 1.04, 95% CI 0.89 to 1.21; 1 study, 398 participants; low-certainty evidence) and adverse events within 28 days (RR 0.95, 95% CI 0.86 to 1.05; 2 studies, 422 participants; low-certainty evidence). None of the studies reporting duration of symptoms were eligible for primary analysis. No study reported hospital admission or quality of life up to 14 days.

Ivermectin compared to no treatment for prevention of SARS-CoV-2 infection

We found one study. Mortality up to 28 days was the only outcome eligible for primary analysis. We are uncertain whether ivermectin reduces or increases mortality compared to no treatment (0 participants died; 1 study, 304 participants; very low-certainty evidence). The study reported results for development of COVID-19 symptoms and adverse events up to 14 days that were included in a secondary analysis due to high risk of bias. No study reported SARS-CoV-2 infection, hospital admission, and quality of life up to 14 days.

Authors' conclusions

Based on the current very low- to low-certainty evidence, we are uncertain about the efficacy and safety of ivermectin used to treat or prevent COVID-19. The completed studies are small and few are considered high quality. Several studies are underway that may produce clearer answers in review updates. Overall, the reliable evidence available does not support the use ivermectin for treatment or prevention of COVID-19 outside of well-designed randomized trials.

PLAIN LANGUAGE SUMMARY

Ivermectin for preventing and treating COVID-19

Is ivermectin effective for COVID-19?

Key messages

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We found no evidence to support the use of ivermectin for treating or preventing COVID-19 infection, but the evidence base is limited.

Evaluation of ivermectin is continuing in 31 ongoing studies, and we will update this review with their results when they become available.

What is ivermectin?

Ivermectin is a medicine used to treat parasites such as intestinal parasites in animals and scabies in humans. It is cheap and is widely used in regions of the world where parasitic infestations are common. It has few unwanted effects.

Tests in the laboratory show ivermectin can slow the reproduction of the COVID-19 (SARS-CoV-2) virus but such effects would need major doses in humans. Medical regulators have not approved ivermectin for COVID-19. It should only be used as part of well-designed studies (called randomized controlled trials) evaluating potential effects.

What did we want to find out?

We wanted to know if ivermectin reduces death, illness, and length of infection in people with COVID-19, or is useful in prevention of the disease. We included studies comparing the medicine to placebo (dummy treatment), no treatment, usual care, or treatments for COVID-19 that are known to work to some extent, such as remdesivir or dexamethasone. We excluded studies that compared ivermectin to other drugs that do not work, such as hydroxychloroquine, or that are not known to be effective against COVID-19.

We evaluated the effects of ivermectin in infected people on:

– people dying;
– whether people's COVID-19 symptoms got better or worse;
– unwanted effects;
– hospital admission or time in hospital;
– viral clearance.

For prevention, we sought the effect on preventing COVID-19 and SARS-CoV-2 infection.

What did we do?

We searched for randomized controlled trials that investigated ivermectin to prevent or treat COVID-19 in humans. People being treated with ivermectin had to have laboratory-test confirmed COVID-19 and be receiving treatment in hospital or as outpatients.

We compared and summarized the results of the studies and rated our confidence in the evidence, based on common criteria as to how reliable the evidence is.

What did we find?

We found 14 studies with 1678 participants that investigated ivermectin compared to no treatment, placebo, or usual care.

For treatment, there were nine studies of people with moderate COVID-19 in hospital and four of outpatients with mild COVID-19. The studies used different doses of ivermectin and different durations of treatment.

One study investigated ivermectin to prevent COVID-19.

We also found 31 ongoing studies, and there are 18 studies still requiring clarification from the authors or not yet published.

Main results

Treating people in hospital with COVID-19

We don't know whether ivermectin compared with placebo or usual care, 28 days after treatment:

– leads to more or fewer deaths (2 studies, 185 people);
– worsens or improves patients' condition assessed by need for ventilation (2 studies, 185 people) or oxygen (1 study, 45 people);
– increases or reduces unwanted events (1 study, 152 people).

Seven days after treatment, we don't know if ivermectin:

– increases or reduces negative COVID-19 tests (2 studies, 159 people).

Ivermectin compared to placebo or usual care may make little or no difference to improving patients' condition 28 days after treatment (1 study, 73 people) or to length of hospital stay (1 study, 45 people).

Treating outpatients with COVID-19

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We don't know whether ivermectin compared with placebo or usual care:

– leads to more or fewer deaths 28 days after treatment (2 studies, 422 people);
– worsens or improves patients' condition 14 days after treatment assessed by need for ventilation (1 study, 398 people);
– increases or reduces negative COVID-19 tests seven days after treatment (1 study, 24 people).

Ivermectin compared to placebo or usual care may make little or no difference to improving outpatients' condition 14 days after treatment (1 study, 398 people) or to the number of unwanted events 28 days after treatment (2 studies, 422 people).

No studies looked at hospital admissions in outpatients.

Preventing COVID-19

We don't know whether ivermectin leads to more or fewer deaths compared with no drug (1 study, 304 people); no participant died 28 days after the drug. This study reported results for development of COVID-19 symptoms (but not confirmed SARS-CoV-2 infection) and unwanted events, but in a way that we could not include in our analyses. This study did not look at hospital admissions.

What are the limitations of the evidence?

Our confidence in the evidence is very low because we could only include 14 studies with few participants and few events, such as deaths or need for ventilation. The methods differed between studies, and they did not report everything we were interested in, such as quality of life.

How up to date is this evidence?

The evidence is up to date to 26 May 2021.

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SUMMARY OF FINDINGS

Summary of findings 1. Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in an inpatient setting

Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in an inpatient setting

Patient or population: people with moderate to severe disease (WHO scale 4–9); all studies contributing results to the summary of findings table included people with moderate disease (WHO scale 4 or 5)

Setting: inpatients

Intervention: ivermectin

Comparison: placebo or standard of care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or standard of care	Risk with ivermectin				
All-cause mortality up to 28 days	96 per 1000	58 per 1000 (13 to 241)	**RR 0.60** (0.14 to 2.51)	185 (2 RCTs)	⊕◯◯◯ **Very low** [a]	We are uncertain whether ivermectin reduces or increases all-cause mortality up to 28 days.
Clinical worsening: need for invasive mechanical ventilation up to 28 days	85 per 1000	47 per 1000 (9 to 220)	**RR 0.55** (0.11 to 2.59)	185 (2 RCTs)	⊕◯◯◯ **Very low** [a]	We are uncertain whether ivermectin reduces or increases clinical worsening assessed by the need for invasive mechanical ventilation up to 28 days.
Clinical worsening: need for oxygen by mask or nasal prongs up to 28 days, in people with WHO scale 4 at baseline	1 study assessed need for oxygen during the study period, but none of the participants in either group required supplemental oxygen (Ahmed 2020).		Not estimable	45 (1 RCT)	⊕◯◯◯ **Very low** [b]	We are uncertain whether ivermectin reduces or increases clinical worsening assessed by the need for oxygen support up to 28 days.
Clinical improvement: participants discharged without respi-	729 per 1000	752 per 1000 (569 to 1000)	**RR 1.03** (0.78 to 1.35)	73 (1 RCT)	⊕⊕◯◯ **Low** [c]	Ivermectin may have little or no effect on clinical improvement assessed by the number of participants discharged without res-

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ratory deterioration or death up to 28 days						piratory deterioration or death up to 28 days.
Adverse events (any grade) up to 28 days	115 per 1000	139 per 1000 (58 to 342)	**RR 1.21** (0.50 to 2.97)	152 (1 RCT)	⊕○○○ **Very low** [d]	We are uncertain whether ivermectin may increase or reduce any adverse events up to 28 days
Quality of life up to 28 days	—	—	—	—	—	No studies reported quality of life up to 28 days.
Duration of hospitalization	The mean duration of hospitalization in the placebo group was 9.7 days	The mean duration of hospitalization in the ivermectin group was **0.1 days fewer** (2.43 days fewer to 2.23 days more)	**MD −0.10** (−2.43 to 2.23)	45 (1 RCT)	⊕⊕○○ **Low** [e]	Ivermectin may have little or no effect on duration of hospitalization.
Viral clearance at 7 days	292 per 1000	531 per 1000 (149 to 1000)	**RR 1.82** (0.51 to 6.48)	159 (2 RCTs)	⊕○○○ **Very low** [f]	We are uncertain whether ivermectin increases or reduces viral clearance at 7 days.

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio; **WHO:** World Health Organization.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

[a]Downgraded one level for serious risk of bias and two levels for very serious imprecision due to few participants, few events, and wide CIs.
[b]Downgraded one level for serious risk of bias and two levels for very serious imprecision due to zero events and few participants.
[c]Downgraded one level for serious risk of bias and one level for serious imprecision due to few participants.
[d]Downgraded one level for serious risk of bias and two levels for very serious imprecision due to few participants and wide CIs. We included studies at high risk of bias in a secondary analysis (RR 1.04, 95% CI 0.61 to 1.79).

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[e]Downgraded one level for serious risk of bias and one level for serious imprecision due to few participants. Another study reported data as medians that were not eligible for meta-analysis. The median duration of hospitalization in the ivermectin group was six days (interquartile range (IQR) 4 to 11 days) compared to five days (IQR 4 to 7 days) in the placebo group.

[f]Downgraded one level for serious risk of bias, one level for serious heterogeneity (I^2 = 77%), and two levels for very serious imprecision due to few participants and wide CIs. We included studies at high risk of bias in a secondary analysis (RR 1.19, 95% CI 0.76 to 1.86).

Summary of findings 2. Ivermectin compared to placebo or standard of care for people with mild COVID-19 treated in an outpatient setting

Ivermectin compared to placebo or standard of care for people with mild COVID-19 treated in an outpatient setting

Patient or population: people with mild disease (WHO scale 1–3); all studies contributing results to the summary of findings table included people with mild disease (WHO scale 2 or 3)

Setting: outpatients

Intervention: ivermectin

Comparison: placebo or standard of care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or standard of care	Risk with ivermectin				
All-cause mortality up to 28 days	5 per 1000	2 per 1000 (1 to 40)	**RR 0.33** (0.01 to 8.05)	422 (2 RCTs)	⊕◯◯◯ **Very low** [a]	We are uncertain whether ivermectin reduces or increases all-cause mortality up to 28 days.
Clinical worsening: need for invasive mechanical ventilation up to 14 days	2 per 1000	5 per 1000 (0 to 122)	**RR 2.97** (0.12 to 72.47)	398 (1 RCT)	⊕◯◯◯ **Very low** [a]	We are uncertain whether ivermectin reduces or increases clinical worsening assessed by the need for invasive mechanical ventilation up to 14 days.
Clinical worsening: need for non-invasive mechanical ventilation or high flow up to 14 days	1 study assessed need for non-invasive mechanical ventilation or high flow at 15 days, but none of the participants in either group required non-invasive mechanical ventilation or high flow (López-Medina 2021).		Not estimable	398 (1 RCT)	⊕◯◯◯ **Very low** [b]	We are uncertain whether ivermectin reduces or increases clinical worsening assessed by the need for non-invasive mechanical ventilation or high flow up to 14 days

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Symptom resolution: participants with symptoms resolved up to 14 days	606 per 1000	630 per 1000 (539 to 733)	**RR 1.04** (0.89 to 1.21)	398 (1 RCT)	⊕⊕◯◯ **Low** [c]	Ivermectin may have little or no effect on clinical improvement assessed by the number of participants with symptoms resolved up to 14 days.
Symptom resolution: duration of symptom resolution	—	—	—	—	—[d]	No study with low risk or some concerns of bias reported symptom resolution.
Admission to hospital up to 14 days	—	—	—	—	—	No study was found that looked at admission to hospital up to 14 days
Adverse events (any grade) up to 28 days	790 per 1000	751 per 1000 (679 to 830)	**RR 0.95** (0.86 to 1.05)	422 (2 RCTs)	⊕⊕◯◯ **Low** [c]	Ivermectin may have little or no effect on any adverse events up to 28 days.
Quality of life up to 14 days	—	—	—	—	—	No study reported quality of life up to 14 days.
Viral clearance at 7 days	28 per 1000	83 per 1000 (4 to 1000)	**RR 3.00** (0.13 to 67.06)	24 (1 RCT)	⊕⊕◯◯ **Low** [e]	We are uncertain whether ivermectin increases or reduces viral clearance at 7 days.

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio; **WHO:** World Health Organization.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

[a]Downgraded one level for serious risk of bias and two levels for very serious imprecision due to few participants, few events, and wide CIs.

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[b]Downgraded one level for serious risk of bias and two levels for very serious imprecision due to zero events and few participants.
[c]Downgraded one level for serious risk of bias and one level for serious imprecision due to few participants.
[d]None of the studies were eligible for primary analysis. One study reported the median duration of symptom resolution in the placebo group was 12 days (interquartile range (IQR) 9 to 13 days) with 10 days (IQR 9 to 13 days) in the ivermectin group. We included one study at high risk of bias in a secondary analysis (mean difference −1.02, 95% CI −2.76 to 0.72).
[e]Downgraded two levels for very serious imprecision due to few participants, few events, and wide CIs.

Summary of findings 3. Ivermectin compared to no treatment for prevention of SARS-CoV-2 infection

Ivermectin compared to no treatment for prevention of SARS-CoV-2 infection

Patient or population: people who were not infected with SARS-CoV-2, but were at high risk of developing the infection (e.g. after high-risk exposure)

Setting: inpatient or outpatients

Intervention: ivermectin

Comparison: no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with ivermectin				
SARS-CoV-2 infection (confirmed by RT-PCR or antigen testing) at 14 days	—	—	—	—	—	No study reported SARS-CoV-2 infection at 14 days.
Development of clinical COVID-19 symptoms up to 14 days	—	—	—	—	—[a]	No study with low risk or some concerns of bias reported development of clinical COVID-19 symptoms up to 14 days.
Adverse events (any grade) up to 14 days	—	—	—	—	—[b]	No study with low risk or some concerns of bias reported adverse events up to 14 days.
All-cause mortality up to 28 days	1 study assessed all-cause mortality during the study period, but 0 participants in either group died (Shoumann 2021).		Not estimable	304 (1 RCT)	⊕◯◯◯ **Very low** [c]	We are uncertain whether ivermectin reduces or increases all-cause mortality up to 28 days.
Admission to hospital up to 14 days	—	—	—	—	—	No study reported admission to hospital up to 14 days.

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Quality of life up to 14 days	—	—	—	—	—	No study reported quality of life up to 14 days.

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomized controlled trial; **RT-PCR:** reverse transcription polymerase chain reaction; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

[a]No evidence available from studies with low risk or some concerns of bias. We included one study with high risk of bias in a secondary analysis (risk ratio (RR) 0.13, 95% CI 0.08 to 0.21).

[b]No evidence available from studies with low risk or some concerns of bias. We included one study with high risk of bias in a secondary analysis (RR 11.50, 95% CI 0.68 to 193.21).

[c]Downgraded one level for serious risk of bias and two levels for very serious imprecision due to zero events and few participants.

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BACKGROUND

Description of the condition

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On 11 March 2020, after spreading from China to more than 144 countries, the World Health Organization (WHO) declared a COVID-19 pandemic. In July 2021, over 180 million cases have been confirmed, including over 3.9 million deaths (WHO 2020a; WHO 2020b).

Available data suggest that one-third of SARS-CoV-2 infections remain asymptomatic (Oran 2021), but there is still uncertainty around this estimate. About 80% of symptomatic cases show mild symptoms, including cough, fever, myalgia, headache, dyspnoea, sore throat, diarrhoea, nausea and vomiting, and loss of smell and taste. Outpatient management is appropriate for most people with a mild course of COVID-19. Moderate, severe, and critical cases (approximately 20%), with the need for oxygen supplementation, ventilatory support, or intensive medical care, cause a considerable burden for healthcare systems. Defined risk factors for severe disease include increasing age (over 60 years) and certain comorbidities (Huang 2020; WHO 2020a). Comorbidities such as cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease and other lung diseases, malignancies, chronic kidney disease, solid organ or haematopoietic stem cell transplantation, and obesity are associated with severe COVID-19 and mortality (Deng 2020; Williamson 2020).

Data on mortality substantially differ between locations, depending on the population structure, the case-mix of infected and deceased individuals, other local factors, and changes during the ongoing outbreak. With an inhospital mortality for people receiving ventilation of over 70% (Karagiannidis 2020), the patients who survive often have considerable consequential damage (Herrmann 2020; Prescott 2020). COVID-19 can lead to death due to a variety of causes, such as severe respiratory failure, septic shock, and multiple organ failure (WHO 2020a). The case–fatality ratio worldwide is currently estimated at 2.2% with large statistical fluctuations (less than 0.1% in Singapore up to almost 20% in Yemen; status July 2021) (Dong 2020). However, these varying rates should not be interpreted as markers for the quality of health care (Karagiannidis 2020), or the aggressiveness of different virus variants. These statistics are influenced by the mean age of a population or of those infected, the quality and extent of local test strategies, and documentation and reporting systems (Kobayashi 2020). The gold standard for confirming a SARS-CoV-2 infection is the reverse transcription polymerase chain reaction (RT-PCR)-based detection of viral ribonucleic acid (RNA) from a nasopharyngeal swab test, sputum, or tracheal secretion, with a sensitivity ranging from 70% to 98%, depending on pretest probability (Watson 2020). Offering lower sensitivity but greater practicality and accessibility, antigen tests are receiving increased attention, especially in point-of-care diagnostics of COVID-19 (WHO 2020c).

Transmission is typically inferred from population-level information. Inherent properties of virus variants of concern, and individual differences in infectiousness among individuals or groups make it difficult to contain its spread in the community (WHO 2021a). Currently, the most effective and ubiquitously available measures to control virus spreading are non-pharmaceutical interventions, including physical distancing, wearing a facemask, especially when distancing cannot be maintained, keeping rooms well ventilated, avoiding crowds and close contact, regularly cleaning your hands, and coughing into a bent elbow or tissue. Research on prophylaxis of SARS-CoV-2 infection and treatment of COVID-19 is being carried out under great pressure worldwide. Evaluating the effectiveness of repurposed drugs represents one important strand of these research efforts. In this context, ivermectin — an antiparasitic intervention — has received substantial attention, especially in South America and parts of Asia.

Description of the intervention

Ivermectin is an antiparasitic agent belonging to the group of avermectins, originally a fermentation metabolite produced by the bacterium *Streptomyces avermitilis*. Ivermectin was introduced for medical use in 1982 and is effective against various types of nematodes and helminths, and ectoparasites such as mites and lice. The mode of action is based on binding to specific cell membrane channels that only occur in invertebrates. Channel activation ultimately leads to blocked cell signal transmission through chloride-induced hyperpolarization. Consequently, parasites are paralysed and die, interrupting their reproduction cycle (Campbell 1983; Dourmishev 2005; Panahi 2015). Ivermectin is on the WHO List of Essential Medicines for its high effectiveness against human ectoparasite infestations (WHO 2019).

In animals and humans, ivermectin is easily resorbed by the mucosa if taken orally or the skin if taken topically. As a lipophilic compound, it accumulates in fat and liver tissue from where it effuses and takes effect. Elimination is processed through bile and faeces. Ivermectin is widely used in veterinary medicine, but it is also approved for human parasitic diseases such as onchocerciasis, lymphatic filariasis, strongyloidiasis, and scabies in several countries (e.g. the USA, Japan, France, Germany, Australia) (González-Canga 2008). The established dosing regimen ranges from 150 µg/kg to 200 µg/kg administered orally, with a one- to two-dose administration generally being effective. Dosing is generally low because of the agent's high potency (Ashour 2019).

Adhering to recommended doses, ivermectin is generally well tolerated. Adverse effects — which seem to arise partially from the rapid death of parasites, leading to hyperinflammation and anaphylactic reactions — include weakness, drowsiness, diarrhoea, nausea, and vomiting. In addition, ivermectin can cause fever and rash. Rare serious adverse effects can occur, such as vision problems, neurotoxicity, and liver damage (González-Canga 2008).

How the intervention might work

One in vitro study showed that ivermectin can inhibit replication of the human-immunodeficiency-virus 1 (HIV-1), via inhibition of the interaction of virus proteins and a human cargo protein complex called importin (IMPα/β1) (Wagstaff 2012). Importin is used by viruses for nuclear import in order to initiate their replication process (Wagstaff 2012). Besides HIV-1, various other RNA viruses use importin as target protein, among them dengue virus, West Nile virus, and influenza. Several research groups have investigated ivermectin's efficiency on those pathogens (Goetz 2016; Tay 2013; Yang 2020). Although ivermectin showed some

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inhibitory potential for virus replication in vitro, there is no evidence of clinical effectiveness to date.

Before the COVID-19 pandemic, only two clinical trials had been registered on ClinicalTrials.gov (clinicaltrials.gov/) using ivermectin as an intervention for treatment of virus diseases. Only one of these had published results (Yamasmith 2018). In this small, single-centre study published as a conference abstract, ivermectin showed a shorter viral protein clearance time compared to placebo in people infected with dengue virus (Yamasmith 2018).

Another member of the beta-coronavirus family, SARS-CoV-1, which also causes respiratory failure, revealed similar dependence on the IMPα/β1 interaction (Wulan 2015). The pathogen causing COVID-19, SARS-CoV-2, is also an RNA virus closely related to SARS-CoV-1. In 2020, ivermectin gained high interest as a promising therapeutic option against SARS-CoV-2, when Caly 2020 published their experimental study results showing that ivermectin inhibits the replication of SARS-CoV-2 in cell culture. So far, the only drugs shown to be clearly effective in COVID-19 treatment are targeting the immune response to a SARS-CoV-2 infection; for example, dexamethasone (RECOVERY 2021). Therefore, ivermectin's potential to restrict the disease's progression, or even its outbreak, indicates that it is possibly an effective antiviral agent. However, until showing success in human clinical trials with patient-relevant outcomes, these findings remain suggestive.

The molecular hypothesis of ivermectin's antiviral mode of action, explained above, suggests an inhibitory effect on virus replication in the early stages of the disease, indicating a benefit especially for people with mild or moderate disease. This has also led to the idea of the possible preventive potency of ivermectin on infection with SARS-CoV-2 in individuals after exposure to a contagious contact, called postexposure prophylaxis. In response to the early promising in vitro studies on ivermectin, mentioned above, several COVID-19 clinical trials have been initiated to investigate the prophylactic and therapeutic effects of ivermectin.

Why it is important to do this review

Ivermectin is an inexpensive and widely used medicine, mainly in low- and middle-income countries with a high burden of parasitic diseases. The recently published in vitro studies, especially the results of Caly 2020, have led to great interest in ivermectin in many countries with high numbers of SARS-CoV-2 infections, including the USA and countries of South America and Asia. In South America in particular, people started liberally self-medicating with ivermectin, and the drug has become part of public health policies without reliable scientific data. For example, in May 2020, Bolivian and Peruvian health officials recommended ivermectin for the treatment of COVID-19 without supplying evidence. In Brazil, it was promoted as a preventive measure by municipalities (Rodríguez-Mega 2020). Due to the rapid increase in interest in ivermectin and the risk of abuse, the US Food and Drug Administration (FDA) discouraged the use of ivermectin intended for animals (FDA 2020).

The increased research interest in ivermectin has led to the registration of numerous trials in clinical trials registries worldwide. As of 2 July 2021, there were 73 trials registered on ClinicalTrials.gov (clinicaltrials.gov/) investigating ivermectin in various settings.

Several studies describe ivermectin's positive effect on resolution of mild COVID-19 symptoms or describe a reduction of inflammatory marker levels or shorter time to viral clearance, while other studies indicate no effect or even a negative effect on disease progression. Many studies are already summarized in existing systematic reviews, meta-analyses, and guidelines (Bryant 2021; Hill 2021; NIH 2021). It has to be kept in mind that many available meta-analyses and reviews, as well as most of the underlying original studies, have not yet been published in peer-reviewed journals and are only available on preprint servers without any supervising authority. Given the pace of the pandemic, it is important and welcome to make new scientific findings immediately available. But non-peer-reviewed results have to be handled with care and should not be used as the sole basis for clinical decisions and recommendations. Methodological limitations in the design of original studies, data integrity, and potential conflicts of interests have to be critically appraised when judging trial results. Many reviews and meta-analyses of ivermectin for COVID-19 are not reliable due to insufficient methodological accuracy and quality.

As of July 2020, the efficacy and safety of ivermectin for COVID-19 treatment and prophylaxis are still subject to debate. The most recent Association of the Scientific Medical Societies in Germany (AWMF) guideline recommends against the use of ivermectin as antiviral treatment (German AWMF Guideline 2021), while in February 2021, the US National Institutes of Health (NIH) revised their COVID-19 treatment guidelines from a recommendation 'against the use of ivermectin' to 'cannot recommend either for or against the use of ivermectin,' giving clinicians leeway in individual case decision-making (NIH 2021). The WHO recommends that the drug only be used within clinical trials as current evidence on the use of ivermectin to treat people with COVID-19 is inconclusive (WHO 2021b).

This review aimed to provide a complete evidence profile, based on current Cochrane standards, for ivermectin with regard to efficacy and safety for postexposure prophylaxis and treatment of COVID-19.

OBJECTIVES

To assess the efficacy and safety of ivermectin compared to no treatment, standard of care, placebo, or any other proven intervention for people with COVID-19 receiving treatment as inpatients or outpatients, and for prevention of an infection with SARS-CoV-2 (postexposure prophylaxis).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) only, as this is the best study design for evaluating the efficacy of interventions (Higgins 2020a). Non-standard RCT designs, such as cluster-randomized and cross-over trials, were not eligible for the review (Higgins 2020b). These designs are not appropriate in this context, since the underlying cause of COVID-19 is an infection with the SARS-CoV-2 virus and the medical condition evolves over time.

We included full-text journal articles published in PubMed-indexed and non-indexed journals, preprint articles, results published in trial registers, and abstract publications. All studies, especially preprint articles that have not been peer-reviewed,

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must have reported robust and valid data on study design, participants' characteristics, interventions, and outcomes, to be eligible for inclusion. We categorized studies in question as 'awaiting classification' until the authors publish further information or clarify certain questions.

We applied no restrictions on the language of publication of the articles.

Types of participants

Treatment of COVID-19

We included studies investigating participants with confirmed SARS-CoV-2 infection (RT-PCR or antigen testing), regardless of age, gender, ethnicity, disease severity, and setting (inpatients and outpatients). If studies included participants with a confirmed or suspected COVID-19 diagnosis, we used only the data for the patient population with confirmed COVID-19 diagnosis. In cases, where data were not reported separately for people with confirmed or suspected COVID-19 diagnosis, we excluded the study.

Prevention of SARS-CoV-2 infection

We included studies investigating participants who were not infected with SARS-CoV-2 at enrolment, but were at high risk of developing the infection (e.g. after high-risk exposure), regardless of age, gender, ethnicity, disease severity, and setting (inpatient and outpatients). Participants may have been hospitalized for reasons other than COVID-19. Eligible trials must have reported the history of previous SARS-CoV-2 infections or serological evidence in included participants. A history of SARS-CoV-2 infection was not an exclusion criterion.

We excluded studies investigating ivermectin for prevention and treatment of other viral diseases.

Types of interventions

All doses and regimens of ivermectin were eligible and pooled for the primary analysis. Dosing schemes were considered and categorized into low (up to 0.2 mg/kg orally, single dose) and high doses (greater than 0.2 mg/kg orally, single dose or with higher frequency). We planned to analyse different doses in subgroup analyses, if sufficient studies are available for review updates.

We compared ivermectin to no treatment, standard of care, or placebo. Co-interventions (standard of care) must have been comparable between the study arms, i.e. ivermectin plus standard of care versus standard of care.

We planned to compare ivermectin to any other active pharmacological comparator with proven efficacy for prevention or treatment of COVID-19. For dexamethasone, it has been shown that mortality from COVID-19 was lower among people who were randomized to receive dexamethasone than among those who received the usual standard of care (RECOVERY 2021; Siemieniuk 2020). Remdesivir showed some benefit for people hospitalized with COVID-19, though to a lesser extent (Beigel 2020). Therefore, dexamethasone and remdesivir will be considered eligible active comparators for review updates. For patients that qualify for (for example) dexamethasone therapy or for another intervention that proves to be beneficial in the future, it would be unethical to further conduct trials that use placebo only. In contrast, studies using comparators (e.g. hydroxychloroquine) without proven efficacy may confound the assessment of the efficacy or safety of ivermectin and were excluded. Although those types of interventions were possibly used at a certain point of time during the pandemic with the best intentions, their use was never supported by actual evidence, and they have potential adverse effects (Singh 2021). From those comparisons, no reliable evidence can be obtained.

Studies investigating various concomitant medications (e.g. doxycycline, hydroxychloroquine, azithromycin, zinc) in addition to ivermectin or as comparator drug were not eligible for this review. Due to unproven efficacy, possible adverse effects, and drug interactions, these comparisons may confound the assessment of the efficacy or safety of ivermectin.

We created these comparisons:

- ivermectin versus no treatment, placebo, or standard of care; and
- ivermectin versus active pharmacological intervention with proven efficacy (no studies available for the current review version).

Types of outcome measures

We analyzed different outcomes for the use of ivermectin for treatment of people with COVID-19 in inpatient and outpatient settings, and for the prevention of SARS-CoV-2 infection. If studies were eligible for inclusion regarding design, population, intervention, and comparator, but did not report outcomes of interest, they were not included for meta-analysis. However, we summarized reported outcomes for all included studies in the Characteristics of included studies table.

Ivermectin for treating COVID-19 in inpatient settings

- All-cause mortality up to 28 days.
- Clinical status, assessed by need for respiratory support with standardized scales (e.g. WHO Clinical Progression Scale (Marshall 2020), hereafter referred to as the WHO scale) up to 28 days. If the study did not use a standardized scale to assess the status of the participants, we categorized their status according to the WHO scale with the information provided by the study. Clinical status is a complex outcome with substantial heterogeneity. We pooled data only if clinically reasonable (see the list of specific outcomes below). When there were only a few studies available that reported different outcomes in terms of clinical status, we describe them in the results narratively.
  - Worsening of clinical status.
    - ☐ Need for invasive mechanical ventilation (i.e. WHO scale 7 to 9, if 6 or less at baseline).
    - ☐ Need for non-invasive mechanical ventilation or high flow (i.e. WHO scale 6, if 5 or less at baseline).
    - ☐ Need for oxygen by mask or nasal prongs (i.e. WHO scale 5, if 4 or less at baseline).

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  * Improvement of clinical status.
    - ☐ Weaning or liberation from invasive mechanical ventilation in surviving participants (i.e. WHO scale 6 or less, if 7 or greater at baseline).
    - ☐ Ventilator-free days (ventilator-free defined as WHO scale 6 or less).
    - ☐ Duration of liberation from invasive mechanical ventilation.
    - ☐ Liberation from supplemental oxygen in surviving participants (i.e. WHO scale 4 or less, if 5 or greater at baseline).
    - ☐ Duration of liberation from supplemental oxygen.
    - ☐ Participants discharged without respiratory deterioration or death at 28 days.
- Adverse events (any grade, grade 1 to 2, grade 3 to 4), defined as number of participants with at least one event within 28 days.

Ivermectin for treating COVID-19 in outpatient settings

- All-cause mortality up to 28 days.
- Clinical status, assessed by need for respiratory support with standardized scales (e.g. WHO scale (Marshall 2020)) up to 14 days. If the study did not use a standardized scale to assess the status of the participants, we categorized their status according to the WHO scale with the information provided by the study. Clinical status is a complex outcome with substantial heterogeneity. We pooled data only if clinically reasonable (see the list of specific outcomes below). When there were only a few studies available that reported different outcomes in terms of clinical status, we described the results narratively.
  * Development of moderate-to-severe clinical COVID-19 symptoms (defined as WHO scale 6 or greater).
    - ☐ Need for invasive mechanical ventilation, non-invasive mechanical ventilation or high flow (i.e. WHO scale ≥ 6, severe disease).
    - ☐ Need for invasive mechanical ventilation (i.e. WHO scale 7 to 9).
    - ☐ Need for non-invasive mechanical ventilation or high flow (i.e. WHO scale 6).
  * Need for hospitalization with or without supplemental oxygen (i.e. WHO scale 4 to 5, moderate disease).
    - ☐ Need for oxygen by mask or nasal prongs (i.e. WHO scale 5).
    - ☐ Need for hospitalization without oxygen therapy (i.e. WHO scale 4).
  * Symptom resolution (i.e. WHO scale 1).
    - ☐ Number of participants with symptoms resolved.
    - ☐ Duration of symptom resolution.
- Admission to hospital.
- Adverse events (any grade, grade 1 to 2, grade 3 to 4), defined as number of participants with at least one event within 28 days.

Ivermectin for preventing SARS-CoV-2 infection

- SARS-CoV-2 infection (confirmed by RT-PCR or antigen testing) at 14 days.
- Development of clinical COVID-19 symptoms up to 14 days; assessed in accordance with individual items of the WHO scale (Marshall 2020). If the study did not use a standardized scale to assess the status of the participants, we categorized their status according to the WHO scale with the information provided by the study.
  * Uninfected (WHO scale 0).
  * Ambulatory mild disease (WHO scale 1 to 3).
  * Hospitalized with moderate disease (WHO scale 4 to 5).
  * Hospitalized with severe disease (WHO scale 7 to 9).
  * Mortality (WHO scale 10).
- Adverse events (any grade, grade 1 to 2, grade 3 to 4), defined as number of participants with at least one event within 14 days.

Timing of outcome measurement

We expected that included studies measured several outcomes — including clinical status, SARS-CoV-2 infection, and adverse events — at different time points. For inpatient setting outcomes, the main time point of interest was 28 days after randomization. For outpatient setting outcomes, the main time point of interest was 14 days after randomization, except for mortality and (serious) adverse events (28 days). For prevention trials, the main time point was 14 days, except for mortality only (28 days). If only a few studies had contributed data to an outcome, we pooled different time points, provided the studies had produced valid data and pooling was clinically reasonable. We reported time points of outcome measurement in the footnotes of the forest plots. If sufficient data are available for review updates, we will group the measurement time points of eligible outcomes into those measured directly after treatment (up to seven days), medium-term outcomes (up to 14 days), and longer-term outcomes (28 days or more).

Ivermectin for treating COVID-19 in inpatient settings

- Serious adverse events, defined as number of participants with at least one event within 28 days.
- Quality of life assessed with the standardized scale, WHOQOL-100, up to 28 days (WHO 2012).
- Admission to intensive care unit (ICU).
- Duration of hospitalization.
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, and three, seven, and 14 days.

Ivermectin for treating COVID-19 in outpatient settings

- Serious adverse events, defined as number of participants with at least one event within 28 days.
- Quality of life assessed with the standardized scale, WHOQOL-100, up to 14 days (WHO 2012).
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, and at three, seven, and 14 days.

Ivermectin for preventing SARS-CoV-2 infection

- All-cause mortality up to 28 days.
- Admission to hospital.
- Quality of life assessed with the standardized scale, WHOQOL-100, up to 14 days (WHO 2012).

Timing of outcome measurement

We expected that included studies measured several outcomes – including serious adverse events, quality of life, and viral clearance – at different time points. We analyzed different time points for viral clearance separately due to the dynamic course of the viral load. For other inpatient setting outcomes, the main time point of interest

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was 28 days after randomization. For other outpatient setting trials outcomes, the main time point of interest was 14 days after randomization, except for mortality (28 days)and (serious) adverse events (28 days). For prevention trials, the main time point of interest was 14 days, except for mortality only (28 days). If only a few studies contributed data to an outcome, we pooled different time points, as long as the studies had produced valid data and pooling was clinically reasonable. We reported time points of outcome measurement in the footnotes of the forest plots. If sufficient data are available for review updates, we will group the measurement time points of eligible outcomes into those measured directly after treatment (up to seven days), medium-term outcomes (up to 14 days), and longer-term outcomes (28 days or more).

Search methods for identification of studies

Electronic searches

On 26 May 2021, the Information Specialist (MIM) conducted systematic searches of the following sources with no restrictions on the language of publication.

- Cochrane COVID-19 Study Register (CCSR) (www.covid-19.cochrane.org; from inception to 26 May 2021), comprising:
  - Cochrane Central Register of Controlled Trials (CENTRAL), monthly updates;
  - MEDLINE (PubMed), daily updates;
  - Embase.com, weekly updates;
  - ClinicalTrials.gov (www.clinicaltrials.gov), daily updates;
  - WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch), weekly updates; and
  - medRxiv (www.medrxiv.org), weekly updates.
- Web of Science Core Collection (Clarivate; from 1 January 2020 to 26 May 2021):
  - Science Citation Index Expanded;
  - Emerging Sources Citation Index.
- Preprint servers (from inception to 26 May 2021):
  - medRxiv (www.medrxiv.org/search);
  - Research Square (www.researchsquare.com/browse).

For detailed search strategies, see Appendix 1.

We did not conduct separate searches of the databases required by the Methodological Expectations of Cochrane Intervention Reviews (MECIR) standards (Higgins 2021), since these databases are already regularly searched for the production of the CCSR. For greater precision, we searched the Web of Science database from 1 January 2020 onwards. We searched all other resources without date limits.

Searching other resources

We searched the reference lists of included studies, systematic reviews, and meta-analyses to identify other potentially eligible studies or ancillary publications. We contacted the investigators of included studies to obtain additional information on the retrieved studies.

We searched for grey literature, which we defined as searching trials registries such as ClinicalTrials.gov and WHO ICTRP contained in the CCSR, as well as searching preprint servers. In addition, we screened the 'All RCTs' section on the website ivmmeta.com, which lists studies related to ivermectin and COVID-19, and the regarding section on COVID-NMA Working Group for eligible trials.

Data collection and analysis

Selection of studies

We performed study selection in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2020). Two review authors (SW, MP) independently screened titles and abstracts of identified records. We retrieved full-text articles and independently assessed eligibility of the remaining records against the predefined eligibility criteria. We resolved discrepancies through discussion between the review authors. We included studies irrespective of whether measured outcome data were reported in a 'usable' way. We collated multiple reports of the same study, so that the study, rather than the report, was the unit of interest in the review.

We documented the study selection process in a PRISMA flow diagram with the total number of studies included, excluded, awaiting classification, and ongoing. We listed the reasons for exclusion and awaiting classification in the Characteristics of excluded studies and Characteristics of studies awaiting classification tables.

Data extraction and management

Two review authors (SW, MP) independently extracted data using a standardized data extraction form, including details of the study, participants, intervention, comparator, and outcomes. If necessary, we tried to obtain missing data by contacting the authors of relevant articles. At each step of data extraction, we resolved any discrepancies through discussion between the review authors.

Assessment of risk of bias in included studies

We assessed the risk of bias in the included studies using the Cochrane risk of bias tool 2 (RoB 2) (Higgins 2020c; Sterne 2019). The effect of interest was the effect of assignment at baseline, regardless of whether the interventions were received as intended (the 'intention-to-treat effect'). We assessed the risk of bias for all results (outcomes) reported in the included studies that we specified as outcomes for the current review and that contributed to the review's summary of findings table.

Two review authors (SW, MP) independently assessed the risk of bias of all results. We resolved any disagreements through discussion with a third review author.

The RoB 2 tool considers the following domains:

- bias arising from the randomization process;
- bias due to deviations from the intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- bias in selection of the reported result.

We assessed the RoB 2 domains using the recommended signalling questions and these response options:

- yes;
- probably yes;
- probably no;

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- no; or
- no information.

RoB 2 algorithms map responses to signalling questions. We used the proposed algorithm after verification to reach a risk of bias judgement, and assigned one of three levels to each domain:

- low risk of bias;
- some concerns; or
- high risk of bias.

Similarly, we reached an overall risk of bias judgement for a specific outcome by considering all domains resulting in one of the three judgement options described above. Overall low risk of bias of the trial result was assumed when all domains were at low risk; some concerns of bias was assumed when the trial result was judged to raise some concerns in at least one domain for this result, but not at high risk of bias for any domain; overall high risk of bias of the trial result was assumed when the trial was at high risk of bias in at least one domain for this result or when it was judged to have some concerns for multiple domains in a way that substantially lowered confidence in the result (Higgins 2020c).

We used the RoB 2 Excel tool to implement RoB 2 (available at www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2). We stored the full RoB 2 data (e.g. completed Excel tool) in an online repository.

The primary analysis included only those studies that had low risk or some concerns of bias. We included studies at high risk of bias in a secondary analysis to assess the impact on the results.

Measures of treatment effect

For dichotomous outcomes, we recorded the number of events and the number of analyzed participants in the intervention and control groups. We used the risk ratio (RR) with 95% confidence interval (CI) as effect measure.

For continuous outcomes, we recorded the mean, the standard deviation (SD), and the number of analyzed participants in the intervention and control groups. If the standard deviation was not reported, we used standard errors, CIs, or P values to calculate the SD with the formulas described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020d). If studies reported data as median with interquartile range (IQR), we assumed that the median was similar to the mean when sample sizes were large and the distribution of the outcome was similar to the normal distribution. In these cases, the width of the IQR is approximately 1.35 SDs (Higgins 2020d). We used the MD with 95% CI as effect measure.

We considered effect estimates of dichotomous outcomes with the range of the 95% CIs not crossing 1 and continuous outcomes with the range of the 95% CIs not crossing 0 as statistically significant effect estimates. A statistically significant effect does not necessarily mean that the estimated effect is clinically relevant. We assessed the clinical relevance of the effect size separately and reported it transparently.

Unit of analysis issues

The unit of analysis for this review was the individually randomized participant.

In studies with multiple intervention groups, we combined groups if reasonable (e.g. study arms with different doses of ivermectin). If it had not been reasonable to pool the groups, we planned to split the 'shared' comparator group to avoid double-counting of participants. There was no need to split shared groups for the current review.

Dealing with missing data

There are many potential sources of missing data in a systematic review or meta-analysis, which can affect the level of studies, outcomes, summary data, individuals, or study-level characteristics (Deeks 2020). Incomplete data can introduce bias into the meta-analysis, if they are not missing at random. We addressed all sources of missing data. Missing studies may be the result of reporting bias, and we addressed this as described in the Assessment of reporting biases section. Missing outcomes and summary data may be the result of selective reporting bias; missing individuals may be the result of attrition from the study or lack of intention-to-treat analysis. We addressed these sources of missing data using the RoB 2 tool (Assessment of risk of bias in included studies). If data were incompletely reported, we contacted the study authors to request additional information.

Assessment of heterogeneity

We used the descriptive statistics reported in the Characteristics of included studies table to assess whether the studies within each pairwise comparison were homogeneous enough, with respect to study and intervention details and population baseline characteristics, that the assumption of homogeneity might be plausible. In case of excessive clinical heterogeneity, we did not pool the findings of included studies.

We measured statistical heterogeneity using the Chi^2 test and the I^2 statistic (Deeks 2020), and the 95% prediction interval (PI) for random-effects meta-analysis (IntHout 2016). The prediction interval helps in the clinical interpretation of heterogeneity by estimating what true treatment effects can be expected in future settings (IntHout 2016). We restricted calculation of a 95% PI to meta-analyses with four or more studies (200 participants or more), since the interval would be imprecise when a summary estimate was based on only a few small studies. In the current review, there are no meta-analyses including four or more studies. We planned to use the open-source statistical software R package meta to calculate 95% PIs in review updates (Meta). We declared statistical heterogeneity if the P value was less than 0.1 for the Chi^2 statistic, or the I^2 statistic was equal to or greater than 40% (40% to 60%: moderate heterogeneity; 50% to 90%: substantial heterogeneity; 75% to 100%: considerable heterogeneity; Deeks 2020), or the range of the 95% PI revealed a different clinical interpretation of the effect estimate compared to the 95% CI.

Assessment of reporting biases

We sought to identify all research that met our predefined eligibility criteria. Missing studies can introduce bias to the analysis. We searched for completed non-published trials in trials registers, contacted authors to seek assurance that the results will be made available, and classified them as 'awaiting classification' until the results are reported. We reported the number of completed non-published trials.

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When there are 10 or more relevant studies pooled in a meta-analysis, we planned to investigate risk of reporting bias (publication bias) in pairwise meta-analyses using contour-enhanced funnel plots. In the current review, there were no meta-analyses including 10 or more studies. For review updates, if funnel plot asymmetry is suggested by a visual assessment, we plan to perform exploratory analyses (e.g. Rücker's arcsine test for dichotomous data and Egger's linear regression test for continuous data) to further investigate funnel plot asymmetry. A P value of less than 0.1 will be considered as the level of statistical significance. In review updates, we will analyse reporting bias using the open-source statistical software R package meta (Meta).

Data synthesis

The primary analysis included only those studies that had low risk or some concerns of bias according to the RoB 2 assessment. We included high risk of bias studies in a secondary analysis to assess the impact on the results (Sensitivity analysis).

We analyzed trials with different intentions of ivermectin use and different participant populations separately, as follows.

- Treatment of COVID-19 in an inpatient setting: participants with confirmed SARS-CoV-2 infection.
- Treatment of COVID-19 in an outpatient setting: participants with confirmed SARS-CoV-2 infection.
- Prevention of SARS-CoV-2 infection (postexposure prophylaxis): participants at high risk of developing the infection.

We created these comparisons.

- Ivermectin versus placebo or standard of care.
- Ivermectin versus active pharmacological intervention with proven efficacy.

We performed meta-analyses according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020).

If clinical and methodological characteristics of individual studies were sufficiently homogeneous, we pooled the data in meta-analyses. When meta-analysis was feasible, we used the random-effects model as we assumed that the intervention effects were related but were not the same for the included studies. For dichotomous outcomes, we performed meta-analyses using the Mantel-Haenszel method under a random-effects model to calculate the summary (combined) intervention effect estimate as a weighted mean of the intervention effects estimated in the individual studies. For continuous outcomes, we used the inverse-variance method.

We used RevMan Web software for meta-analyses (RevMan Web 2020).

Subgroup analysis and investigation of heterogeneity

For ivermectin used as treatment for COVID-19 in an inpatient setting, we planned to perform a subgroup analysis independent of heterogeneity for the following characteristic.

- Severity of condition at baseline (moderate (WHO scale 4 to 5) versus severe disease (WHO scale 6 to 9)).

Since only one study investigated participants with moderate-to-severe COVID-19, the planned subgroup analysis for severity at baseline could not be performed.

For ivermectin used to prevent SARS-CoV-2 infection, we planned to perform a subgroup analysis independent of heterogeneity for the following characteristic.

- Studies including participants with a history of SARS-CoV-2 infection versus studies including only participants with no history of infection.

We investigated heterogeneity by visual inspection of the forest plot. We reported details of the intervention and age of the population for each study in the footnotes of the forest plot. We planned to investigate heterogeneity by subgroup analysis to calculate RR or MD in conjunction with the corresponding CI for each subgroup, if sufficient studies had been available (at least 10 studies per outcome). In the current review, there were not enough studies available. In review updates, we will perform subgroup analyses if statistical heterogeneity is present ($P < 0.1$ for the Chi^2 test of heterogeneity, I^2 of 50% or greater, or a different clinical conclusion of 95% CI versus 95% PI).

In review updates, we will perform subgroup analyses to investigate heterogeneity for the following characteristics.

- Ivermectin used as treatment (inpatients and outpatients):
  - dose of ivermectin (low versus high);
  - age (children versus adults).
- Ivermectin used for prevention:
  - dose of ivermectin (low versus high);
  - mode of exposure (e.g. working place, nursing home) and burden of exposure (e.g. living in a high-risk area, high-risk medical contact) in prevention studies;
  - confirmation of SARS-CoV-2 infection (RT-PCR versus antigen testing; for the outcome 'SARS-CoV-2 infection').

Sensitivity analysis

We used sensitivity analyses to test the robustness of the meta-analyses. We excluded:

- non-peer reviewed studies (including preprint articles);
- studies reporting data as median instead of mean for continuous outcomes; in the current review version there were no data reported as median that were eligible for a transformation into mean.

Since high risk of bias trials were excluded from the primary analysis, we performed a secondary analysis including the studies judged as overall high risk of bias to assess the impact of those studies on the results.

Summary of findings and assessment of the certainty of the evidence

We presented the main results of the review in summary of findings tables, including a rating of the certainty of evidence based on the GRADE approach. We followed current GRADE guidance as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2020).

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Two review authors (SW, MP) assessed the certainty of evidence, considering risk of bias, inconsistency, imprecision, indirectness, and publication bias. We used the overall RoB 2 assessment to inform the risk of bias judgement underlying the assessment of the certainty of evidence. The primary analysis including only studies at overall low risk or some concerns of bias were used as data basis for the summary of findings tables.

We created separate summary of findings tables for the use of ivermectin with different intentions (e.g. treatment of people with COVID-19 in inpatient and outpatient settings, and prevention of SARS-CoV-2 infection) and for different comparisons with regard to the intervention and comparator. For the current review, we found no studies with active comparators. The summary of findings tables included the following outcomes (primary analysis).

For use of ivermectin with intention to treat COVID-19 in an inpatient setting:

- all-cause mortality up to 28 days;
- clinical worsening or improvement of symptoms up to 28 days, assessed as need for respiratory support;
- adverse events (any grade) up to 28 days;
- quality of life up to 28 days;
- duration of hospitalization;
- viral clearance at seven days.

For use of ivermectin with intention to treat COVID-19 in an outpatient setting:

- all-cause mortality up to 28 days;
- clinical worsening or improvement of symptoms up to 14 days, assessed as need for respiratory support;
- admission to hospital;
- adverse events (any grade) up to 28 days;
- quality of life up to 14 days;
- viral clearance at 7 days.

For use of ivermectin with intention to prevent SARS-CoV-2 infection:

- SARS-CoV-2 infection (confirmed by RT-PCR or antigen testing) at 14 days;
- development of clinical COVID-19 symptoms up to 14 days; assessed in accordance with the WHO scale;
- adverse events (any grade) up to 14 days;
- all-cause mortality up to 28 days;
- admission to hospital at day 14;
- quality of life up to 14 days.

The GRADE assessment resulted in one of four levels of certainty and these express our confidence in the estimate of effect (Balshem 2011).

- High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We used the MAGICapp to create summary of findings tables (MAGICapp), and incorporated the results into RevMan Web manually (RevMan Web 2020).

Methods for future updates

Living systematic review considerations

Our information specialist (MIM) will provide us with new search records each week, which two review authors will screen, extract, evaluate, and integrate following the guidance for Cochrane living systematic reviews (Cochrane LSR).

We will manually check platform trials for new treatment arms investigating ivermectin.

We will wait until the accumulating evidence changes our conclusions of the implications of research and practice before republishing the review. We will consider one or more of the following components to inform this decision.

- The findings of one or more prioritized outcomes.
- The credibility (e.g. GRADE rating) of one or more prioritized outcomes.
- New settings, populations, interventions, comparisons, or outcomes studied.

In case of emerging policy relevance because of global controversies around the intervention, we will consider republishing an updated review even though our conclusions remain unchanged. We will review the review scope and methods approximately monthly, or more frequently if appropriate, in light of potential changes in COVID-19 research (e.g. when additional comparisons, interventions, subgroups, or outcomes, or new review methods become available).

RESULTS

Description of studies

Results of the search

The literature search resulted in 326 records. A handsearch of reference lists identified a further 22 records, resulting in an overall 348 records. After removing duplicates, 318 records remained. During title and abstract screening, 175 records were judged as irrelevant as they did not meet the prespecified inclusion criteria. We proceeded to full-text screening with 143 records, considering published full texts or, if these were unavailable, trial register entries. We excluded 57 records related to 38 studies after full-text assessment. Twelve studies investigated combined treatments including ivermectin, eight studies used an active comparator without proven efficacy, and five studies analyzed inappropriate study populations including RT-PCR-negative participants. Furthermore, nine studies were not RCTs and four studies focused on an intervention other than ivermectin. We identified 31 ongoing studies with 37 records and 18 studies with 20 records awaiting assessment. Fourteen studies with 29 records

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met our eligibility criteria and were used for qualitative synthesis. One study did not report on outcome time points relevant to this review, hence, 13 studies contributed data to our meta-analyses (quantitative syntheses). The search process is shown in Figure 1.

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Figure 1.

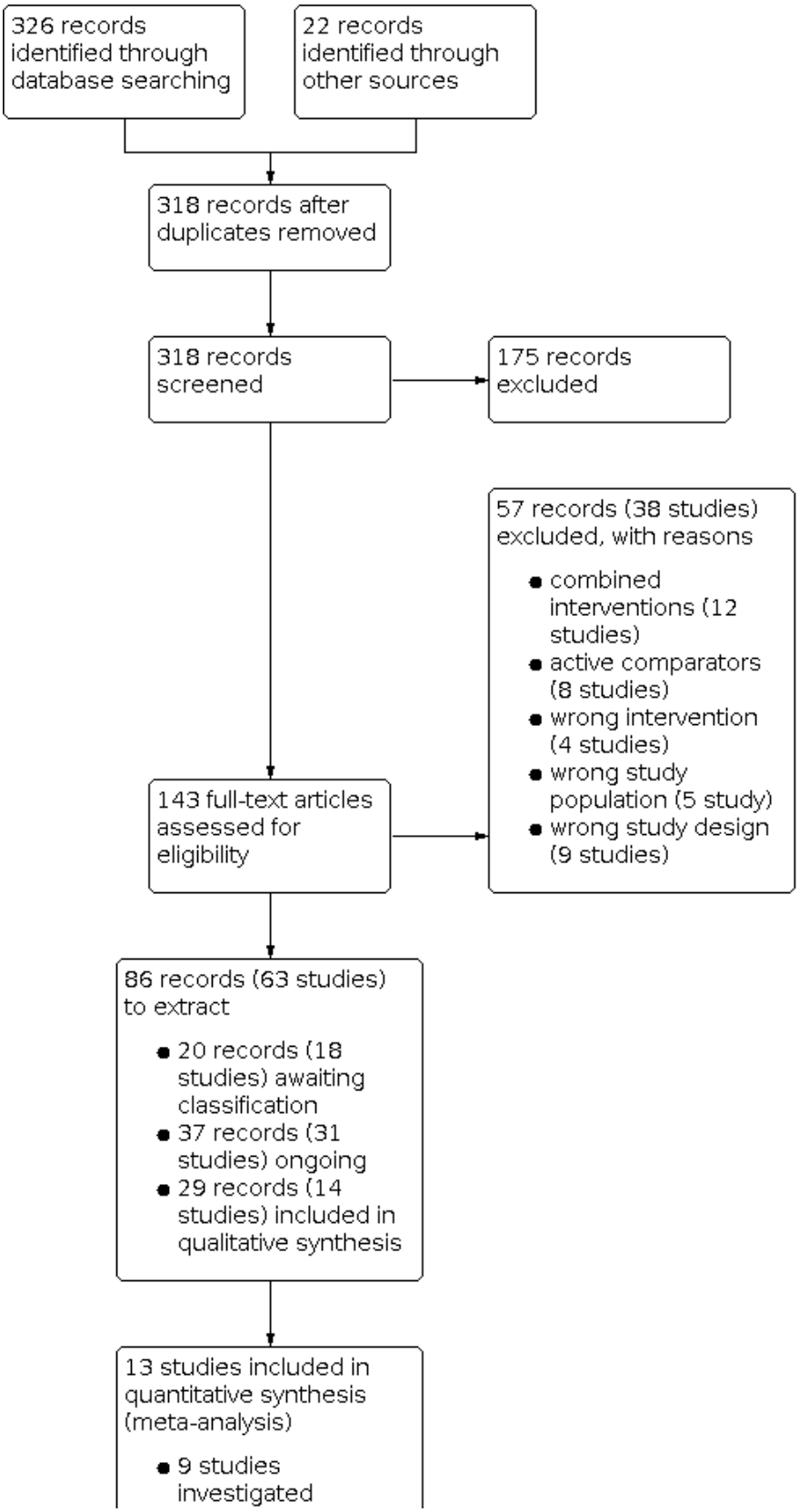

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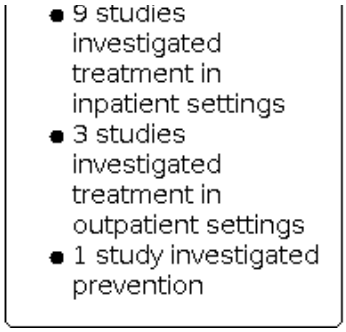
Figure 1. (Continued)



Designs of the studies and publication status

See Characteristics of included studies table.

We included 14 studies describing 1678 adults randomized to study arms relevant for the review question (Ahmed 2020; Chaccour 2021; Chachar 2020; Gonzalez 2021; Kirti 2021; Kishoria 2020; Krolewiecki 2020; López-Medina 2021; Mohan 2021; Okumuş 2021; Podder 2020; Pott-Junior 2021; Shah Bukhari 2021; Shoumann 2021). Eight studies had an open-label design (Chachar 2020; Kishoria 2020; Krolewiecki 2020; Okumuş 2021; Podder 2020; Pott-Junior 2021; Shah Bukhari 2021; Shoumann 2021), and the other six studies were double-blind and placebo-controlled (Ahmed 2020; Chaccour 2021; Gonzalez 2021; Kirti 2021; López-Medina 2021; Mohan 2021). Three studies were multicentre studies in Argentina (Krolewiecki 2020), Turkey (Okumuş 2021), and Egypt (Shoumann 2021). The remaining 11 studies were single-centre studies in Bangladesh (Ahmed 2020; Podder 2020), Brazil (Pott-Junior 2021), Columbia (López-Medina 2021), India (Mohan 2021; Kirti 2021; Kishoria 2020), Mexico (Gonzalez 2021), Pakistan (Chachar 2020; Shah Bukhari 2021), and Spain (Chaccour 2021).

None of the included studies had a trial size greater than 500 participants. Chaccour 2021 had the smallest sample size of 24 randomized participants. López-Medina 2021 had the largest trial with 476 randomized participants.

Five studies were published as preprint articles by the end of May 2021 (Gonzalez 2021; Kirti 2021; Krolewiecki 2020; Mohan 2021; Shah Bukhari 2021). The remaining nine studies were available as journal publications. Three of the nine studies were published in non-indexed journals (Chachar 2020; Kishoria 2020; Podder 2020).

Eight studies registered a study protocol prospectively (Chaccour 2021; Gonzalez 2021; Kirti 2021; Krolewiecki 2020; López-Medina 2021; Mohan 2021; Pott-Junior 2021; Shoumann 2021), one study registered the protocol during the recruitment period (Shah Bukhari 2021), two studies registered the study protocol retrospectively (Chachar 2020; Okumuş 2021), and three studies did not register any study protocol (Ahmed 2020; Kishoria 2020; Podder 2020).

Seven studies reported detailed information on the responsible ethics committee and approval reference number in their publication (Gonzalez 2021; López-Medina 2021; Mohan 2021; Okumuş 2021; Pott-Junior 2021; Shah Bukhari 2021; Shoumann 2021). Two study authors provided all the information through personal communication (Chaccour 2021; Krolewiecki 2020). Three studies only indicated the name of their ethics committee, but not the approval reference number (Ahmed 2020; Chachar 2020; Kirti 2021). Two studies gave no information on those aspects (Kishoria 2020; Podder 2020). We contacted those studies with insufficient or no information regarding details on their ethics approval.

Four studies were funded by pharmaceutical companies producing ivermectin, including Beximco Pharmaceuticals Ltd (Ahmed 2020), Laboratorio Elea Phoenix SA (Krolewiecki 2020), Windlas Biotech Ltd (Mohan 2021), and Sun Pharma Ltd (Kirti 2021). One study was funded by NeuTec Pharma (Okumuş 2021), which provided ivermectin for the study. It is unclear from the website whether NeuTec Pharma distributes ivermectin commercially. Eight studies were funded by departmental resources (Chaccour 2021; Chachar 2020; Gonzalez 2021; López-Medina 2021; Podder 2020; Pott-Junior 2021; Shah Bukhari 2021; Shoumann 2021). One study did not reported funding (Kishoria 2020).

Participants

One study investigated ivermectin for prevention of SARS-CoV-2 infections and included asymptomatic household close contacts to confirmed COVID-19 index case (Shoumann 2021). The remaining 13 studies investigated ivermectin for treatment of COVID-19 and included participants with SARS-CoV-2 infection confirmed by RT-PCR or antigen testing. Of the 13 studies with intention to treat COVID-19, four studies were in an outpatient setting (Chaccour 2021; Chachar 2020; López-Medina 2021; Podder 2020), and nine studies were in an inpatient setting (Ahmed 2020; Gonzalez 2021; Kirti 2021; Kishoria 2020; Krolewiecki 2020; Mohan 2021; Okumuş 2021; Pott-Junior 2021; Shah Bukhari 2021).

Participants included in three of the four outpatient studies had mostly mild COVID-19 according to a patient state of 2 to 3 on the WHO scale (Chaccour 2021; Chachar 2020; Podder 2020). Participants in López-Medina 2021 had mostly mild COVID-19 defined as WHO scale 2 to 3, but less than 1% of participants were hospitalized with or without supplemental oxygen.

Five studies were conducted in an inpatient setting and included participants with moderate COVID-19 and with or without supplemental oxygen according to WHO scale 4 to 5 (Kirti 2021; Krolewiecki 2020; Mohan 2021; Pott-Junior 2021; Shah Bukhari 2021). In Ahmed 2020 and Kishoria 2020, none of the participants received supplemental oxygen. In Gonzalez 2021, all participants received supplemental oxygen. Okumuş 2021 included participants with moderate-to-severe COVID-19 according to WHO scale 4 to 9.

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The overall population mean age of the included studies was 43 years. Chaccour 2021 included the youngest participants with a population median age of 28 years. Okumuş 2021 included the oldest participants with a population mean age of 62 years.

The mean proportion of men in all included studies was 59%. The lowest proportions of men were included in Chachar 2020 and López-Medina 2021 with 42% men, while Shah Bukhari 2021 included the highest proportion with 85% men.

The studies partially reported comorbidities and relevant risk factors such as obesity, diabetes, respiratory diseases, hypertension, and immunosuppression (see Characteristics of included studies table). Two studies excluded existing comorbidities and specified them in the inclusion and exclusion criteria (Chaccour 2021; Krolewiecki 2020). Four studies reported no data on risk factors in their publications or study reports (Ahmed 2020; Kishoria 2020; Podder 2020; Pott-Junior 2021).

Interventions and comparators

All studies administered ivermectin orally. The daily dosages varied between fixed doses of 12 mg and 24 mg or weight-adjusted doses of 100 µg/kg and 400 µg/kg. Four studies used low doses (200 µg/kg orally, single dose) in at least one study arm (Mohan 2021; Podder 2020; Pott-Junior 2021; Shah Bukhari 2021). All other studies applied higher doses either in one single dose or multiple doses for up to five days. Participants received single-dose ivermectin in five studies (Chaccour 2021; Kishoria 2020; Mohan 2021; Podder 2020; Shah Bukhari 2021), two doses in two studies (Kirti 2021; Shoumann 2021), three doses over 24 hours in one study (Chachar 2020), and five doses in five studies (Ahmed 2020; Gonzalez 2021; Krolewiecki 2020; López-Medina 2021; Okumuş 2021). In one study, there was insufficient detail in the journal publication and the trial registry on whether the participants received ivermectin as a single or double dose (Pott-Junior 2021).

We found no studies comparing ivermectin to an active comparator with proven efficacy. Six studies administered placebo tablets as the control intervention (Ahmed 2020; Chaccour 2021; Gonzalez 2021; Kirti 2021; López-Medina 2021; Mohan 2021). The remaining seven studies administered standard of care as control intervention (Chachar 2020; Kishoria 2020; Krolewiecki 2020; Okumuş 2021; Podder 2020; Pott-Junior 2021; Shah Bukhari 2021). Standard of care varied between studies, but was comparable between the study arms of the individual studies. Four studies did not provide details of standard of care (Ahmed 2020; Chaccour 2021; Chachar 2020; Krolewiecki 2020). Three studies used a combination of interventions including hydroxychloroquine, favipiravir, and azithromycin (Kirti 2021; Mohan 2021; Okumuş 2021). One study combined hydroxychloroquine, vitamin C, and paracetamol (Kishoria 2020). Five studies administered corticosteroids such as dexamethasone (Gonzalez 2021; Kirti 2021; López-Medina 2021; Mohan 2021; Pott-Junior 2021). Shah Bukhari 2021 administered vitamin C and D_3 as additional standard of care. López-Medina 2021 and Podder 2020 utilized antipyretic drugs for symptomatic treatment.

The only prevention study compared ivermectin to no treatment (Shoumann 2021).

Outcome measures

One study did not report outcomes eligible for meta-analysis due to a short follow-up period of seven days (Chachar 2020).

In trials with intention to treat COVID-19, the most investigated primary outcomes as defined by the study were either (time to) viral clearance or a reduction in the viral load reported in eight studies (Ahmed 2020; Chaccour 2021; Kirti 2021; Kishoria 2020; Krolewiecki 2020; Mohan 2021; Pott-Junior 2021; Shah Bukhari 2021). Chachar 2020 and López-Medina 2021 defined resolution of symptoms as primary outcomes, and Ahmed 2020 defined remission of fever and cough as an additional primary outcome. The primary outcomes in Gonzalez 2021 were duration of hospitalization until discharge due to clinical improvement and duration of hospitalization. The primary outcome in Okumuş 2021 was clinical response. Two studies defined safety outcomes as additional primary outcomes (Gonzalez 2021; Okumuş 2021). Podder 2020 did not define any primary outcome.

In the only prevention trial, the primary outcome was development of COVID-19 typical symptoms (Shoumann 2021).

Primary outcomes as defined by the review for studies with intention to treat COVID-19 were only reported by a minority of the included studies. Two studies reported all-cause mortality up to 28 days in inpatient settings (Gonzalez 2021; Kirti 2021), and two studies in outpatient settings (Chaccour 2021; López-Medina 2021). Three studies in an inpatient setting reported data useable to assess worsening of clinical status up to 28 days (Ahmed 2020; Gonzalez 2021; Kirti 2021), and one study in an outpatient setting reported data at 15 days (López-Medina 2021). One study reported improvement of clinical status in an inpatient setting as "patients discharged without respiratory deterioration or death at 28 days" (Gonzalez 2021). This outcome was clinically useful and was added as new primary outcome during preparation of this review. In an outpatient setting, one study reported improvement of clinical status as participants with symptoms resolved at 15 days (López-Medina 2021). Two studies reported duration to symptom resolution in an outpatient setting (López-Medina 2021; Podder 2020). Four studies in an inpatient setting reported the number of participants with adverse events within 14 to 28 days (Krolewiecki 2020; Mohan 2021; Pott-Junior 2021; Shah Bukhari 2021). Two studies in an outpatient setting reported adverse events within 21 to 28 days (Chaccour 2021; López-Medina 2021). No studies reported data for the following primary outcomes in an inpatient setting, including all outcomes summarized as 'improvement of clinical status' and need for non-invasive mechanical ventilation or high-flow. For the outpatient setting, none of the included studies reported data for the primary outcomes admission to hospital and need for hospitalization with or without supplemental oxygen.

The only included study with intention to prevent SARS-CoV-2 infection reported two of the primary outcomes defined by the review, including development of clinical COVID-19 symptoms at 14 days and adverse events within 14 days (Shoumann 2021). The number of participants with confirmed SARS-CoV-2 infection was not investigated.

Excluded studies

See Characteristics of excluded studies table.

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We excluded 38 studies that did not match our inclusion criteria. Twelve studies evaluated a combination of ivermectin with other treatments that were different between groups (Chahla 2021a; Chowdhury 2021; Hashim 2020; IRCT20200408046987N2; Mahmud 2021; NCT04360356; NCT04392427; NCT04447235; NCT04482686; NCT04551755; NCT04768179; Spoorthi 2020). Eight studies investigated active comparators without proven efficacy (Babalola 2021; CTRI/2020/08/027282; CTRI/2020/08/027394; CTRI/2020/10/028335; Elgazzar 2020; Galan 2021; NCT04435587; Seet 2021). One of these studies was retracted by Research Square on 14 July 2021 due to an expression of concern (Elgazzar 2020; The Guardian 2021). Four studies investigated a wrong intervention (NCT04345419; NCT04374279; NCT04382846; NCT04723459). Five studies analyzed a wrong study population including RT-PCR negative participants (IRCT20180922041089N4; NCT04530474; NCT04703608; Niaee 2020; Shahbaznejad 2021). Nine studies were not RCTs (Behera 2020; Cadegiani 2020; Camprubi 2020; Carvallo 2020; Chahla 2021b; Gorial 2020; Lima-Morales 2021; Morgenstern 2020; Rajter 2021).

Studies awaiting classification

See Characteristics of studies awaiting classification table.

Eighteen studies are awaiting classification until publication of results, a protocol update, or clarification of details by the study authors. If eligible we will consider them in the next review update (2020-001971-33/ES; 2020-002091-12/BG; CTRI/2020/04/024948; CTRI/2020/06/025960; Faisal 2020; Hosseini 2021; IRCT20190602043787N3; IRCT20200408046987N3; IRCT20200422047168N2; ISRCTN90437126; NCT04351347; NCT04374019; NCT04407130; NCT04407507; NCT04716569; NCT04746365; NCT04891250; Samaha 2021).

Three studies had already been published or had results posted in the trial registry (Faisal 2020; NCT04407507; Samaha 2021). However, despite using the term 'randomized controlled trial,' there were contradictory details throughout the published text or protocol that led us to believe those studies were not fulfilling criteria of genuine RCTs. We contacted study authors for clarification but received no response at the time of review publication.

We identified five completed and potentially eligible RCTs from trial register entries, but there were no results available or published (2020-002091-12/BG; Hosseini 2021; IRCT20190602043787N3; IRCT20200422047168N2; NCT04407130). Three studies investigated ivermectin with standard of care versus standard of care alone in 220 participants in an inpatient setting (Hosseini 2021; IRCT20190602043787N3; IRCT20200422047168N2), another two completed studies used placebo as comparator in 192 participants (2020-002091-12/BG; NCT04407130). Ten studies were not explicit enough in their protocol to make a final decision on eligibility. First, none of the following eight studies reported a clear description of the type of control intervention used as comparator (2020-001971-33/ES; CTRI/2020/04/024948; CTRI/2020/06/025960; NCT04351347; NCT04374019; NCT04716569; NCT04746365; NCT04891250). Additionally, for two of those trials, it was unclear if an RT-PCR-confirmed COVID-19 diagnosis was required for inclusion (NCT04351347; NCT04716569). Similarly, two studies investigating prevention were not well-defined regarding the inclusion criteria of high-risk exposure to an index patient (ISRCTN90437126; NCT04891250). Finally, for another trial, we could not evaluate the actual rationale or the considered patient population due to inconclusive PICO details (IRCT20200408046987N3).

Ongoing studies

See Characteristics of ongoing studies table.

We classified 31 studies as ongoing. With intention to treat COVID-19, 18 studies are comparing ivermectin to placebo of which seven were to be completed by the end of May 2021, and planned to evaluate between 100 and 500 participants (ACTRN12620000982910; NCT04712279; Garcia 2021; NCT04429711; NCT04729140; NCT04834115; Vallejos 2020). However, according to the trial registry, these studies are either not yet recruiting or still recruiting at the time of review publication. Nine of 13 studies, evaluating between 60 and 2724 participants, are due to be completed by the end of 2021 (IRCT20200404046937N4; NCT04438850; NCT04472585; NCT04703205; NCT04836299; NCT04886362) or 2022 (IRCT20111224008507N4; IRCT20111224008507N5; NCT04727424). Anticipating 15,000 participants, the largest ongoing trial will be completed in 2023 (NCT04885530). One trial, which plans to evaluate 266 participants, has not reported the recruiting status or an expected completion date (2020-001994-66/ES). Regarding the patient setting, 13 ongoing studies described above are using ivermectin in an outpatient setting (2020-001994-66/ES; ACTRN12620000982910; NCT04712279; Garcia 2021;IRCT20111224008507N4; NCT04438850; NCT04703205; NCT04727424; NCT04729140; Vallejos 2020; NCT04834115; NCT04885530; NCT04886362), three in an inpatient setting (IRCT20200404046937N4; IRCT20111224008507N5; NCT04836299), and two are unclear about this issue in their protocol (NCT04429711; NCT04472585).

Ten of 31 ongoing studies are comparing ivermectin plus standard of care to standard of care alone, and plan to evaluate between 50 and 240 participants. Six of 10 studies include participants in inpatients settings (CTRI/2020/05/025068; CTRI/2020/05/025224; NCT04403555; NCT04425707; NCT04602507; PACTR202102588777597), one study includes outpatients (NCT04673214), and three studies are unclear about this issue in their protocol (IRCT20190624043993N2; NCT04445311; NCT04510233). Most of those studies were expected to be completed by May 2021, but according to the trial registry, five are still recruiting (NCT04403555; NCT04425707; NCT04445311; NCT04602507; NCT04673214), one has not started recruitment yet (NCT04510233), and one does not report the recruitment status (IRCT20190624043993N2). One trial that is currently recruiting is expected to be completed in 2022 (PACTR202102588777597). The two studies without an indicated completion date have not started recruiting yet (CTRI/2020/05/025068; CTRI/2020/05/025224).

Five studies are comparing ivermectin to placebo or no treatment with the intention to prevent SARS-CoV-2 infection in close contacts of COVID-19 index cases. Two of those are planned as substudies on close contacts that also investigate treatment in 266 (2020-001994-66/ES) and 240 (PACTR202102588777597) participants. Three larger trials, all of which are using placebo as control, are solely focusing on the period after high-risk exposure to COVID-19. One trial with 750 close contacts is still recruiting, but expected to be completed during the time of review publication

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(NCT04894721), another one including 2000 close contacts will be completed in October 2021 (PACTR202102848675636). Finally, one study is evaluating postexposure prophylaxis in 550 healthcare workers (NCT04527211). This study was supposed to be completed in December 2020, but according to the trial registry has not started recruiting yet.

We found no studies comparing ivermectin to an active comparator eligible for this review.

Risk of bias in included studies

We assessed methodological quality and risk of bias for 13 RCTs contributing results to our prioritized outcomes using the RoB 2 tool (Ahmed 2020; Chaccour 2021; Gonzalez 2021; Kirti 2021; Kishoria 2020; Krolewiecki 2020; López-Medina 2021; Mohan 2021; Okumuş 2021; Podder 2020; Pott-Junior 2021; Shah Bukhari 2021; Shoumann 2021). We did not judge risk of bias for Chachar 2020, as this study reported no results eligible for any of our prioritized outcomes. In total, the 13 studies contributed 41 study results to 23 outcomes of this review that were finally assessed using RoB 2. The RoB 2 judgements for all study results per outcomes and for all domains are available in an interactive risk-of-bias table (Supplementary File_Ivermectin_Risk of Bias), and are briefly summarized below.

Overall risk of bias by study

Most of the 41 study results (56.1%) had some concerns for the overall risk of bias. Thirteen (31.7%) of the 41 study results were at overall high risk of bias. We excluded studies with overall high risk of bias from the primary meta-analyses of the review. The main reasons a study result was assessed at high risk of bias were missing outcome data and measurement of the outcome. Studies with high risk of bias were included in secondary meta-analyses. Two studies contributing five study results (12.2%) to four outcomes, including all-cause mortality, adverse events, and viral clearance at three and seven days, were at overall low risk of bias (Chaccour 2021; Mohan 2021).

Overall risk of bias by outcome

The following section summarizes the risk of bias per outcome (primary analysis) for all outcomes included in the summary of findings tables (Summary of findings 1; Summary of findings 2; Summary of findings 3).

Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in an inpatient setting

All-cause mortality up to 28 days

Two studies contributed results to the primary analysis of mortality up to 28 days and risk of bias was assessed as some concerns. Gonzalez 2021 provided insufficient information on allocation concealment and blinding of healthcare providers, and did not define the time point of outcome measurement in the protocol. Kirti 2021 performed an inappropriate analysis (per-protocol analysis).

Worsening of clinical status

Need for invasive mechanical ventilation up to 28 days

Two studies contributed results to the primary analysis of need for invasive mechanical ventilation up to 28 days and risk of bias was assessed as some concerns. Gonzalez 2021 provided insufficient information on allocation concealment and blinding of healthcare providers, and did not define the time point of outcome measurement in the protocol. Kirti 2021 performed an inappropriate analysis (per-protocol analysis).

Need for oxygen by mask or nasal prongs up to 28 days

One study contributed results to the primary analysis of need for oxygen by mask or nasal prongs up to 28 days and risk of bias was assessed as some concerns. Ahmed 2020 provided insufficient information on randomization, allocation concealment, and blinding of participants and healthcare providers, and did not provide a prospectively registered protocol.

Improvement of clinical status

Participants discharged without respiratory deterioration or death at 28 days

One study contributed results to the primary analysis of patients discharged without respiratory deterioration or death at 28 days and risk of bias was assessed as some concerns. Gonzalez 2021 provided insufficient information on allocation concealment and blinding of healthcare providers and did not register the outcome in the protocol.

Any adverse events within 28 days

One study contributed results to the primary analysis of any adverse events within 28 days and risk of bias was assessed as some concerns. Mohan 2021 provided insufficient information on definition and measurement of the outcome, and did not prespecify the outcome in the prospectively registered protocol.

Three studies with high risk of bias were not eligible for the primary analysis (Krolewiecki 2020; Pott-Junior 2021; Shah Bukhari 2021). All three studies provided insufficient information on definition, and measurement of the outcome and outcome assessors were not blinded. One study had missing outcome data of more than 14% (Shah Bukhari 2021). Participants withdrew against medical advice before completion of the study.

Duration of hospitalization

One study contributed results to the primary analysis of duration of hospitalization and risk of bias was assessed as some concerns. Ahmed 2020 provided insufficient information on randomization, allocation concealment, and blinding of participants and healthcare providers, and did not provide a prospectively registered protocol.

Viral clearance at seven days

Two studies contributed results to the primary analysis of viral clearance at seven days and risk of bias was assessed as some concerns. Mohan 2021 was at overall low risk of bias. Ahmed 2020 provided insufficient information on randomization, allocation concealment, blinding of participants and healthcare providers, and did not provide a prospectively registered protocol.

Two studies with high risk of bias were not eligible for the primary analysis (Kirti 2021; Pott-Junior 2021). Kirti 2021 had more than 30% of missing data due to discharge or inconclusive results. In Pott-Junior 2021, participants and those delivering the intervention were aware of the intervention received and 25% of participants

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(one of four) in the control group were excluded due to protocol violations (per-protocol analysis). Protocol violations were not described.

Ivermectin compared to placebo or standard of care for people with mild COVID-19 treated in an outpatient setting

All-cause mortality up to 28 days

Two studies contributed results to the primary analysis of mortality up to 28 days and risk of bias was assessed as some concerns. Chaccour 2021 was at overall low risk of bias. In López-Medina 2021, the primary analysis was per-protocol due to a labelling error that resulted in 16% of participants receiving the wrong intervention. Both participants and those delivering the intervention were unaware of intervention received and reported an as-treated sensitivity analysis where results did not differ.

Development of moderate-to-severe clinical COVID-19 symptoms – worsening of clinical status

Need for invasive mechanical ventilation up to 14 days

One study contributed results to the primary analysis of need for invasive mechanical ventilation at 14 days and risk of bias was assessed as some concerns. In López-Medina 2021, the primary analysis was per-protocol due to a labelling error that resulted in 16% of participants receiving the wrong intervention. Both participants and those delivering the intervention were unaware of intervention received and reported an as-treated sensitivity analysis where results did not differ.

Need for non-invasive mechanical ventilation or high flow up to 14 days

One study contributed results to the primary analysis of need for non-invasive mechanical ventilation or high flow up to 14 days and risk of bias was assessed as some concerns. In López-Medina 2021, the primary analysis was per-protocol due to a labelling error that resulted in 16% of participants receiving the wrong intervention. Both participants and those delivering the intervention were unaware of intervention received and reported an as-treated sensitivity analysis where results did not differ.

Symptom resolution

Number of participants with symptoms resolved up to 14 days

One study contributed results to the primary analysis of number of participants with symptoms resolved up to 14 days and risk of bias was assessed as some concerns. In López-Medina 2021, the primary analysis was per-protocol due to a labelling error that resulted in 16% of participants receiving the wrong intervention. Both participants and those delivering the intervention were unaware of intervention received and reported an as-treated sensitivity analysis where results did not differ.

Duration of symptom resolution

No study reporting duration of symptom resolution was eligible for primary analysis.

One study reported data as median with interquartile range, which were not eligible for meta-analysis (López-Medina 2021). The other study was not eligible for a primary analysis because of an overall high risk of bias assessment due to inadequate randomization and lack of blinding of participants, healthcare providers, and outcome assessors, and due to missing outcome data and lack of a registered protocol (Podder 2020).

Any adverse events within 28 days

Two studies contributed results to the primary analysis of any adverse events within 28 days and risk of bias was assessed as some concerns. Chaccour 2021 was at overall low risk of bias. In López-Medina 2021, the primary analysis was per-protocol due to a labelling error that resulted in 16% of participants receiving the wrong intervention. Both participants and those delivering the intervention were unaware of intervention received and reported an as-treated sensitivity analysis where results did not differ.

Viral clearance at seven days

One study contributed results to the primary analysis of viral clearance at seven days and risk of bias was assessed as low. Chaccour 2021 was at low risk of bias in all domains.

Ivermectin compared to no treatment for prevention of SARS-CoV-2 infection

Development of clinical COVID-19 symptoms up to 14 days

No study reporting development of clinical COVID-19 symptoms up to 14 days was eligible for primary analysis.

One study reported results that were not eligible for the primary analysis because of an overall high risk of bias assessment due to lack of information on measurement of the outcome and lack of blinding of outcome assessors (Shoumann 2021).

Any adverse events within 14 days

No study reporting any adverse events within 14 days was eligible for primary analysis.

One study reported results that were not eligible for the primary analysis because of an overall high risk of bias assessment due to lack of information on measurement of the outcome and lack of blinding of outcome assessors (Shoumann 2021).

All-cause mortality up to 28 days

One study contributed results to the primary analysis of mortality up to 28 days and risk of bias was assessed as some concerns. Shoumann 2021 provided insufficient information on randomization, allocation concealment, and missing outcome data, and did not prospectively register the outcome.

Effects of interventions

See: **Summary of findings 1** Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in an inpatient setting; **Summary of findings 2** Ivermectin compared to placebo or standard of care for people with mild COVID-19 treated in an outpatient setting; **Summary of findings 3** Ivermectin compared to no treatment for prevention of SARS-CoV-2 infection

We included 14 studies in the qualitative synthesis of this review (Ahmed 2020; Chaccour 2021; Chachar 2020; Gonzalez 2021; Kirti 2021; Kishoria 2020; Krolewiecki 2020; López-Medina 2021; Mohan 2021; Okumuş 2021; Podder 2020; Pott-Junior 2021; Shah Bukhari 2021; Shoumann 2021). With exception to one study (Chachar 2020), we included 13 studies in meta-analyses

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(quantitative synthesis). All included studies compared ivermectin to no treatment, placebo, or standard of care, and we found no studies that compared ivermectin to an active comparator with proven efficacy.

Nine studies investigated ivermectin compared to placebo or standard of care for treating COVID-19 in an inpatient setting and contributed data to meta-analyses (Ahmed 2020; Gonzalez 2021; Kirti 2021; Kishoria 2020; Krolewiecki 2020; Mohan 2021; Okumuş 2021; Pott-Junior 2021; Shah Bukhari 2021). Only one study investigated participants with moderate-to-severe COVID-19 (Okumuş 2021). All other studies investigated only participants with moderate COVID-19. Therefore, planned subgroup analyses for severity at baseline were not possible. The main findings are summarized in Summary of findings 1.

Three studies investigated ivermectin compared to placebo or standard of care for treating COVID-19 in an outpatient setting and contributed data to meta-analyses (Chaccour 2021; López-Medina 2021; Podder 2020). The main findings are summarized in Summary of findings 2.

One study investigated ivermectin compared to no treatment for preventing SARS-CoV-2 infection and contributed data to meta-analyses (Shoumann 2021). The main findings are summarized in Summary of findings 3.

Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in an inpatient setting

All-cause mortality up to 28 days

Two studies comparing ivermectin to placebo reported data on mortality at 28 days for 185 participants with moderate disease (Gonzalez 2021; Kirti 2021). Both studies were included in the primary meta-analysis due to the overall risk of bias assessment (Analysis 1.1). In the meta-analysis, five participants died in the ivermectin group and nine participants in the placebo group. We are uncertain whether ivermectin reduces or increases all-cause mortality up to 28 days compared to placebo (RR 0.60, 95% CI 0.14 to 2.51; 2 RCTs, 185 participants; very low-certainty evidence). We downgraded the certainty of evidence one level for serious risk of bias and two levels for very serious imprecision due to few participants, few events, and wide CIs. Both studies were published as preprint articles.

Two studies in an inpatient setting reported mortality at time points not eligible for meta-analysis. Mohan 2021 reported mortality at 14 days, which is too short, and Okumuş 2021 reported an unclear time frame of follow-up. In both cases, data were not comparable with studies reporting our predefined time point of 28 days.

Worsening of clinical status

Need for invasive mechanical ventilation up to 28 days

Two studies comparing ivermectin to placebo reported data on clinical worsening assessed by need for invasive mechanical ventilation at 28 days for 185 participants with moderate disease (Gonzalez 2021; Kirti 2021). Both studies were included in the primary meta-analysis due to the overall risk of bias assessment (Analysis 1.2). In the meta-analysis, four participants in the ivermectin group and eight participants in the placebo group showed clinical worsening. We are uncertain whether ivermectin reduces or increases clinical worsening assessed by the need for invasive mechanical ventilation compared to placebo up to 28 days (RR 0.55, 95% CI 0.11 to 2.59; 2 studies, 185 participants; very low-certainty evidence). We downgraded the certainty of evidence one level for serious risk of bias and two levels for very serious imprecision due to few participants, few events, and wide CIs. Both studies were published as preprint articles.

Two studies in an inpatient setting reported worsening of clinical status at seven days (Krolewiecki 2020) and 14 days (Mohan 2021), which was clinically not comparable with studies reporting our predefined time point of 28 days. Therefore, those studies were not eligible for meta-analysis.

Need for non-invasive mechanical ventilation or high flow up to 28 days

No study reported data for need for non-invasive mechanical ventilation or high flow up to 28 days.

Need for oxygen by mask or nasal prongs up to 28 days

One study comparing ivermectin to placebo assessed need for oxygen by mask or nasal prongs during the study period (14 days) for 45 participants without supplemental oxygen at baseline, but none of the participants in either group required supplemental oxygen during the study (Ahmed 2020). We accepted the shorter time point of 14 days for the outcome as there are no other data available that would cause clinical incompatibility. The study was included in the primary meta-analysis due to the overall risk of bias assessment (Analysis 1.3). We are uncertain whether ivermectin reduces or increases clinical worsening assessed by the need for oxygen support up to 28 days compared to placebo (RR not estimable; 1 study, 45 participants; very low-certainty evidence). We downgraded the certainty of evidence one level for serious risk of bias and two levels for very serious imprecision due to zero events and few participants. Ahmed 2020 was published as a journal article.

Improvement of clinical status

Weaning or liberation from invasive mechanical ventilation in surviving participants up to 28 days

No study reported data for weaning or liberation from invasive mechanical ventilation in surviving participants up to 28 days.

Ventilator-free days

No study reported data for ventilator-free days.

Duration of liberation from invasive mechanical ventilation

No study reported data for duration of liberation from invasive mechanical ventilation.

Liberation from supplemental oxygen in surviving participants up to 28 days

No study reported data for liberation from supplemental oxygen in surviving participants up to 28 days.

Duration of liberation from supplemental oxygen

No study reported data for duration of liberation from supplemental oxygen.

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Participants discharged without respiratory deterioration or death at 28 days

One study comparing ivermectin to placebo in 73 participants with moderate disease reported patients discharged without respiratory deterioration or death at 28 days (Gonzalez 2021). The study was included in the primary meta-analysis due to the overall risk of bias assessment (Analysis 1.4). In both groups, 27 participants were discharged without respiratory deterioration or death at 28 days. Ivermectin may have little or no effect on clinical improvement assessed by the number of participants discharged without respiratory deterioration or death up to 28 days compared to placebo (RR 1.03, 95% CI 0.78 to 1.35; 1 study, 73 participants; low-certainty evidence). We downgraded the certainty of evidence one level for serious risk of bias and one level for serious imprecision due to few participants. Gonzalez 2021 was published as a preprint article.

Any adverse events within 28 days

Four studies comparing ivermectin to placebo or standard of care reported any adverse events within 14 days (Mohan 2021), 28 days (Pott-Junior 2021; Shah Bukhari 2021), and one month (Krolewiecki 2020) in 314 participants with moderate disease. One of these studies was included in the primary analysis due the overall risk of bias assessment (Analysis 1.5) (Mohan 2021). We are uncertain whether ivermectin may increase or reduce any adverse events up to 28 days compared to placebo (RR 1.21, 95% CI 0.50 to 2.97; 1 study, 152 participants; very low-certainty evidence). We downgraded the certainty of evidence one level for serious risk of bias and two levels for very serious imprecision due to few participants and wide CIs. The other three studies with high risk of bias were included in a secondary analysis (Analysis 1.6) (Krolewiecki 2020; Pott-Junior 2021; Shah Bukhari 2021). The effect estimate of the secondary analysis was comparable to the primary analysis (RR 1.04, 95% CI 0.61 to 1.79; 4 studies, 314 participants). Only the study included in the primary analysis was published as a preprint article (Mohan 2021).

Okumuş 2021 reported adverse events within five days and was not eligible for meta-analysis on adverse events within 28 days due to the short follow-up period.

Serious adverse events within 28 days

Three studies comparing ivermectin to placebo or standard of care reported serious adverse events within 14 days (Ahmed 2020; Mohan 2021) and 30 days (Krolewiecki 2020) in 242 participants with moderate disease. Two of these studies with 197 participants were included in the primary analysis due the overall risk of bias assessment (Analysis 1.7) (Krolewiecki 2020; Mohan 2021). We are uncertain whether ivermectin increases or reduces serious adverse events up to 28 days compared to placebo or standard of care (RR 1.55, 95% CI 0.07 to 35.89; 2 studies, 197 participants). The other study with high risk of bias was included in a secondary analysis (Analysis 1.8) (Ahmed 2020). The effect estimate of the secondary analysis is identical to the primary analysis as the study contributed no events (RR 1.55, 95% CI 0.07 to 35.89; 3 studies, 242 participants). The two studies included in the primary analysis were published as preprint articles (Krolewiecki 2020; Mohan 2021).

Quality of life up to 28 days

No study reported data for quality of life up to 28 days.

Admission to intensive care unit

Two studies comparing ivermectin to placebo or standard of care reported the number of participants who were admitted to ICU at 28 days for participants with moderate disease (Kirti 2021; Pott-Junior 2021). Both studies with 143 participants were included in the primary analysis due the overall risk of bias assessment (Analysis 1.9). We are uncertain whether ivermectin increases or reduces the number of participants who were admitted to the ICU at 28 days compared to placebo or standard of care (RR 0.53, 95% CI 0.11 to 2.51; 2 studies, 143 participants). One study was published as a preprint article (Kirti 2021), the other was published as journal publication (Pott-Junior 2021). The sensitivity analysis including only the study published in a journal estimated the intervention effect at RR 0.15 (95% CI 0.01 to 1.93; 1 study, 31 participants).

Duration of hospitalization

Two studies comparing ivermectin to placebo reported duration of hospitalization (Ahmed 2020; Gonzalez 2021). One of these studies reported data as median with IQR on duration of hospitalization in 73 participants with moderate disease (Gonzalez 2021). The median duration of hospitalization in the ivermectin group was six days (IQR 4 to 11 days) compared to five days (IQR 4 to 7 days) in the placebo group. Ahmed 2020, investigating 45 participants with moderate disease, was included in the primary meta-analysis due to the overall risk of bias assessment and reporting data as means with SDs (Analysis 1.10). Ivermectin may have little or no effect on duration of hospitalization compared to placebo (MD −0.10 days, 95% CI −2.43 to 2.23; 1 study, 45 participants; low-certainty evidence). We downgraded the certainty of evidence one level for serious risk of bias and one level for serious imprecision due to few participants. Ahmed 2020 was published as a journal article and Gonzalez 2021 was published as a preprint article.

Viral clearance at three days

Four studies comparing ivermectin to placebo or standard of care reported viral clearance at three days in 288 participants with moderate disease (Ahmed 2020; Kishoria 2020; Mohan 2021; Shah Bukhari 2021). Two of the studies with 170 participants were included in the primary analysis due to the overall risk of bias assessment (Analysis 1.11) (Ahmed 2020; Mohan 2021). We are uncertain whether ivermectin increases or reduces viral clearance at three days compared to placebo (RR 1.02, 95% CI 0.45 to 2.32; 2 studies, 170 participants). The other two studies with high risk of bias were included in a secondary analysis (Analysis 1.12) (Kishoria 2020; Shah Bukhari 2021). The point estimate of the secondary analysis favoured ivermectin, but the 95% CI was wide including 1 and heterogeneity was high (RR 1.73, 95% CI 0.59 to 5.04; I^2 = 73%; 4 studies, 288 participants). One study included in the primary analysis was published as a preprint article (Mohan 2021), the other study was published as a journal article (Ahmed 2020). The sensitivity analysis including only the study published in a journal estimated the intervention effect at RR 2.09 (95% CI 0.42 to 10.29; 1 study, 45 participants).

Viral clearance at seven days

Four studies comparing ivermectin to placebo or standard of care reported viral clearance at seven days in 265 participants with moderate disease (Ahmed 2020; Kirti 2021; Mohan 2021; Pott-Junior 2021). Two of the studies with 159 participants were included in the primary analysis due the overall risk of bias

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assessment (Analysis 1.13) (Ahmed 2020; Mohan 2021). We are uncertain whether ivermectin increases or reduces viral clearance at seven days compared to placebo (RR 1.82, 95% CI 0.51 to 6.48; 2 studies, 159 participants; very low-certainty evidence). We downgraded the certainty of evidence one level for serious risk of bias, one level for serious heterogeneity (I^2 = 77%), and two levels for very serious imprecision due to few participants and wide CIs. The other two studies with high risk of bias were included in a secondary analysis (Analysis 1.14) (Kirti 2021; Pott-Junior 2021). The point estimate of the secondary analysis lay closer to 1 and the 95% CI was wide and included 1 (RR 1.19, 95% CI 0.76 to 1.86; 4 studies, 265 participants). One study included in the primary analysis was published as a preprint article (Mohan 2021), the other study was published as a journal article (Ahmed 2020). The sensitivity analysis including only the study published in a journal favoured ivermectin compared to placebo (RR 3.83, 95% CI 1.23 to 11.93; 1 study, 45 participants).

Viral clearance at 14 days

Two studies comparing ivermectin to placebo or standard of care reported viral clearance at 14 days in 69 participants with moderate-to-severe disease (Ahmed 2020; Okumuş 2021). One of the studies with 45 participants was included in the primary analysis due the overall risk of bias assessment (Analysis 1.15) (Ahmed 2020). Ivermectin may increase viral clearance at 14 days compared to placebo (RR 1.97, 95% CI 1.13 to 3.45; 1 study, 45 participants). The other study with high risk of bias was included in a secondary analysis (Analysis 1.16) (Okumuş 2021). The effect estimate of the secondary analysis was comparable to the primary analysis (RR 2.07, 95% CI 1.28 to 3.33; 2 studies, 69 participants). The study included in the primary analysis was published as a journal article (Ahmed 2020).

Ivermectin compared to placebo or standard of care for people with mild COVID-19 treated in an outpatient setting

All-cause mortality up to 28 days

Two studies comparing ivermectin to placebo reported data on mortality at 21 days (López-Medina 2021) and at 28 days (Chaccour 2021) for 422 participants with mild disease. Both studies were included in the primary meta-analysis due to the overall risk of bias assessment (Analysis 2.1). In the meta-analysis, none of the participants died in the ivermectin group and one participant died in the placebo group. We are uncertain whether ivermectin reduces or increases all-cause mortality up to 28 days compared to placebo (RR 0.33, 95% CI 0.01 to 8.05; 2 studies, 422 participants; very low-certainty evidence). We downgraded the certainty of evidence one level for serious risk of bias and two levels for very serious imprecision due to few participants, few events, and wide CIs. Both studies were published as journal articles.

Development of moderate-to-severe clinical COVID-19 symptoms – worsening of clinical status

Need for invasive mechanical ventilation, or non-invasive mechanical ventilation or high flow

Need for invasive mechanical ventilation up to 14 days

One study comparing ivermectin to placebo reported data on clinical worsening assessed by need for invasive mechanical ventilation at 15 days in 398 participants with mild disease (López-Medina 2021). The study was eligible for the primary meta-analysis due to the overall risk of bias assessment (Analysis 2.2). One participant in the ivermectin group and no participants in the placebo group showed clinical worsening. We are uncertain whether ivermectin reduces or increases clinical worsening assessed by the need for invasive mechanical ventilation compared to placebo up to 14 days (RR 2.97, 95% CI 0.12 to 72.47; 1 study, 398 participants; very low-certainty evidence). We downgraded the certainty of evidence one level for serious risk of bias and two levels for very serious imprecision due to few participants, few events, and wide CIs. The study was published as a journal article.

Need for non-invasive mechanical ventilation or high flow up to 14 days

One study comparing ivermectin to placebo reported the need for non-invasive mechanical ventilation or high flow at 15 days in 398 participants with mild disease (López-Medina 2021). None of the participants in either group required non-invasive mechanical ventilation or high flow at 15 days. The study was eligible for the primary analysis due to the overall risk of bias assessment (Analysis 2.3). We are uncertain whether ivermectin reduces or increases clinical worsening assessed by the need for non-invasive mechanical ventilation or high flow at 15 days compared to placebo (RR not estimable; 1 study, 398 participants; very low-certainty evidence). We downgraded the certainty of evidence one level for serious risk of bias and two levels for very serious imprecision due to zero events and few participants. López-Medina 2021 was published as a journal article.

Need for hospitalization with or without supplemental oxygen

López-Medina 2021 reported hospitalization with or without supplemental oxygen. The data were not eligible for meta-analysis as less than 1% of the participants already had a WHO status of 4 and 5 at baseline. Therefore, these data were not useful to judge clinical worsening.

Need for oxygen by mask or nasal prongs up to 14 days

No study reported data for need for oxygen by mask or nasal prongs up to 14 days.

Need for hospitalization without oxygen therapy up to 14 days

No study reported data for need for hospitalization without oxygen therapy up to 14 days.

Symptom resolution

Number of participants with symptoms resolved up to 14 days

One study comparing ivermectin to placebo reported data on symptom resolution at 15 days in 398 participants with mild disease (López-Medina 2021). The study was eligible for the primary meta-analysis due to the overall risk of bias assessment (Analysis 2.4). Ivermectin may have little or no effect on clinical improvement assessed by the number of participants with symptoms resolved up to 14 days (RR 1.04, 95% CI 0.89 to 1.21; 1 study, 398 participants; low-certainty evidence). We downgraded the certainty of evidence one level for serious risk of bias and one level for serious imprecision due to few participants. The study was published as a journal article.

Chachar 2020 reported symptom resolution within seven days, which was too early and clinically not comparable to our predefined time point of 14 days.

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Duration of symptom resolution

Two studies reported data on duration of symptom resolution (López-Medina 2021; Podder 2020). One studies comparing ivermectin to placebo reported data as median with IQR on duration of symptom resolution in 398 participants with mild disease (López-Medina 2021). The median duration of symptom resolution in the ivermectin group was 10 days (IQR 9 to 13 days) compared to 12 days (IQR 9 to 13 days) in the placebo group. The study was not eligible for meta-analysis due to an asymmetric distribution of the data. The other study comparing ivermectin to standard of care reported data as means with SDs on duration to symptom resolution in 62 participants with mild disease (Podder 2020). The study was not eligible for a primary analysis due to the overall risk of bias assessment. This study with high risk of bias was analyzed in a secondary analysis (Analysis 2.5). The effect estimate of the secondary analysis showed no clinically relevant difference in the duration to symptom resolution (MD −1.02 days, 95% CI −2.76 to 0.72; 1 study, 62 participants). Both studies were published as journal articles.

Admission to hospital

No study reported data for admission to hospital.

Any adverse events within 28 days

Two studies comparing ivermectin to placebo reported any adverse events within 21 days (López-Medina 2021) and 28 days (Chaccour 2021) in 422 participants with mild disease. Both studies were included in the primary analysis due the overall risk of bias assessment (Analysis 2.6). Ivermectin may have little or no effect on any adverse events compared to placebo (RR 0.95, 95% CI 0.86 to 1.05; 2 studies, 422 participants; low-certainty evidence). We downgraded the certainty of evidence one level for serious risk of bias and one level for serious imprecision due to few participants. Both studies were published as journal articles.

Chachar 2020 reported adverse events within seven days, which was not eligible for meta-analysis due to the short follow-up period.

Serious adverse events within 28 days

Two studies comparing ivermectin to placebo reported serious adverse events within 21 days (López-Medina 2021) and 28 days (Chaccour 2021) in 422 participants with mild disease. Both studies were included in the primary analysis due the overall risk of bias assessment (Analysis 2.7). Chaccour 2021 reported zero events in both groups. We are uncertain whether ivermectin increases or reduce serious adverse events within 28 days compared to placebo (RR 0.99, 95% CI 0.14 to 6.96; 2 studies, 422 participants). Both studies were published as journal articles.

Quality of life up to 14 days

No study reported data for quality of life up to 14 days.

Viral clearance at three days

No study reported data for viral clearance at three days.

Viral clearance at seven days

One study comparing ivermectin to placebo reported viral clearance at seven days in 24 participants with mild disease (Chaccour 2021). The study was eligible for the primary analysis due the overall risk of bias assessment (Analysis 2.8). We are uncertain whether ivermectin increases or reduces viral clearance at seven days compared to placebo (RR 3.00, 95% CI 0.13 to 67.06; 1 study, 24 participants; low-certainty evidence). We downgraded the certainty of evidence two levels for very serious imprecision due to few participants, few events, and wide CIs. The study was published as a journal article.

Viral clearance at 14 days

One study comparing ivermectin to standard of care reported viral clearance at 14 days in 40 participants with mild disease (Podder 2020). The study was not eligible for the primary analysis due the overall risk of bias assessment. The data of Podder 2020 with high risk of bias were included in a secondary analysis (Analysis 2.9). Ivermectin may have no effect on viral clearance at 14 days compared to standard of care (RR 0.95, 95% CI 0.79 to 1.13; 1 study, 40 participants). The study was published as a journal article.

Ivermectin compared to no treatment for prevention of SARS-CoV-2 infection

SARS-CoV-2 infection (confirmed by RT-PCR or antigen testing) at 14 days

No study reported data for SARS-CoV-2 infection (confirmed by RT-PCR or antigen testing) at 14 days.

Development of clinical COVID-19 symptoms up to 14 days

One study comparing ivermectin to no treatment reported the development of clinical COVID-19 symptoms at 14 days in 304 asymptomatic participants with household close contacts to confirmed COVID-19 index case (Shoumann 2021). The study result was not eligible for the primary analysis due to the overall risk of bias assessment. The data of Shoumann 2021 with high risk of bias were included in a secondary analysis (Analysis 3.1). Ivermectin may reduce the development of clinical COVID-19 symptoms in participants in contact with confirmed COVID-19 index cases compared to no treatment (RR 0.13, 95% CI 0.08 to 0.21; 1 study, 304 participants). The study was published as a journal article.

Any adverse events within 14 days

One study comparing ivermectin to no treatment reported any adverse events within 14 days in 304 asymptomatic participants with household close contacts to confirmed COVID-19 index case n (Shoumann 2021). The study result was not eligible for the primary analysis due to the overall risk of bias assessment. The data of Shoumann 2021 with high risk of bias were included in a secondary analysis (Analysis 3.2). We are uncertain whether ivermectin increases or reduces any adverse events in participants in contact with confirmed COVID-19 index cases compared to no treatment (RR 11.50, 95% CI 0.68 to 193.21; 1 study, 304 participants). The study was published as a journal article.

All-cause mortality up to 28 days

One study comparing ivermectin to no treatment reported mortality within 14 days in 304 asymptomatic participants with household close contacts to confirmed COVID-19 index case (Shoumann 2021). The study result was included in the primary meta-analysis due to the overall risk of bias assessment (Analysis 3.3). We are uncertain whether ivermectin reduces or increases mortality up to 28 days compared to no treatment as none of the participants in either group died (RR not estimable; 1 study, 304 participants; very low-certainty evidence). We downgraded the

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certainty of evidence one level for serious risk of bias and two levels for very serious imprecision due to zero events and few participants. The study was published as a journal article.

Admission to hospital

No study reported data for admission to hospital.

Quality of life up to 14 days

No study reported data for quality of life up to 14 days.

DISCUSSION

Summary of main results

This review included 14 studies with 1678 participants investigating ivermectin compared to placebo or standard of care. With intention to treat COVID-19, nine studies were conducted in inpatient settings with mainly moderate COVID-19 (WHO 4 to 5) and four studies in outpatient settings with mild COVID-19 (WHO 2 to 3). One study investigated ivermectin for the prevention of SARS-CoV-2 infection. The included studies contributed 41 study results to the review of which about one third were assessed at overall high risk of bias. The main findings of this review are summarized in Summary of findings 1 (treatment; inpatients), Summary of findings 2 (treatment; outpatients), and Summary of findings 3 (prevention). The number of studies per outcome was low. Only one or two studies per outcome provided useful data for our prioritized outcomes included in the summary of findings tables.

Ivermectin showed no evidence of an effect on increasing or decreasing mortality at 28 days, the most important outcome during this pandemic, neither in inpatients (two studies), outpatients (two studies), or the preventive setting (one study). The certainty for this finding was very low. The same accounts for clinical worsening up to 28 days in an inpatient setting and up to 14 days in an outpatient setting.

With regard to clinical improvement, ivermectin may have little or no effect compared to placebo or standard of care on clinical improvement up to 28 days and duration of hospitalizations in an inpatient setting. For outpatients, ivermectin may have little or no effect on the number of participants with symptoms resolved up to 14 days. Based on very low certainty evidence, there was no significant increase in viral clearance at seven days in participants treated with ivermectin in inpatient settings and based on low-certainty evidence for outpatient settings. For adverse events, ivermectin may have little or no difference on occurrence of adverse events within 14 days in an outpatient setting, while we are uncertain about the effect of ivermectin on adverse events within 28 days in an inpatient setting.

The most significant outcome for participants not infected but at high risk of developing the infection following high-risk exposure was development of confirmed SARS-CoV-2 infection, which no studies reported. One study reported development of clinical COVID-19 symptoms, which we could not include in the primary analysis due to high risk of bias. The same accounted for adverse events within 14 days.

Overall completeness and applicability of evidence

Nine of 14 included studies were conducted in inpatient settings. However, participants mostly had moderate-severity COVID-19. Only one study included participants with severe COVID-19 requiring mechanical ventilation at baseline (Okumuş 2021). Therefore, the findings of this review are transferable to inpatients with moderate COVID-19 only. Four of 14 included studies were conducted in an outpatient setting with mild COVID-19 symptoms, though only two studies reported relevant outcomes and also had overall low risk or some concerns of bias (Chaccour 2021; López-Medina 2021). Based on the eligible study pool, there is currently no evidence available for the use of ivermectin in severely ill people with COVID-19 or those at high risk of disease progression. Most studies reported a mean age far below 60 years (overall mean age was 43 years with a mean range from 28 to 62 years) and included people with very few or no comorbidities (e.g. obesity). This major risk factor for severe COVID-19, was only reported in three studies (Chachar 2020; Krolewiecki 2020; López-Medina 2021). Considering age and pre-existing conditions as the most important risk factors for developing severe COVID-19, the current evidence is not applicable to patients who are at most risk of death from COVID-19.

Hence, for outpatients as well as for inpatients we are still in need of good-quality trials in relevant populations to obtain evidence that would justify the use of ivermectin in regular patient care. In June 2021, the PRINCIPLE trialists announced inclusion of ivermectin in their platform trial, which might provide us with applicable data that helps to complete evidence for outpatient treatment (PRINCIPLE trial).

Only 1 of 14 included studies investigated the potential of ivermectin for prevention of SARS-CoV-2 infection in people after high-risk exposure. The study did not report results free of high risk of bias for one of the primary outcomes of interest for this review. Therefore, it is currently unclear whether ivermectin can prevent SARS-CoV-2 infection in people who have had a high-risk contact.

Seven studies were conducted in Asia, four studies in South America, two in Europe, and one in Africa. In some countries where studies were conducted, uncontrolled ivermectin use is making it difficult to test the effectiveness of the antiparasite drug against SARS-CoV-2 (Rodríguez-Mega 2020). With Chaccour 2021, only one study was conducted in a country with high healthcare expenditure.

All studies administered ivermectin per mouth, but the doses and durations of administration varied. We set 200 µg/kg orally per day as the low dose based on the dosing recommendation for strongyloidiasis (WHO 2019). Four of the 14 studies used low doses in at least one study arm. All other studies utilized higher doses either in a single dose or over two to five days. Due to the small number of studies per outcome, we did not perform any subgroup analyses with low versus high doses and no evidence or clinical implication can be obtained regarding a certain dosing regimen.

We found no studies that compared ivermectin to an active comparator with confirmed efficacy such as dexamethasone. Eight of the 14 studies had an open-label design and used no treatment or standard of care as comparators. Six studies were placebo-controlled studies. Standard of care must be comparable between the studies' arms. There are several studies circulating that investigate various concomitant medications (e.g. doxycycline, hydroxychloroquine, azithromycin, zinc) in addition to ivermectin. Due to unproven efficacy and possible adverse effects, these comparisons may confound the assessment of the efficacy or safety of ivermectin, and we considered the inclusion of such

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combination therapies inappropriate. The same accounts for the comparison of ivermectin with an active comparator that has no proven efficacy in COVID-19. Although those types of interventions (e.g. hydroxychloroquine) were possibly used at a certain point of the pandemic with the best intentions, their use was never supported by actual evidence, and they have potential adverse effects (Singh 2021). As we do not know the effect of many of those experimental comparators in people with COVID-19, consequently no reliable evidence for ivermectin can be obtained from those comparisons either.

Although 14 studies were eligible for the review questions, primary outcomes for studies with intention to treat COVID-19, as defined by the review, were only reported by a minority of studies. For some outcomes, different time points of outcome assessment or different outcome definitions prevented clinically useful pooling of the study results. Clinical worsening and improvement were heterogeneously reported, including outcomes that represent competing risks. Few studies followed the WHO Clinical Progression Scale (Marshall 2020). One study reported improvement and worsening of clinical status in an inpatient setting as the number of 'patients discharged without respiratory deterioration or death at 28 days' and as 'patients with respiratory deterioration or death at 28 days' (Gonzalez 2021). If reported at the same day, both outcomes give useful information on the clinical status of the study population in both directions – improvement and worsening – without containing competing risks. The outcome 'patients discharged without respiratory deterioration or death at 28 days' was deemed to be clinically useful and was added as a new primary outcome during preparation of this review. With further studies reporting these two very precise and unambiguous endpoints, evidence on ivermectin becomes more complete and patient-relevant.

Finally, 31 studies are ongoing and 18 studies are awaiting classification due to an unpublished status or requiring clarification due to inconsistencies. When the studies are published or inconsistencies are clarified by study authors via personal communication, we will include them in a review update and conclusions of this review may change. Especially the most recently registered trials are proposing much larger numbers of participants than those of published trials so far. With group sizes ranging within the thousands, those trials may help to increase the certainty of evidence on the efficacy and safety of ivermectin. So far, we included only one study with intention to prevent SARS-CoV-2 infection. We identified several ongoing and unpublished studies focusing on this rationale. We are awaiting publication of those results to close the current gaps in the evidence on ivermectin used in postexposure prophylaxis.

Quality of the evidence

The certainty of evidence for prioritized outcomes presented in the summary of findings tables ranged from very low to low (Summary of findings 1; Summary of findings 2; Summary of findings 3).

For the summary of findings and assessment of the certainty of the evidence according to Schünemann 2020, we used the results from the primary meta-analyses. Primary meta-analyses included only studies with low risk or some concerns of bias. We excluded studies at high risk of bias for their respective outcome and only analyzed them in secondary analyses to test the robustness of the results. One third of the study results were at overall high risk of bias. Most study results had some concerns for risk of bias. Two studies contributing five study results to four outcomes, including all-cause mortality, adverse events, and viral clearance at three and seven days, were at overall low risk of bias (Chaccour 2021; Mohan 2021). For the summary of findings, the certainty of evidence was downgraded one level due to serious risk of bias because most of the results were assessed as 'some concerns' of bias. Details of the risk of bias assessments per outcome are reported in Risk of bias in included studies. We could only include one study with overall low risk of bias on viral clearance at day seven in an outpatient setting in the primary analysis (Chaccour 2021). The certainty of evidence was not downgraded for study limitations. Nevertheless, this effect estimate was associated with high uncertainty based on the low number of participants and few events.

Another limitation for the certainty of evidence was the low number of participants, or events, or both, leading to wide CIs and high uncertainty of the estimated effects. All outcomes included in the summary of findings tables were downgraded one or two levels for imprecision.

Heterogeneity was rarely a reason to downgrade the certainty of evidence. This is mainly due to the small number of studies per meta-analysis. The only outcome with high heterogeneity ($I^2 = 77\%$) included in the summary of findings tables was viral clearance at day seven in an inpatient setting. Two studies with conflicting results, one favouring ivermectin (Ahmed 2020), and one showing no important difference between ivermectin and placebo (Mohan 2021), caused the high statistical heterogeneity.

We did not downgrade any of the outcomes included in the summary of findings tables for indirectness. In all cases, the effect estimates were based on comparisons of interest, on the population of interest, and on outcomes of interest.

In the current phase of the pandemic, it is impossible to reliably assess the risk of publication bias. Most of the registered studies are still ongoing or, in the case of a completed study status, their results have not yet been published. We will follow the publication and trial history of each ongoing study and study awaiting classification. Currently, we did not suspect publication bias for any outcome included in this review. However, this may change in updates of this review.

Potential biases in the review process

This review aimed to provide a complete evidence profile for ivermectin with regard to efficacy and safety for postexposure prophylaxis and treatment of COVID-19 based on current Cochrane standards (Higgins 2020a).

The review team is part of the German research project 'CEOsys' (COVID-19 Evidence-Ecosystem). CEOsys is a consortium of clinical and methodological experts supported by the German Federal Ministry of Education and Research to synthesize clinical evidence during this global pandemic. The involved medical information specialists of this consortium carried out a rigorous search of electronic databases including preprint servers and clinical trial registries to identify the complete extent of published and ongoing trials on this topic. Additionally, we compared our search results with those from 'living' meta-analysis and reviews (COVID-NMA Working Group; ivmmeta.com). Therefore, we are confident that we identified all relevant studies and are monitoring

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ongoing studies as well as full publication of preprints closely after the publication of this review.

Five studies were preprint articles. We are aware that articles may change following peer-review. Nevertheless, we are convinced that including all eligible data in a highly dynamic situation such as the COVID-19 pandemic is crucial to be up-to-date and to provide timely information on potentially promising treatment options. Journal publications and corresponding preprint articles were compared in terms of consistency and all study results were assessed for their risk of bias.

The immense amount of ongoing RCTs reflects the persistent lack of clarity on this intervention and the need for an update of this review. It should be considered that conclusions of the updated version differ from those of the present review. Review updates may allow for a more concise judgement of the effectiveness and the safety of ivermectin for treatment and prevention of COVID-19.

To minimise errors in screening, data extraction, and risk of bias assessment, two review authors independently conducted all processes. Analyses were conducted by one review author and checked by a second review author. We provided reasons for the exclusion of studies from this systematic review and described each included study in full detail and made explicit judgements on individual risk of bias.

We contacted study authors if the publication included unclear or inconclusive information or in case of missing information. Unfortunately, not all attempts of gathering data were successful. Details of the communication with authors are provided in the Characteristics of included studies table.

For three studies that had already published results, we could not finally judge eligibility due to inconsistencies in their study design description (Faisal 2020; NCT04407507; Samaha 2021). We contacted the corresponding authors to clarify those questions, though we have not received any satisfying response at the time of review publication. Another 15 trials classified as awaiting classification have not yet published results appropriately. We will monitor trials that have completed recruitment according to the trial registry closely for publication in the near future.

None of the members of the review author team has any affiliation with any stakeholder group who favours or disapproves of ivermectin or the comparators used in relevant studies.

Agreements and disagreements with other studies or reviews

Numerous reviews have been conducted investigating the efficacy of ivermectin for the treatment and prophylaxis of COVID-19 with inconsistent results in meta-analyses and conclusions, in many cases conflicting with our findings. Conflicts are mainly due to inclusion of studies investigating active comparators with unproven efficacy (e.g. hydroxychloroquine), pooling of studies with active and inactive comparators, different definitions of outcomes or outcomes assessment times, and different interpretations of the certainty of evidence.

In this context, two groups are especially worth a mention, the Front Line COVID-19 Critical Care Alliance (FLCCC) and the British Ivermectin Recommendation Development (BIRD) group, which were, to some extent, founded and supported by the same scientists. Both groups and individual group associates conducted various systematic reviews and meta-analyses, all with conclusions strongly in favour of the effectiveness of ivermectin for treatment and prevention of COVID-19 (BIRD 2021; Bryant 2021; Kory 2021). Additionally, there is an online and regularly updated analysis of published and emerging trials available (ivmmeta.com), postulating a strong beneficial effect of ivermectin for people with COVID-19. The website does not provide authorship details, though states the FLCCC and BIRD as its resources. Hill and colleagues published another large systematic review in favour of ivermectin (Hill 2021). Main findings of the reviews and disagreements to our findings are briefly summarized in the following paragraphs.

Hill 2021 identified 18 RCTs up to December 2020 and was a preprint article. The author team used the Cochrane Risk of Bias tool 1 for critical appraisal. However, the certainty of evidence was not assessed. Six RCTs investigating people with moderate-to-severe COVID-19 were pooled for the meta-analysis on mortality with a benefit of 75% for ivermectin (RR 0.25, 95% CI 0.12 to 0.52). Hill 2021 compared ivermectin alone or in combination with doxycycline to control interventions, including placebo, standard of care, or hydroxychloroquine, and pooled all in one comparison. We did not include five of the six studies in our meta-analysis on mortality of people with moderate COVID-19, including Elgazzar 2020, Hashim 2020, Mahmud 2021, Niaee 2020, and Okumuş 2021. Hashim 2020 and Mahmud 2021 combined ivermectin with doxycycline, which makes it impossible to isolate any potential effect to the individual drugs used. Elgazzar 2020 compared ivermectin to hydroxychloroquine. The latter is not effective for the treatment of COVID-19 and has resulted in clinical adverse effects (Singh 2021). We did not consider hydroxychloroquine an eligible comparator to investigate the efficacy and safety profile of ivermectin for the treatment of COVID-19. Niaee 2020 included a population of about 30% of people who were SARS-CoV-2-negative, which we did not consider appropriate to investigate SARS-CoV-2-specific antiviral effect of ivermectin. Okumuş 2021 compared ivermectin to an eligible comparator and investigated an eligible population, but reported mortality at an ineligible time point (e.g. on average three months). Finally, there is only one small study with broad CIs and high uncertainty for a mortality benefit (RR 0.12, 95% CI 0.01 to 2.09), which is also included in our meta-analysis on mortality of people with moderate COVID-19 (Kirti 2021). However, we included mortality at day 28 rather than in-hospital mortality, which was different in one participant who died in the control group.

Kory 2021 identified seven RCTs on the efficacy of ivermectin in outpatients with mild COVID-19 and six RCTs in hospitalized people with COVID-19. The review was published in the *American Journal of Therapeutics* and did not provide any search date or other methodological details used for meta-analyses. Kory 2021 concluded there was a mortality benefit based on the inclusion of six of the 13 studies (odds ratio (OR) 0.13, 95% CI 0.07 to 0.28), which was not a valid inclusion because Elgazzar 2020, Hashim 2020, Mahmud 2021, and Niaee 2020 were not eligible for the reasons described above, and Cadegiani 2020 was not an RCT. As described for Hill 2021, there remains only one small study (Kirti 2021), and a high degree of uncertainty for a mortality benefit.

The most recent systematic review with meta-analysis was published by Bryant 2021 in the *American Journal of Therapeutics* (same journal as Kory 2021). The review stated

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they followed the Cochrane's rapid review template and had a review protocol that was not registered on an appropriate register (e.g. PROSPERO). The author team used the Cochrane Risk of Bias tool 1 for critical appraisal and GRADE to assess the certainty of evidence. A meta-analysis of 15 trials found that ivermectin reduced the risk of death by an average of 62% compared with no ivermectin treatment (RR 0.38, 95% CI 0.19 to 0.73). The certainty of evidence was moderate due to study design limitations. The author team conducted several sensitivity analyses excluding outlier studies, studies at high risk of bias, and studies with active comparators. The effect estimates remained robust. However, even the sensitivity analysis excluding studies with active comparators, which was the most comparable analysis to our analysis on mortality, based their conclusion on studies that did not meet eligibility criteria for this current Cochrane Review (RR 0.41, 95% CI 0.23 to 0.74). Hashim 2020 and Mahmud 2021 combined ivermectin with doxycycline. Niaee 2020 and Rezai 2020 (Shahbaznejad 2021) included a mixed population with about 30% (Niaee 2020) and 75% (Rezai 2020 (Shahbaznejad 2021)) of participants with negative SARS-CoV-2 PCR tests. The registry entry of Petkov 2020 (2020-002091-12/BG) was eligible for our review, though there is no scientific publication of results except a press release on the manufacturer's website. Okumuş 2021 and Mohan 2021 reported mortality at an ineligible time point and Ahmed 2020 did not report mortality in the journal publication. Finally, the four remaining studies were included in our meta-analyses for outpatients (Chaccour 2021; López-Medina 2021) and inpatients (Gonzalez 2021; Kirti 2021) with COVID-19. All studies had broad CIs with a high uncertainty for a mortality benefit. Moreover, Bryant 2021 used a trial sequential analysis to test whether there was sufficient evidence to detect or reject intervention effects and to address imprecision of the effect estimates in this way. They concluded that there may have been sufficient evidence accrued before the end of 2020 to show a significant benefit of ivermectin over control for all-cause mortality. However, trial sequential analysis cannot adjust for risk of bias or wrong comparators. Therefore, inclusion of all trials in this context into the analysis does not yield reliable results.

Even if not eligible for the Cochrane Review, two studies in Bryant 2021 and all the other meta-analyses were notable because of the size of the effect reported and the narrow CIs: Elgazzar 2020 and Niaee 2020 help drive the large effects seen in the random-effects analysis. Elgazzar 2020, for example, reported among people with severe disease two deaths out of 100 in the ivermectin group and 20 deaths out of 100 in the chloroquine group; and Niaee 2020 reported two deaths out of 100 in the ivermectin group and 11 deaths out of 60 in the control group. These effect sizes are extreme. A recent press release claimed that the large trial by Elgazzar 2020 showed clear signs of fraudulence and should be withdrawn over ethical concerns (The Guardian 2021). Research Square withdrew this preprint on 14 July 2021 due to an expression of concern (Elgazzar 2020).

The website ivmmeta.com provides several meta-analyses of pooled effects including up to 60 studies. This website shows pooled estimates suggesting significant benefits with ivermectin, which has resulted in confusion for clinicians, patients, and decision-makers (Garegnani 2021). The analyses are misleading and have several limitations. As described for the other reviews, several ineligible interventions and comparators were pooled. Additionally, different outcomes were pooled and reported as percentage improvement with ivermectin studied in RCTs ranging from 40% improvement when used as late treatment to 83% improvement when used as prophylaxis. However, there is no full prospective protocol available describing the relevant review methodology, and there is no assessment of the risk of bias or the certainty of evidence.

National and international guidelines regarding the use of ivermectin for the treatment or prevention of COVID-19 have been developed over the past 12 months. Recommendations from the WHO, updated 31 March 2021 (WHO 2021b); European Medicines Agency, updated 22 March 2021 (EMA 2021); Infectious Diseases Society of America, updated 13 February 2021 (IDSA 2021); and the COVID Management Guidelines India Group, updated 15 May 2021 (COVID Guidelines India 2021), concur that ivermectin should only be used for treatment of COVID-19 in the context of clinical trials. The EMA additionally advises against the use of ivermectin for prophylaxis outside RCTs. (EMA 2021). The US NIH guidance updated on 11 February 2021 describes 'insufficient data' to permit a recommendation for or against the use of ivermectin for the treatment of COVID-19 (NIH 2021). One statement in February 2021 by Merck, a manufacturer of ivermectin, describes the conclusions of their review of the evidence as providing "no meaningful evidence for clinical activity or efficacy in patients with COVID-19" (Merck 2021).

AUTHORS' CONCLUSIONS

Implications for practice

Based on the current very low- to low-certainty evidence, we are uncertain about the efficacy and safety of ivermectin used to treat people with COVID-19 in the inpatient and outpatient settings and to prevent a SARS-CoV-2 infection in people after having high-risk exposure. There is also no evidence available from the study pool as to which is the best dose and regimen of ivermectin. Overall, the reliable evidence available does not support the use ivermectin for treatment or prevention of COVID-19 outside of well-designed randomized controlled trials (RCTs). With respect to the number of identified studies in trial registries and with accordance to the living approach of this review, we will continually update our search and include eligible trials.

Implications for research

There remains insufficient evidence regarding the efficacy and safety of ivermectin used for the treatment of people with COVID-19 in the inpatient and outpatient settings and to prevent SARS-CoV-2 infection in people after high-risk exposure. Based on our review, we define the following gaps in the evidence.

- High-quality RCTs: double-blind, placebo-controlled, randomized studies with sufficient power and conducted in accordance to the CONSORT 2010 Statement.
- Reporting of patient-relevant outcomes with clear definition and relevant time points of outcome measurement (see Types of outcome measures).
- Complete and transparent reporting of participants' characteristics and patient status according to World Health Organization Clinical Progression Scale (Marshall 2020).
- Studies including people with severe COVID-19.
- Dose-finding studies.

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Currently, there is an urgent need for good-quality evidence, based on RCTs with appropriate randomization procedures, comparability of study arms, and a preferably double-blind design. We identified 31 ongoing RCTs in trial registries and another 18 studies which are potentially eligible but have either not published their results yet or where we require additional clarifications from the study investigators. The findings from these studies may help to answer more clearly the question of ivermectin and its effects in treating and preventing COVID-19 in the future. In accordance with the living approach of this review, we will continually update our search and include eligible trials.

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Yang 2020

Yang SN, Atkinson SC, Wang C, Lee A, Bogoyevitch MA, Borg NA, et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. *Antiviral Research* 2020;**177**:e104760. [DOI: 10.1016/j.antiviral.2020.104760]

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Popp 2021

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahmed 2020

Study characteristics	
Methods	• Trial design: double-blind RCT with 3 parallel arms, only 2 arms relevant; the third arm investigated ivermectin plus another active treatment (doxycycline) • Type of publication: journal publication • Setting: inpatient • Recruitment dates: NR • Country: Bangladesh • Language: English

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Ahmed 2020 *(Continued)*

	• Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NA • Date of registration: NA
Participants	• Number of participants (randomized/analyzed): 72/68 (relevant arms: 48/45) • Age (mean): overall 42 (SD NR) years • Males, n: overall 33 (46%) • Severity of condition according to study definition: hospitalized, no participants required oxygen • Severity of condition according to WHO scale: 4 • Co-morbidities: NR • Virus detection performed at baseline (test-positive at baseline): RT-PCR (100%) • Inclusion criteria: aged 18–65 years; admitted to hospital within last 7 days; presence of fever (37.5 °C), cough, sore throat, or a combination; diagnosed positive for SARS-CoV-2 by rRT-PCR • Exclusion criteria: allergic to ivermectin or doxycycline, or if here was the potential for a drug–drug interaction with ivermectin or doxycycline; had chronic illnesses (e.g. ischaemic heart disease, heart failure, documented cardiomyopathy, chronic kidney disease, chronic liver disease); had received ivermectin or doxycycline (or both) in the last 7 days; were pregnant or lactating; or had participated in any other clinical trial within last month

Interventions	• Details of intervention for relevant arms
	  * Type and dose: ivermectin 12 mg, once daily for 5 days
	  * Route of administration: oral
	• Treatment details of control group
	  * Placebo
	• Concomitant therapy: NA
	• Duration of follow-up: NR
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  * Time to viral clearance
	  * Remission of fever and cough within 7 days
	• Relevant review outcomes reported
	  * Worsening of clinical status (need for oxygen) at 14 days
	  * Serious adverse events within 14 days
	  * Duration of hospitalization
	  * Viral clearance (RT-PCR) at 3, 7, and 14 days
	• Additional study outcomes reported
	  * Proportion of participants with remission of fever, cough, and sore throat
	  * Time to viral clearance (hazard ratio)
	  * Blood biomarkers were measured on enrolment and on day 7 CRP, ferritin, LDH, and procalcitonin)

Notes	• Date of publication: 2 December 2020 • Sponsor/funding: Beximco Pharmaceutical Limited, Bangladesh • Correspondence with the author team: author request sent (follow-up period for serious adverse events and mortality, details on baseline characteristics); no response received from author • Information on ethics votum: name of responsible ethics committee reported; no reference number of proposal or votum provided in publication. Sent author request; no response received

Chaccour 2021

Study characteristics

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Chaccour 2021 *(Continued)*

Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of publication: journal publication • Setting: outpatient • Recruitment dates: July to September 2020 • Country: Spain • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04390022 • Date of registration: 15 May 2020
Participants	• Number of participants (randomized/analyzed): 24/24 • Age (median): overall 28 years • Males, n: overall 12 (50%) • Severity of condition according to study definition: outpatients with non-severe symptoms • Severity of condition according to WHO scale: 2 to 3 • Co-morbidities: existing co-morbidity was specified as exclusion criterion. • Virus detection performed at baseline (test-positive at baseline): RT-PCR (100%) • Inclusion criteria: consecutive outpatients attending the emergency department of the Clinica Universidad de Navarra (Pamplona, Spain) with symptoms compatible with COVID-19; no more than 72 hours of fever or cough; positive PCR for SARS-CoV-2 • Exclusion criteria: positive IgG against SARS-CoV-2; co-morbidities considered risk factors for severe disease or COVID-19 pneumonia at baseline

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.4 mg/kg, single dose
	  * Route of administration: oral
	• Treatment details of control group
	  * Placebo
	• Concomitant therapy: NA
	• Duration of follow-up: 28 days
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  * Proportion of patients with a positive SARS-CoV-2 PCR
	• Relevant review outcomes reported
	  * Mortality at 28 days
	  * Viral clearance (RT-PCR, E-gene) at 7 days
	  * Adverse events within 28 days
	  * Serious adverse events within 28 days
	• Additional study outcomes reported
	  * Viral load evolution within 21 days
	  * Viral clearance (RT-PCR, N-gene) at 7 days
	  * Patient-days of any symptoms, cough, and ansomia
	  * IgG-titres at 21 days

Notes	• Date of publication: 23 February 2021 • Sponsor/funding: departmental resources • Additional results posted in registry • Information on ethics votum: name of responsible ethics committee, reference number of proposal, and votum provided by author via personal correspondence

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Chachar 2020

Study characteristics	
Methods	• Trial design: open-label RCT with 2 parallel arms • Type of publication: journal publication • Setting: outpatient • Recruitment dates: May to June 2020 • Country: Pakistan • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04739410 • Date of registration: 4 February 2021
Participants	• Number of participants (randomized/analyzed): 50/50 • Age (mean): overall 42 (SD 15.7) years • Men, n: overall 31 (62%) • Severity of condition according to study definition: outpatients with mild symptoms • Severity of condition according to WHO scale: 2 to 3 • Co-morbidities: obesity, diabetes hypertension, respiratory disease • Virus detection performed at baseline (test-positive at baseline): RT-PCR (100%) • Inclusion criteria: people diagnosed with COVID-19 infection with positive RT-PCR test, willing to participate in study; aged 18–75 years; male or female; mild symptoms of COVID-19 and RT- PCR positive for SARS-CoV-2; ability to take oral medication and willing to adhere to drug regimen • Exclusion criteria: known severe allergic reactions to ivermectin; pregnancy or breastfeeding; severe symptoms likely attributed to cytokine release storm; malignant disease; chronic kidney disease; cirrhosis liver with Child class B or C

Interventions	• Details of intervention
	  * Type and dose: ivermectin 12 mg, 3 times over 24 hours
	  * Route of administration: oral
	• Treatment details of control group
	  * No treatment except standard of care
	• Concomitant therapy: standard of care including only symptomatic treatment administered in both study arms
	• Duration of follow-up: 7 days
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  * Symptom resolution at 7 days
	• Relevant review outcomes reported
	  * None (time point not eligible)
	• Additional study outcomes reported
	  * Adverse events at 7 days

Notes	• Date of publication: September 2020 • Sponsor/funding: departmental resources • Correspondence with the author team: author request sent (outcome data including number of participants, events for participants, and follow-up period for adverse events); no response received from the author • Information on ethics votum: name of responsible ethics committee reported; no reference number of proposal or votum provided in publication. Contacted author; no response received

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Gonzalez 2021

Study characteristics	
Methods	• Trial design: double-blind RCT with 3 parallel arms, only 2 arms relevant; the third arm investigated hydroxychloroquine • Type of publication: preprint • Setting: inpatient • Recruitment dates: May to August 2020 • Country: Mexico • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04391127 • Date of registration: 18 May 2020
Participants	• Number of participants (randomized/analyzed): 108/106 (relevant arms: NR/73) • Age (mean): overall 54 (SD 16.9) years • Males, n: overall 66 (62%) • Severity of condition according to study definition: hospitalized, with need for supplemental oxygen, but not high flow oxygen high flow oxygen • Severity of condition according to WHO scale: 5 • Co-morbidities: any pre-existing condition, diabetes, hypertension, respiratory disease • Virus detection performed at baseline (test-positive at baseline): RT-PCR (100%) • Inclusion criteria: positive RT-PCR for SARS-CoV-2 by nasal and oropharyngeal swabbing; pneumonia, diagnosed by X-ray or high-resolution chest CT scan, with a pattern suggesting involvement due to coronavirus; recently established hypoxaemic respiratory failure or acute clinical deterioration of pre-existing lung or heart disease • Exclusion criteria: requirement of high oxygen volumes (face mask > 10 L/minute); predictors of a poor response to high-flow oxygen nasal prong therapy or requirement mechanical ventilation

Interventions	• Details of intervention for relevant arms
	  * Type and dose: ivermectin 12 mg (< 80 kg) or 18 mg (> 80 kg), once daily for 5 days
	  * Route of administration: oral
	• Treatment details of control group
	  * Placebo with standard of care
	• Concomitant therapy: standard of care including dexamethasone, thromboprophylaxis and antibiotics administered in both study arms
	• Duration of follow-up: 28 days
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  * Hospitalization duration until discharge due to clinical improvement
	  * Total duration of hospitalization
	  * Duration of hospitalization until respiratory deterioration or death
	• Relevant review outcomes reported
	  * Mortality at 28 days
	  * Duration of hospitalization, reported as median
	  * Worsening of clinical status – need for invasive mechanical ventilation at 28 days
	  * Improvement of clinical status – patients discharged without respiratory deterioration or death at 28 days
	• Additional study outcomes reported
	  * None

Notes	• Date of publication: 23 February 2021

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Gonzalez 2021 *(Continued)*

- Sponsor/funding: departmental resources
- Correspondence with the author team: author request sent (publication status, proportion of participants with confirmed SARS-CoV-2 infection (RT-PCR) at baseline, patient status at baseline, randomization method, time point of outcome assessment for mortality, need of invasive mechanical ventilation, patients discharged without respiratory deterioration or death); author responded
- Information on ethics votum: name of responsible ethics committee, reference number of proposal, and votum reported

Kirti 2021

Study characteristics	
Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of publication: preprint • Setting: inpatient • Recruitment dates: August to October 2020 • Country: India • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: CTRI/2020/08/027225 • Date of registration: 18 August 2020
Participants	• Number of participants (randomized/analyzed): 115/112 • Age (mean): overall 53 (SD 14.7) years • Males, n: overall 81 (SD 72) • Severity of condition according to study definition: hospitalized, with mild-to-moderate symptoms, and without admission to ICU • Severity of condition according to WHO scale: 4 to 5 • Co-morbidities: diabetes, hypertension, respiratory disease • Virus detection performed at baseline (test-positive at baseline): RT-PCR or rapid antigen test (100%) • Inclusion criteria: RT-PCR positive or rapid antigen test positive; mild-to-moderate COVID-19; aged > 18 years • Exclusion criteria: known allergy to or adverse drug reaction with ivermectin; unwillingness or inability to provide consent to participation; prior use of ivermectin during the course of this illness; pregnancy, lactation

Interventions	• Details of intervention
	  * Type and dose: ivermectin 12 mg, once daily for 2 days
	  * Route of administration: oral
	• Treatment details of control group
	  * Placebo with standard of care
	• Concomitant therapy: standard of care including hydroxychloroquine, chloroquine, steroids, enoxaparin, antibiotics, remdesivir, convalescent plasma, tocilizumab administered to both study arms
	• Duration of follow-up: 28 days
	• Treatment cross-overs: none

Outcomes	• Primary study outcome * RT-PCR negativity at 6 days

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Kirti 2021 *(Continued)*

- Relevant review outcomes reported
  * RT-PCR negativity at 6 days
  * Mortality at 28 days
  * Worsening of clinical status – need for invasive mechanical ventilation at 28 days
  * ICU admission within 28 days
  * Symptom resolution at 28 days
- Additional study outcomes reported
  * Discharged at 10 days

Notes	• Date of publication: 9 January 2021 • Sponsor/funding: Sun Pharma Pvt Ldt and AIIMS, Patna administration • Correspondence with the author team: author request sent (publication status, outcome data including number of participants and events at day 28 for mortality, need of invasive mechanical ventilation, ICU admission); author responded • Information on ethics votum: name of responsible ethics committee reported; reference number of proposal and votum provided by author via personal communication

Kishoria 2020

Study characteristics	
Methods	• Trial design: open-label RCT with 2 parallel arms • Type of publication: journal publication • Setting: inpatient • Recruitment dates: NR • Country: India • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NA • Date of registration: NA
Participants	• Number of participants (randomized/analyzed): 35/32 • Age (mean): overall 38 (SD NR) years • Males, n: overall 23 (72%) • Severity of condition according to study definition: hospitalized, asymptomatic or mild symptoms • Severity of condition according to WHO scale: 4 including people without symptoms • Co-morbidities: NR • Virus detection performed at baseline (test-positive at baseline): RT-PCR (100%) • Inclusion criteria: men or women, aged ≥ 18 years; tested positive after completion of standard care treatment for SARS-CoV-2 confirmed by RT-PCR assay; mild symptoms or asymptomatic; no comorbidities affecting the patient's prognosis, rendering them at high risk; documented acceptance to participate by means of the execution of the informed consent • Exclusion criteria: allergy or hypersensitivity to ivermectin or its inactive ingredients, or both; respiratory distress or requiring intensive care; used immunosuppressants (including systemic corticosteroids) in the last 30 days; known HIV infection with CD4 count < 300 cell/L; pregnancy or lactating women; medical conditions such as mal-absorption syndromes affecting proper ivermectin absorption; autoimmune disease or decompensated chronic diseases, or both; uncontrolled, intercurrent diseases including renal impairment, hepatic impairment, symptomatic congestive heart failure, unstable chest angina, or heart arrhythmia; treated in any other study in the previous 30 days; concomitant administration of enzyme inducers (such as carbamazepine) that could affect the effectiveness of the drug and people receiving CYP3A4 substrates (such as statins) due to the risk of increased toxicity

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Kishoria 2020 *(Continued)*

Interventions	• Details of intervention for relevant arms
	  * Type and dose: ivermectin 12 mg, single dose
	  * Route of administration: oral
	• Treatment details of control group
	  * No treatment except standard of care
	• Concomitant therapy: standard of care including hydroxychloroquine, vitamin C, and paracetamol administered in both study arms
	• Duration of follow-up: 6 days
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  * Negative throat swab report for SARS-CoV-2 conducted by RT-PCR after 48 hours of day 1 of research therapy
	• Relevant review outcomes reported
	  * Viral clearance at 3 days
	• Additional study outcomes reported
	  * Viral clearance at 5 days
	  * Hospitalization status at end of study

Notes	• Date of publication: August 2020 • Sponsor/funding: NR • Correspondence with the author team: author request sent (date of recruitment, reason for withdrawals, baseline characteristics regarding compensated comorbidities, reason for missing patients at 5 days); no response received from the author • Information on ethics votum: no name of responsible ethics committee, reference number of proposal, or votum provided in publication. Sent author request; no response received

Krolewiecki 2020

Study characteristics	
Methods	• Trial design: open-label RCT with 2 parallel arms • Type of publication: preprint • Setting: inpatient • Recruitment dates: May to September 2020 • Country: Argentina • Language: English • Number of centres: 4 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04381884 • Date of registration: 11 May 2020
Participants	• Number of participants (randomized/analyzed): 45/45 • Age (mean): overall 41 (SD 12.48) years • Males, n: overall 25 (56%) • Severity of condition according to study definition: hospitalized, with mild-to-moderate disease • Severity of condition according to WHO scale: 4 to 5 • Co-morbidities: obesity, diabetes, hypertension, respiratory disease • Virus detection performed at baseline (test-positive at baseline): RT-PCR (100%) • Inclusion criteria: men or women; aged 18–69 years; SARS-CoV-2 confirmed by PCR; hospitalized people with symptoms onset 5 days before executing the informed consent; no co-morbidities affecting the patient's prognosis, rendering them at high risk; documented acceptance to participate by means

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Krolewiecki 2020 *(Continued)*

	of the execution of the informed consent; women of childbearing age must have a negative pregnancy test and use adequate contraceptive methods during participation in the study and for 1 month after the last medication dose in the case of those receiving ivermectin • Exclusion criteria: allergy or hypersensitivity to ivermectin or its inactive ingredients, or both; people meeting COVID-19 severity criteria, with respiratory distress or requiring intensive care; using medications having potential activity against SARS-CoV-2 such as hydroxychloroquine, chloroquine, lopinavir, ritonavir, remdesivir, or azithromycin in the last 3 months; use of immunodepressants (including systemic corticosteroids) in the last 30 days; known HIV infection with CD4 count < 300 cell/µL; pregnancy or lactating; other infectious diseases or medical conditions such as malabsorption syndromes affecting proper ivermectin absorption; acute allergy conditions or with severe allergic reactions background; autoimmune disease or decompensated chronic diseases, or both; uncontrolled, intercurrent diseases including renal impairment, hepatic impairment, symptomatic congestive heart failure, unstable chest angina, heart arrhythmia or psychiatric conditions that may limit adherence to CT requirements
Interventions	• Details of intervention * Type and dose: ivermectin 0.6 mg/kg (rounding to the lower full (6 mg) or half (3 mg) dose), once daily for 5 days * Route of administration: oral • Treatment details of control group * No treatment except standard of care • Concomitant therapy: standard of care (no details provided) administered in both study arms • Duration of follow-up: 30 days • Treatment cross-overs: none
Outcomes	• Primary study outcome * Reduction in SARS-CoV-2 viral load at 5 days • Relevant review outcomes reported * Adverse events within 30 days * Serious adverse events within 30 days • Additional study outcomes reported * Need for invasive mechanical ventilation at 7 days * Relationship between ivermectin plasma concentrations and the primary outcome * Clinical evolution at 7 days
Notes	• Date of publication: 11 November 2020 • Sponsor/funding: Laboratorio Elea Phoenix S.A. (provided intervention drug) • Correspondence with the author team: author request sent (publication status); author responded • Information on ethics votum: name of responsible ethics committee, reference number of proposal, and votum provided by author via personal correspondence

López-Medina 2021

Study characteristics	
Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of publication: journal publication • Setting: outpatient (< 1% inpatients at baseline) • Recruitment dates: July to December 2020 • Country: Columbia • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04405843

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López-Medina 2021 *(Continued)*

	• Date of registration: 28 May 2020
Participants	• Number of participants (randomized/analyzed): 476/398 • Age (median): overall 37 years • Males, n: overall 167 (42%) • Severity of condition according to study definition: mild disease, defined as being at home or hospitalized but not receiving high-flow nasal oxygen or mechanical ventilation • Severity of condition according to WHO scale: 2 to 3 (< 1% of included patients 4 to 5) • Co-morbidities: any pre-existing condition, obesity, diabetes, hypertension, respiratory disease • Virus detection performed at baseline (test-positive at baseline): RT-PCR or rapid antigen test (100%) • Inclusion criteria: aged ≥ 18 years; confirmed SARS-CoV-2 by RT-PCR or antigen detection in a Colombian NIH-approved laboratory; beginning of symptoms in the past 7 days; mild disease; informed consent • Exclusion criteria: pre-existing liver disease; hypersensitivity to ivermectin; participants in other clinical trials for therapies against COVID-19; severe pneumonia; pregnant or breastfeeding women; concomitant use of warfarin, erdafitinib, or quinidine; use of ivermectin in the 5 days prior to randomization; inability to obtain a blood sample needed to assess liver transaminases; elevation of transaminases > 1.5 times the normal level; participant whose first contact with the study personnel occurs between days 5 and 7 and at that time manifests significant and progressive resolution of COVID-19 related signs and symptoms

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.3 mg/kg, once daily for 5 days
	  * Route of administration: oral
	• Treatment details of control group
	  * Placebo with standard of care
	  * Up to 26 August 2020, the placebo was a mixture of 5% dextrose in saline and 5% dextrose in distilled water, after which placebo was a solution with similar organoleptic properties to ivermectin
	• Concomitant therapy: standard of care including NSAIDs, antipyretic drugs, antibiotics, steroids, anticoagulants administered in both study arms
	• Duration of follow-up: 21 days
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  * Time to resolution of symptoms (hazard ratio)
	  * Symptom resolution at 21 days
	• Relevant review outcomes reported
	  * Mortality at 21 days
	  * Worsening of clinical status – need for invasive mechanical ventilation at 15 days
	  * Worsening of clinical status – need for non-invasive mechanical ventilation or high flow at 15 days
	  * Symptom resolution at 15 days
	  * Duration to symptom resolution, reported as median
	  * Adverse events within 21 days
	  * Serious adverse events within 21 days

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López-Medina 2021 *(Continued)*

- Additional study outcomes reported
  * Deterioration of ≥ 2 points in an ordinal 8-point scale
  * Overall number of participants hospitalized with or without supplemental oxygen (could not be judged as either worsening or improvement due to overlap with status at baseline)
  * Fever since randomization
  * Median duration of febrile episode
  * Emergency department visits or telemedicine consultations, number of participants
  * Escalation of care since randomization and escalation of care occurring ≥ 12 hours since randomization including
    - ☐ mortality at 15 days
    - ☐ worsening of clinical status – need for invasive mechanical ventilation at 21 days
    - ☐ worsening of clinical status – need for non-invasive mechanical ventilation or high flow at 21 days

Notes	• Date of publication: 4 March 2021 • Sponsor/funding: Centro de Estudios en Infectología Pediátrica • Information on ethics votum: name of responsible ethics committee, reference number of proposal, and votum reported

Mohan 2021

Study characteristics	
Methods	• Trial design: double-blind RCT with 3 parallel arms, the 2 intervention arms were pooled for this review • Type of publication: preprint • Setting: inpatient • Recruitment dates: July to September 2020 • Country: India • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: CTRI/2020/06/026001 • Date of registration: 21 June 2020
Participants	• Number of participants (randomized/analyzed): 157/152 (test-positive population 157/125) • Age (mean): overall 35 (10.4%) • Males, n: overall 111 (89%) • Severity of condition according to study definition: hospitalized, non-severe symptoms • Severity of condition according to WHO scale: 4 to 5 including people who were asymptomatic • Co-morbidities: diabetes, hypertension • Virus detection performed at baseline (test-positive at baseline): RT-PCR (relevant population 100% test-positive) • Inclusion criteria: aged ≥ 18 years; diagnosed with non-severe COVID-19, i.e. SpO_2 > 90% in room air and with no hypotension or requirement of mechanical ventilation; diagnosis of COVID-19 was based on a positive result on either SARS-CoV-2 RT-PCR or rapid antigen test • Exclusion criteria: no informed consent; pregnancy or lactation; known hypersensitivity to ivermectin, chronic kidney disease with creatinine clearance < 30 mL/minutes; elevated transaminase levels (> 5 × upper limit of normal); myocardial infarction or heart failure within 90 days prior to enrolment; prolonged corrected QT interval (> 450 mseconds) on ECG; any other severe comorbidity as per investigator's assessment; enrolment in a concomitant clinical trial

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Mohan 2021 *(Continued)*

Interventions	• Details of intervention
	  * Type and dose: ivermectin 12 mg and 24 mg (pooled), single dose
	  * Route of administration: oral
	• Treatment details of control group
	  * Placebo with standard of care
	• Concomitant therapy: standard of care including hydroxychloroquine, favipiravir, remdesivir, dexamethasone, dalteparin, azithromycin, amoxycillin/clavulanate, doxycycline, or ceftriaxone administered in both study arms
	• Duration of follow-up: 14 days or until hospital discharge
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  * Reduction of viral load and conversion to negativity of nasopharyngeal/oropharyngeal RT-PCR at 3, 5, and 7 days
	• Relevant review outcomes reported
	  * Viral clearance (RT-PCR) at 3 and 7 days
	  * Adverse events within 14 days
	  * Serious adverse events within 14 days
	• Additional study outcomes reported
	  * Mortality at 14 days
	  * Need for invasive mechanical ventilation at 14 days
	  * Change in WHO Ordinal Scale score between day 0 to 14
	  * Any clinical worsening during treatment
	  * Duration of symptom resolution
	  * Discharge at 14 days
	  * Hospital-free days at day 28

Notes	• Date of publication: 2 February 2021 • Sponsor/funding: Department of Science and Technology, Government of India and WindLas BioTech Ltd Haryana • Correspondence with the author team: author request sent (publication status, clarification of healthcare setting, proportion of only symptomatic participants reaching symptom resolution in modified intention-to-treat); author responded only to publication status. • Information on ethics votum: name of responsible ethics committee, reference number of proposal, and votum reported

Okumuş 2021

Study characteristics	
Methods	• Trial design: open-label RCT with 2 parallel arms • Type of publication: journal publication • Setting: inpatient • Recruitment dates: May to September 2020 • Country: Turkey • Language: English • Number of centres: 4 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04646109 • Date of registration: 27 November 2020
Participants	• Number of participants (randomized/analyzed): 66/60

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Okumuş 2021 *(Continued)*

- Age (mean): overall 62 (SD NR) years
- Males, n: overall 40 (67%)
- Severity of condition according to study definition: hospitalised with severe pneumonia
- Severity of condition according to WHO scale: 4–9
- Co-morbidities: diabetes hypertension, respiratory disease, immunosuppression
- Virus detection performed at baseline (test-positive at baseline): RT-PCR (100%)
- Inclusion criteria: hospitalized and a prediagnosis of 'severe COVID-19 pneumonia' and thereafter diagnosis of COVID-19 was also confirmed microbiologically with PCR positivity in respiratory tract samples; ≥ 1 of the following criteria were accepted as severe COVID-19 pneumonia: presence of tachypnoea ≥ 30 breaths/minute; SpO_2 level < 90% in room air; PaO_2/FiO_2 < 300 in oxygen-receiving participant; presence of specific radiological finding for COVID-19 in lung tomography; mechanical ventilation requirement; acute organ dysfunction findings; people with sepsis-related organ failure assessment score > 2
- Exclusion criteria: aged < 18 years; chronic liver or kidney disease; pregnancy; known ivermectin allergy; for modified intention-to-treat analysis mutation, carriers were excluded after randomization

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.2 mg/kg, once daily for 5 days
	  * Route of administration: oral
	• Treatment details of control group
	  * No treatment except standard of care
	• Concomitant therapy: standard of care including hydroxychloroquine, favipiravir, or azithromycin administered in both study arms
	• Duration of follow-up: "average of 3 months"
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  * Clinical responses and drug adverse effects at 5 days
	• Relevant review outcomes reported
	  * Mortality, time point unclear
	  * Viral clearance at 10 days
	• Additional study outcomes reported
	  * Adverse events within 5 days
	  * Clinical responses and drug adverse effects at 10 days
	  * Changes in SpO_2 and PaO_2/FiO_2 between enrolment and end of treatment period
	  * Blood biomarkers measured on enrolment and end of treatment period (blood lymphocyte count, CRP, ferritin, D-dimers, changes in polymorphonuclear leukocyte/lymphocyte ratio)
	  * Genetic examination results relation to adverse effects

Notes	• Date of publication: 4 May 2021 • Sponsor/funding: Afyonkarahisar Health Science University – Scientific Research Project Coordination Unit and NeuTec Pharma • Correspondence with the author team: author request sent (outcome data including clarification of follow-up period for mortality); no response received from the author • Information on ethics votum: name of responsible ethics committee, reference number of proposal, and votum reported

Podder 2020

Study characteristics	
Methods	• Trial design: open-label RCT with 2 parallel arms • Type of publication: journal publication

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Podder 2020 *(Continued)*

	• Setting: outpatient • Recruitment dates: May to July 2020 • Country: Bangladesh • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NA • Date of registration: NA
Participants	• Number of participants (randomized/analyzed): 82/62 • Age (mean): overall 39 (SD 12.07) years • Males, n: overall 44 (71%) • Severity of condition according to study definition: outpatients with mild-to-moderate disease • Severity of condition according to WHO scale: 2 to 3 • Co-morbidities: NR • Virus detection performed at baseline (test-positive at baseline): RT-PCR (100%) • Inclusion criteria: RT-PCR positive; mild-to-moderate COVID-19; aged > 18 years; either sex • Exclusion criteria: known pre-existing hypersensitivity to ivermectin; pregnant and lactating mothers; receiving other antimicrobials or hydroxychloroquine

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.2 mg/kg, single dose
	  * Route of administration: oral
	• Treatment details of control group
	  * No treatment except standard of care
	• Concomitant therapy: standard of care including antipyretics, cough suppressants, and capsule doxycycline (100 mg every 12 hours for 7 days) administered in both study arms
	• Duration of follow-up: until symptom resolution
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  * Not defined
	• Relevant review outcomes reported
	  * Duration to symptom resolution (from enrolment)
	  * Viral clearance at 10 days
	• Additional study outcomes reported
	  * Duration of individual symptoms (fever, cough, shortness of breath, myalgia, fatigue)
	  * Duration to symptom resolution (from illness onset)

Notes	• Date of publication: July 2020 • Sponsor/funding: 'self financed' • Information on ethics votum: no name of responsible ethics committee, reference number of proposal, or votum provided in publication. Sent author request; no response received

Pott-Junior 2021

Study characteristics	
Methods	• Trial design: open-label RCT with 4 parallel arms, the 3 intervention arms were pooled for this review • Type of publication: journal publication • Setting: inpatient • Recruitment dates: July to December 2020

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Pott-Junior 2021 *(Continued)*

	• Country: Brazil • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04431466 • Date of registration: 16 June 2020
Participants	• Number of participants (randomized/analyzed): 32/31 • Age (mean): overall 49 (SD 14.6) years • Males, n: overall 17 (45%) • Severity of condition according to study definition: hospitalized, mild clinical symptoms • Severity of condition according to WHO scale: unclear; available information: minimum category 4, 20% in category 5 • Co-morbidities: NR • Virus detection performed at baseline (test-positive at baseline): RT-PCR (100%) • Inclusion criteria: diagnosis of infection by SARS-CoV-2 by symptoms of acute respiratory tract infection (sudden onset of ≥ 1 of the following: cough, fever, shortness of breath) and biomolecular diagnosis of SARS-CoV-2 infection or any acute respiratory disease AND biomolecular diagnosis of SARS-CoV-2 infection or severe acute respiratory infection (fever and ≥ 1 sign/symptom of respiratory disease, e.g. cough, fever, shortness of breath); need of hospitalization; biomolecular diagnosis of SARS-CoV-2 infection; Eastern Cooperative Oncology Group Performance Status score 0 to 1; National Early Warning Score 0–4; ability to understand and consent to participate in this clinical trial, manifested by signing the informed consent form. • Exclusion criteria: inability to ingest study drug orally through spontaneous ingestion or use of enteral tubes; risk to participant in the trial judged by physician, based on patient history, clinical observation, laboratory test findings, ECG examination; known hypersensitivity to the components of the drugs used during the study; women in pregnancy or breastfeeding; bodyweight < 15 kg; estimated glomerular filtration rate < 30 mL/minute; AST or ALT > 5 times the upper limit of normality; refusal to participate or to sign the informed consent form

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.1 mg/kg, 0.2 mg/kg, and 0.4 mg/kg cumulative over 72 hours, unclear frequency scheme (pooled)
	  * Route of administration: oral
	• Treatment details of control group
	  * No treatment except standard of care
	• Concomitant therapy: standard of care including thromboprophylaxis, steroids, antibiotics administered in both study arms, but unbalanced between groups
	• Duration of follow-up: 28 days
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  * Time to RT-PCR negativity
	• Relevant review outcomes reported
	  * Viral clearance (RT-PCR) at 7 days
	  * Adverse events within 28 days
	  * ICU admission within 28 days
	• Additional study outcomes reported
	  * Viral load variation clearance in nasopharyngeal swab at 7 days
	  * Time to undetectable viral load in nasopharyngeal swab at 7 days
	  * Change in cycle threshold values (RT-PCR) within 7 days

Notes	• Date of publication: 9 March 2021 • Sponsor/funding: Federal University of Sao Carlos, Brazil

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Pott-Junior 2021 *(Continued)*

- Correspondence with the author team: author request sent (details of intervention, especially deviations between protocol and publication); no response received from the author
- Information on ethics votum: name of responsible ethics committee, reference number of proposal, and votum reported

Shah Bukhari 2021

Study characteristics	
Methods	• Trial design: open-label RCT with 2 parallel arms • Type of publication: preprint • Setting: inpatient • Recruitment dates: March to June 2020 • Country: Pakistan • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04392713 • Date of registration: 19 May 2020
Participants	• Number of participants (randomized/analyzed): 100/86 • Age (mean): overall 41 (SD NR) years • Males, n: overall 73 (85%) • Severity of condition according to study definition: hospitalized, mild-to-moderate symptoms • Severity of condition according to WHO scale: 4 to 5 • Co-morbidities: diabetes, hypertension • Virus detection performed at baseline (test-positive at baseline): RT-PCR (100%) (relevant population 100% test-positive) • Inclusion criteria: provision of signed and dated informed consent form; stated willingness to comply with all study procedures and admission for the duration of the study; male or female; aged 15–65 years; in good general health with no or mild-to-moderate symptoms of COVID-19; PCR positive for SARS-CoV-2; ability to take oral medication • Exclusion criteria: SARS-CoV-2 infection with severe symptoms, likely due to cytokine release syndrome; uncontrolled co-morbidities, and immunocompromised states; history of ivermectin allergy; receiving CYP 3A4-inhibitors or -inducers

Interventions	• Details of intervention
	  * Type and dose: ivermectin 12 mg, single dose
	  * Route of administration: oral
	• Treatment details of control group
	  * No treatment except standard of care
	• Concomitant therapy: standard of care including vitamin C, vitamin D_3, paracetamol administered in both study arms; unclear whether standard of care included chloroquine as stated in the protocol
	• Duration of follow-up: 28 days
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  * Days to achieve RT-PCR negativity
	• Relevant review outcomes reported
	  * Viral clearance (RT-PCR) at 3, 7, and 14 days
	  * Adverse events within 28 days

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Shah Bukhari 2021 *(Continued)*

	• Additional study outcomes reported * None
Notes	• Date of publication: 5 February 2021 • Sponsor/funding: departmental resources • Correspondence with the author team: author request sent (publication status, outcome data including number of participants and events for participants with negative RT-PCR at 7 and 14 days); no response received from the author • Information on ethics votum: name of responsible ethics committee, reference number of proposal, and votum reported

Shoumann 2021

Study characteristics	
Methods	• Trial design: open-label RCT with 2 parallel arms • Type of publication: journal publication • Setting: household contacts to COVID-19 cases (after high-risk exposure) • Recruitment dates: June to July 2020 • Country: Egypt • Language: English • Number of centres: NR, multicentred • Study purpose (treatment, prevention): prevention • Trial registration number: NCT04422561 • Date of registration: 9 June 2020
Participants	• Number of participants (randomized/analyzed): 340/304 • Age (mean): overall 40 (SD 14.94) years • Males, n: overall 156 (51%) • Severity of condition according to study definition: asymptomatic household close contacts to confirmed COVID-19 index case • Severity of condition according to WHO scale: 0, postexposure risk • Co-morbidities: diabetes, hypertension, respiratory disease • Virus detection performed at baseline (test-positive at baseline): NR; no participant reported ever having experienced symptoms suggestive of COVID-19 before enrolment • Inclusion criteria: asymptomatic household close contacts to confirmed RT-PCR COVID-19 index case; aged ≥ 16 years; signed informed consent • Exclusion criteria: any contact developed symptoms or diagnosed as COVID-19 before enrolment; index case; failure to follow-up contacts for 14 days; failure to document the index case when there was > 1 case in a family

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.2–0.3 mg/kg, once daily on day 1 and 3
	  * Route of administration: oral
	• Treatment details of control group
	  * No intervention
	• Concomitant therapy: NA
	• Duration of follow-up: 14 days
	• Treatment cross-overs: none

Outcomes	• Primary study outcome * Development of COVID-19 typical symptoms at 14 days

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Shoumann 2021 *(Continued)*

- Relevant review outcomes reported
  * Development of clinical COVID-19 symptoms at 14 days
  * Adverse events within 14 days
  * Mortality at 14 days
- Additional study outcomes reported
  * Time until development of symptoms
  * Correlation between contact time in days and number of contacts that developed symptoms
  * Severity of symptoms

Notes

- Date of publication: February 2021
- Sponsor/funding: Zagazig University
- Correspondence with the author team: author request sent (participants status at baseline regarding COVID-19 infection); author responded
- Information on ethics votum: name of responsible ethics committee, reference number of proposal, and votum reported

ALT: alanine transaminase; AST: aspartate aminotransferase; CRP: C-reactive protein; CT: computer tomography; ECG: electrocardiograph; ICU: intensive care unit; IgG: immunoglobulin G; LDH: lactose dehydrogenase; PaO_2/FiO_2: partial pressure of oxygen/fraction of inspired oxygen; PCR: polymerase chain reaction; n: number; NA: not available; NIH: National Institutes of Health; NR: not reported; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial; RT-PCR: reverse transcription polymerase chain reaction; rRT-PCR: real-time reverse transcription polymerase chain reaction; SD: standard deviation; SpO_2: oxygen saturation; WHO World Health Organization.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Babalola 2021	**Active comparator:** ivermectin compared to a control (lopinavir/ritonavir) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect.
Behera 2020	**Wrong study design:** case-control study.
Cadegiani 2020	**Wrong study design:** historical control group, i.e. no RCT.
Camprubi 2020	**Wrong study design:** retrospective study.
Carvallo 2020	**Wrong study design:** prospective cohort study; additionally ivermectin was administered in combination with other active drugs with unknown influence on COVID-19.
Chahla 2021a	**Combined intervention:** ivermectin administered in combination with another active substance (iota-carrageenan) with unknown influence on prevention of COVID-1,9 which we did not consider eligible to determine ivermectin's true effect.
Chahla 2021b	**Wrong study design:** cluster-randomised trial.
Chowdhury 2021	**Combined intervention:** ivermectin administered in combination with another active drug (doxycycline) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect. Additionally, the study used an active comparator with unproven efficacy (hydroxychloroquine + azithromycin).
CTRI/2020/08/027282	**Active comparator:** ivermectin compared to a control (vitamin supplements) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect.
CTRI/2020/08/027394	**Active comparator:** ivermectin compared to a control (chloroquine/azithromycin/vitamin supplements) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect.

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Study	Reason for exclusion
CTRI/2020/10/028335	**Active comparator:** ivermectin was compared to a control (tinefcon) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect. Additionally, ivermectin was administered in combination with another active drug (hydroxychloroquine) with unknown influence on COVID-19.
Elgazzar 2020	**Active comparator (treatment arm):** ivermectin was compared to a control (hydroxychloroquine) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect. **Wrong population (prevention arm):** participants investigated formed a distinguishable group with both pre-exposure and postexposure risk. No examination on possible infection that had already taken place at randomization. **Study retracted due to ethical concerns on 14 July 2021.**
Galan 2021	**Active comparator:** ivermectin compared to control arms (hydroxychloroquine/chloroquine) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect.
Gorial 2020	**Wrong study design:** historical control group, i.e. no RCT.
Hashim 2020	**Combined intervention:** ivermectin administered in combination with another active drug (doxycycline) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect.
IRCT20180922041089N4	**Wrong population:** study plans to also include participants with diagnosis of COVID-19 based on suspect CT scan without PCR or antigen test confirmation.
IRCT20200408046987N2	**Combined intervention:** ivermectin administered in combination with another active drug (sofosbuvir/daclatasvir) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect.
Lima-Morales 2021	**Wrong study design:** prospective cohort study; additionally ivermectin was administered in combination with other active drugs (azithromycin, montelukast, aspirin) with unknown influence on COVID-19.
Mahmud 2021	**Combined intervention:** ivermectin administered in combination with another active drug (doxycycline) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect.
Morgenstern 2020	**Wrong study design:** retrospective study.
NCT04345419	**Wrong intervention:** registry entry changed investigated intervention from ivermectin to remdesivir.
NCT04360356	**Combined intervention:** ivermectin administered in combination with another active drug (nitazoxanide) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect.
NCT04374279	**Wrong intervention:** registry entry changed investigated intervention from ivermectin to only bicalutamide.
NCT04382846	**Wrong intervention:** registry entry changed investigated intervention from ivermectin to only nitazoxanide.

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Study	Reason for exclusion
NCT04392427	**Combined intervention:** ivermectin administered in combination with another active drug (nitazoxanide/ribavirin) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect.
NCT04435587	**Active comparator:** ivermectin was compared to a control (darunavir/ritonavir/hydroxychloroquine) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect.
NCT04447235	**Combined intervention:** ivermectin administered in combination with another active drug (losartan) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect.
NCT04482686	**Combined intervention:** ivermectin administered in combination with another active drug (doxycycline) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect.
NCT04530474	**Wrong population:** study plans to include participants with diagnosis of COVID-19 only based on suspect symptoms without PCR or antigen test confirmation.
NCT04551755	**Combined intervention:** ivermectin administered in combination with another active drug (doxycycline) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect.
NCT04703608	**Wrong population:** study plans to also include participants with diagnosis of COVID-19 based on suspect clinical or radiological symptoms without PCR or antigen test confirmation.
NCT04723459	**Wrong intervention:** study plans to investigate ivermectin in impregnated masks, not its systemic effect in the human body.
NCT04768179	**Combined intervention:** ivermectin administered in combination with another active drug (aspirin) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect.
Niaee 2020	**Wrong population:** study included around 30% of SARS-CoV-2-negative participants, which we did not consider appropriate to include into evidence regarding treatment of COVID-19.
Rajter 2021	**Wrong study design:** retrospective study.
Seet 2021	**Active comparator:** ivermectin compared to control arms (hydroxychloroquine/povidone-iodine/vitamin supplements) with unknown influence on prevention of COVID-19, which we did not consider eligible to determine ivermectin's true effect.
Shahbaznejad 2021	**Wrong population:** study included 76.8% participants with unknown or negative SARS-CoV-2 status, which we did not consider appropriate to include into evidence regarding treatment of COVID-19.
Spoorthi 2020	**Combined intervention:** ivermectin administered in combination with another active drug (doxycycline) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect.

CT: computer tomography; PCR: polymerase chain reaction; RCT: randomized controlled trial.

Characteristics of studies awaiting classification *[ordered by study ID]*

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2020-001971-33/ES

Methods	• Trial design: double-blind RCT with 3 parallel arms • Type of record: trial register entry • Sample size: 45 • Setting: outpatient • Country: Spain • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: 2020-001971-33/ES • Date of registration: 22 July 2020
Participants	• Inclusion criteria * People aged > 50 years with comorbidities, diagnosed with SARS-CoV-2 infection by PCR or another diagnostic test performed in the emergency department, who are in the first week of clinic, without pneumonia and without admission criteria * People aged 18–70 years inclusive with pneumonia associated to SARS-Co2 infection: cough or expectoration or fever > 38 °C with or without radiological infiltrate in Rxtórax; with SARS-CoV-2 PCR or radiological, clinical and analytical findings of COVID-19 * Evolution time of initial symptoms between 3 and 8 days * Basal oxygen saturation ≥ 93% by breathing ambient air * Have signed the informed consent • Exclusion criteria * People with pneumonia due to SARS-CoV-2 that requires hospital admission, due to multilobar involvement, respiratory failure PO_2 < 93% ambient air or < 92% for people with COPD; with analytical criteria of severity (D-dimer > 600, CRP > 50, lymphopenia < 900, ferritin > 700 mg/dL, interleukin-6 or organ failure of the organ or who have significant comorbidities: renal insufficiency > 3B; immunosuppression, cancer; chronic cirrhosis or liver disease, diabetes mellitus, atherosclerosis of any territory, heart rhythm disturbances (including prolonged QT), poorly controlled hypertension) * People with QT range > 500 mseconds * People aged < 18 years * Child-Pugh C liver failure * Impossibility of giving treatment for non-suppressible drugs with the risk of QT prolongation or interactions (antidepressants, antihistamines, quinolones, statins except pitavastatin) or allergy to the drug * Taking any of the drugs in the trial within 7 days prior to inclusion in the study * Pregnancy, lactation
Interventions	• Details of intervention * Type and dose: ivermectin 0.2–0.4 mg/kg, no details on frequency scheme * Route of administration: oral • Treatment details of control group * Placebo, azithromycin, hydroxychloroquine are named in the protocol as comparatory, but unclear design of study arms • Concomitant therapy: unclear
Outcomes	• Primary study outcome * Efficacy will be measured by comparing clinical cure, microbiology, need for hospital admission due to clinical or analytical, blood gas, radiological deterioration, or a combination of these for each arm. • Relevant review outcomes planned * To assess the clinical cure rate after 2 weeks of treatment * To evaluate the microbiological cure rate 72 hours after treatment * To analyze adverse events to treatment

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2020-001971-33/ES *(Continued)*

	• Additional study outcomes * To analyze the improvement in clinical parameters (symptoms and physical examination) * To assess the failure rate and admission requirements for disease progression * To analyze the factors of weak or poor response to ivermectin
Notes	• Reason for awaiting classification: unclear control arms • Recruitment status: NR • Prospective completion date: NR • Date last update posted: NR • Sponsor/funding: Carmen Hidalgo

2020-002091-12/BG

Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 120 • Setting: inpatient • Country: Bulgaria • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: 2020-002091-12/BG • Date of registration: 5 May 2020
Participants	• Inclusion criteria * Men or women aged ≥ 18 years * Signed informed consent * Admitted to hospital for treatment of COVID-19 * Hospitalization must be for medical and not for social reasons * Patient within 7 days from symptom onset and within 72 hours after laboratory diagnosis (SARS-CoV-2 RT-PCR) * Mild-to-moderate COVID-19 disease defined as clinical status category 3 or 4 on the WHO 9-point ordinal scale ☐ Hospitalized, no oxygen treatment ☐ Oxygen by mask or nasal prongs * Presence of ≥ 1 symptom characteristic for COVID-19 disease, e.g. fever, cough, sore throat, myalgia, fatigue, gastrointestinal; disorders, skin lesions, etc. * In women of childbearing potential, negative pregnancy test and commitment to use contraceptive method throughout study

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2020-002091-12/BG *(Continued)*

- Exclusion criteria
  * Critical patients with expected survival time < 72 hours
  * Presence of respiratory failure, shock, combined failure of other organs that requires ICU monitoring, or a combination
  * Participation in the trial is not in the person's best interest based on the judgement of the investigator
  * Presence of the following laboratory values at screening
    - ☐ White blood cell count < 1.5×10^9/L
    - ☐ Platelet count < 100,000 mm^3 (< 1.00×10^9/L)
    - ☐ Total bilirubin > 2 × ULN
    - ☐ ALT or GGT > 3 × ULN
  * Clinical suspicion for a bacterial superinfection at screening
  * Allergic or hypersensitive to the investigational medicinal product or any of the ingredients
  * Patients who cannot take drugs orally, or have severe gastro-intestinal disorders, extensive bowel resection or bowel obstruction
  * Previous (in the past 3 months) or concurrent use of any other investigational product
  * Use of the prohibited medications during the treatment with investigational product, as defined in the protocol
  * People with end-stage liver disease (Child-Pugh C score)
  * History or presence of serious or acute heart disease such as uncontrolled cardiac dysrhythmia or arrhythmia, uncontrolled angina pectoris, cardiomyopathy, or uncontrolled congestive heart failure (New York Heart Association class III or IV)
  * Presence of acute stroke at screening or a history of acute stroke within the last 6 months
  * Pregnant or breastfeeding
  * Legal incapacity, limited legal capacity, or any other condition that makes the patient unable to provide consent for the trial
  * Patients who are institutionalized due to judicial order
  * Employee or immediate relative of the investigator or sponsor
  * Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including asthma and COPD), renal, hepatic, endocrine (including uncontrolled diabetes mellitus) or gastrointestinal disorder, that according to investigator could jeopardize the safety of the patient, or the integrity of the study

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.4 mg/kg, single dose
	  * Route of administration: oral
	• Treatment details of control group
	  * Placebo with standard of care
	• Concomitant therapy: standard of care (no details provided) administered in both study arms

Outcomes	• Primary study outcome
	  * Rate of participant's conversion to negative SARS-CoV-2 (qualitative) test on 7 days
	• Relevant review outcomes planned
	  * Time to hospital discharge
	  * Number of participants who have needed high flow oxygen therapy
	  * Number of participants who have needed ICU treatment
	  * Time to achieving clinical improvement within 28 days
	  * Rate of participant's conversion to negative SARS-CoV-2 (qualitative) test at 4, 7, and 14 days
	• Additional study outcomes
	  * Number of participants achieving clinical recovery on day 7
	  * Number of participants achieving clinical recovery on day 14
	  * Time to conversion to a negative SARS-CoV-2 test within 28 days
	  * Rate of participant's conversion to negative SARS-CoV-2 (qualitative) test at 9 and 12 days
	  * Inflammatory and full blood count markers

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2020-002091-12/BG *(Continued)*

Notes	• Reason for awaiting classification: study completed, no results published yet • Recruitment status: completed • Prospective completion date: 8 October 2020 • Date last update posted: NR • Sponsor/funding: HUVEPHARMA EOOD, Bulgaria • Study report on the drug company's website is not an eligible publication format for this review

CTRI/2020/04/024948

Methods	• Trial design: open-label RCT with 4 parallel arms, only 2 arms relevant; the third arm investigates hydroxychloroquine, the fourth arm investigates ciclesonid • Type of record: trial register entry • Sample size: 120 • Setting: inpatient • Country: India • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: CTRI/2020/04/024948 • Date of registration: 30 April 2020

Participants	• Inclusion criteria
	  * Adults aged ≥ 18 years with COVID-19. A positive throat swab (by RT-PCR) obtained from a person suspected to have COVID-19 or from a contact (or healthcare worker) of people with COVID-19 will be considered to be a COVID-19 case.
	  * Presence of moderate COVID-19 disease as defined by presence of pneumonia (clinical and radiological signs) with respiratory rate 15–30 per minute or SpO_2 90–94% on room air.
	• Exclusion criteria
	  * People with renal or hepatic dysfunction (serum creatinine > 1.5 mg/dL and serum transaminase levels > 120 U/L)
	  * People with clinical heart failure/known coronary artery disease
	  * Known cases of neoplasms or immunodeficiency syndromes
	  * People receiving chemotherapy, immunosuppressive agents, steroids, or antiviral agents, or have received in the preceding 4 weeks
	  * Pregnant and lactating women
	  * Uncooperative patients (in the opinion of the investigator, if it is difficult to ensure patient cooperation during the study)

Interventions	• Details of intervention for relevant arms
	  * Type and dose: ivermectin 12 mg, once daily for 7 days
	  * Route of administration: oral
	• Treatment details of control group
	  * Standard of care, no details provided
	• Concomitant therapy: NR

Outcomes	• Primary study outcome
	  * Proportion of participants having virological cure at 6 days
	• Relevant review outcomes planned
	  * Adverse effects noted within 14 days
	  * Proportion of participants having virological cure at 6 days

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CTRI/2020/04/024948 *(Continued)*

	• Additional study outcomes
	  * Individual proportion of prespecified rescue criteria
	  * Proportion of participants having resolution of symptoms/signs at 7 and 14 days

Notes	• Reason for awaiting classification: unclear if standard of care administered in ivermectin group • Recruitment status: not yet recruiting • Prospective completion date: NR • Date last update posted: 30 April 2020 • Sponsor/funding: Lady Hardinge Medical College

CTRI/2020/06/025960

Methods	• Trial design: open-label RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 100 • Setting: inpatient • Country: India • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NextCTRI/2020/06/025960 • Date of registration: 18 June 2020

Participants	• Inclusion criteria
	  * Symptomatic people infected with SARS-CoV-2 virus diagnosed on RT-PCR test, admitted to hospital
	  * Age 18–70 years
	• Exclusion criteria
	  * Age < 18 and > 70 years
	  * Pregnant and lactating women
	  * Unwilling to give written informed consent
	  * Seriously ill people requiring intensive care
	  * Known hypersensitivity to ivermectin
	  * People who have participated in another investigational drug or research study within 30 days of screening
	  * People who are using any medication or has any disease which in the judgment of the Investigator will interfere with the conduct or interpretation of the study

Interventions	• Details of intervention
	  * Type and dose: ivermectin 12 mg, once daily for 3 days
	  * Route of administration: oral
	• Treatment details of control group
	  * Standard of care, no details provided
	• Concomitant therapy: NR

Outcomes	• Primary study outcome
	  * Eradication of virus by testing for SARS-CoV-2 by RT-PCR test at 7 days
	• Relevant review outcomes planned
	  * Viral clearance at 7 days
	  * Duration of hospitalization
	  * Safety of ivermectin within 15 days

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CTRI/2020/06/025960 *(Continued)*

	• Additional study outcomes
	  * Reduction in inflammatory markers at days 1, 5, and 10
	  * Resolution of signs and symptoms of COVID-19 at 3, 5, and 10 days

Notes	• Reason for awaiting classification: unclear if standard of care administered in ivermectin group • Recruitment status: not yet recruiting • Prospective completion date: NR • Date last update posted: 18 June 2020 • Sponsor/funding: Symbiosis Medical College for Women, Lavale

Faisal 2020

Methods	• Trial design: clinical study of unclear design with 2 parallel arms • Type of record: journal publication • Sample size: 100 • Setting: outpatient • Country: Pakistan • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NR • Date of registration: NR

Participants	• Inclusion criteria
	  * Positive PCR for COVID-19
	• Exclusion criteria
	  * People with associated severe co-morbidities such as diabetes mellitus, cardiovascular problems, chronic renal failure, and oxygen-dependency

Interventions	• Details of intervention
	  * Type and dose: ivermectin 12 mg, once daily for 5 days
	  * Route of administration: oral
	• Treatment details of control group
	  * No treatment except standard of care
	• Concomitant therapy: standard of care including azithromycin, vitamin D, vitamin C, zinc, and paracetamol administered in both study arms

Outcomes	• Primary study outcome
	  * Duration until disappearance of COVID-19 symptoms
	  * Frequency of participants with disappearance of COVID-19 symptoms
	• Relevant review outcomes planned
	  * Symptom resolution at 10 days
	• Additional study outcomes
	  * None

Notes	• Reason for awaiting classification: unclear study design and fulfilment of randomization criteria; author request sent (even though the term randomization is used, within the method section the study is described as 'cross-sectional;' additionally the definition of being symptom-free and the method of assuring symptom resolution at a certain day needs to be clarified); no response received from the author • Date of publication: 15 October 2020 • Sponsor/funding: no funding

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Faisal 2020 *(Continued)*

- Information on ethics votum: no name of responsible ethics committee, reference number of proposal, or votum provided in publication; author request sent; no response received

Hosseini 2021

Methods	• Trial design: open-label RCT with 2 parallel arms • Type of record: trial register entry and published protocol • Sample size: 120 • Setting: inpatient and outpatient • Country: Iran • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: IRCT20200506047323N6 • Date of registration: 17 November 2020

Participants	• Inclusion criteria
	  * Age ≥ 20 years old
	  * Weight ≥ 35 kg
	  * Positive PCR test for COVID-19
	  * Non-hospitalized people with mild COVID-19 as well as hospitalized (≤ 48 hours) people with moderate COVID-19
	  * Signed informed consent voluntarily and knowingly
	• Exclusion criteria
	  * Severe and critical pneumonia due to COVID-19
	  * Underlying diseases, including AIDS, asthma, loiasis, and severe liver and kidney disease
	  * Use of anticoagulants (e.g. warfarin) and angiotensin-converting enzyme inhibitors (e.g. captopril)
	  * History of drug allergy to ivermectin
	  * Pregnancy or breastfeeding

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.2 mg/kg, single dose
	  * Route of administration: oral
	• Treatment details of control group
	  * No treatment except standard of care according to patient setting
	• Concomitant therapy
	  * Outpatients: standard of care including hydroxychloroquine administered in both study arms
	  * Inpatients: standard of care including lopinavir/ritonavir and interferon beta-1a administered in both study arms

Outcomes	• Primary study outcome
	  * Length of hospital stay within 7 days
	  * Need for ICU within 7 days
	  * Need for mechanical ventilation within 7 days
	  * For outpatients only: need for hospitalization within 7 days
	• Relevant review outcomes planned
	  * For outpatients: incidence of serious adverse reactions within 7 days
	• Additional study outcomes
	  * For inpatients: incidence of serious adverse reactions within 7 days

Notes	• Reason for awaiting classification: study completed, but results not published yet

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Hosseini 2021 *(Continued)*

- Recruitment status: completed
- Prospective completion date: 25 February 2021
- Date last update posted: 17 November 2020
- Sponsor/funding: Bandare-abbas University of Medical Sciences

IRCT20190602043787N3

Methods	• Trial design: open-label RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 40 • Setting: inpatient • Country: Iran • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: IRCT20190602043787N3 • Date of registration: 20 July 2020

Participants	• Inclusion criteria
	  * People with COVID-19 whose diagnosis is confirmed by: physicians' clinical diagnosis with participants' clinical symptoms, SpO_2 < 93% laboratory parameters (ESR, CRP, ferritin, complete blood count and lymphocyte count, D-dimer), positive RT-PCR test for SARS-CoV-2
	  * Age 16–75 years
	• Exclusion criteria
	  * Pregnancy and breastfeeding
	  * Concomitant use of warfarin in people aged > 75 years

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.2 mg/kg, single dose
	  * Route of administration: oral
	• Treatment details of control group
	  * No treatment except standard of care
	• Concomitant therapy: standard of care including hydroxychloroquine administered in both study arms

Outcomes	• Primary study outcome
	  * Duration of hospital stay within 30 days
	• Relevant review outcomes planned
	  * None
	• Additional study outcomes
	  * Illness severity, measured by general condition, clinical symptoms, improvement of laboratory parameters (ESR, CRP, ferritin, complete blood count, lymph count, D-dimer (if available)) and improvement SpO_2
	  * Need to mechanical ventilation, time point unclear

Notes	• Reason for awaiting classification: study completed, no results published yet • Recruitment status: completed • Prospective completion date: 20 November 2020 • Date last update posted: 20 July 2020 • Sponsor/funding: Mashhad University of Medical Sciences

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IRCT20200408046987N3

Methods	• Trial design: double-blind RCT with 4 parallel arms; 2 arms investigate prevention, 2 arms investigate treatment • Type of record: trial register entry • Sample size: 800 • Setting: after high-risk exposure • Country: Iran • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): prevention • Trial registration number: IRCT20200408046987N3 • Date of registration: 6 December 2020
Participants	• Inclusion criteria * Healthy people exposed directly and constantly to people with COVID-19 (whose disease is confirmed by RT-PCR test and low-to-moderate severity (Grade < 3). People with SpO_2 > 94% who fit outpatient protocol) * Having consent for participating in study • Exclusion criteria * Pregnant or breastfeeding women * People with a certain central nervous system disease * People with an uncontrolled disease (asthma, COPD, cardiovascular disease, diabetes, kidney or liver dysfunction, cancer, hepatitis, AIDS, immunodeficiency) * People receiving immunosuppressive drugs * People receiving any P-450 or P-gp blockers or any medication interacting with ivermectin * People receiving antiviral therapy * People receiving any corticosteroid (inhaled, oral, or injection) * Any known sensitivity to ivermectin or starch or history of lactose intolerability (for placebo) * People with positive SARS-CoV-2-specific antibody
Interventions	• Details of intervention for relevant arms * Type and dose: ivermectin 0.2 mg/kg, single dose * Route of administration: oral • Treatment details of control group * Placebo • Concomitant therapy: index patient receives placebo in both relevant arms
Outcomes	• Primary study outcome * Percentage of participants in family members * Duration of illness * Severity of disease • Relevant review outcomes planned * Proportion of deaths at 28 days * Considering the drug adverse effects during the study * Duration of the illness with recheck of RT-PCR at 3 and 7 days • Additional study outcomes * Considering the changes in serum antibody level of IgA and IgM * Proportion of subjects needing oxygen use within 28 days * Proportion of subjects needing high-flow oxygen therapy or non-invasive ventilation within 28 days * Proportion of hospitalizations at 28 days * Proportion of mechanical ventilation use at 28 days * Duration of hospitalization within 28 days

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IRCT20200408046987N3 *(Continued)*

Notes	• Reason for awaiting classification: unclear study description regarding main rationale of the study: postexposure prophylaxis or treatment (intervention arms are partially for treatment, outcomes are mainly focused on the index patient); study completed, no results published yet • Recruitment status: completed • Prospective completion date: 20 December 2020 • Date last update posted: 6 December 2020 • Sponsor/funding: Akam Tejarat Fartak Farasoo Company

IRCT20200422047168N2

Methods	• Trial design: single-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 60 • Setting: inpatient • Country: Iran • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: IRCT20200422047168N2 • Date of registration: 30 May 2020

Participants	• Inclusion criteria
	  * Aged > 18 years
	  * RT-PCR test results for SARS-CoV-2 virus were positive after sampling (nasopharynx and oropharynx swab samples)
	  * Manifestations of virus pneumonia in CT scans of their lungs were quite obvious
	  * SpO_2 saturation ≤ 93%
	• Exclusion criteria
	  * History of renal failure
	  * Taking drugs that interfere with ivermectin
	  * People who have been admitted to other clinical trials

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.15–0.2 mg/kg, single dose
	  * Route of administration: oral
	• Treatment details of control group
	  * No treatment except standard of care
	• Concomitant therapy: standard of care including chloroquine, lopinavir/ritonavir (Kaletra) administered in both study arms

Outcomes	• Primary study outcome
	  * Unclear from protocol, either mortality or participants discharged within 7 days
	• Relevant review outcomes planned
	  * None

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IRCT20200422047168N2 *(Continued)*

	• Additional study outcomes * Treatment period * Duration of infection * Duration of admission time * Duration of ICU admission time * Fever, blood SpO_2 percentage, respiratory rate, heart rate, discharge situation within 7 days * Use of non-invasive respiratory methods within 7 days * Use of invasive respiratory methods within 7 days
Notes	• Reason for awaiting classification: study completed, but results not published yet • Recruitment status: completed • Prospective completion date: NR • Date last update posted: 30 May 2020 • Sponsor/funding: Ahvaz University of Medical Sciences

ISRCTN90437126

Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 800 • Setting: unclear • Country: Brazil • Language: English • Number of centres: 2 • Study purpose (treatment, prevention): prevention • Trial registration number: ISRCTN90437126 • Date of registration: 11 November 2020
Participants	• Inclusion criteria * Adults susceptible to be infected by SARS-CoV-19 (not previous infection) tested negative for IgM and IgG immunological test * No symptoms of COVID-19 * Written informed consent signed by participant • Exclusion criteria * Pregnant or breastfeeding * Known allergy to study medications used at intervention * Known or reported history of liver disease * Use of coumarin (anticoagulant)
Interventions	• Details of intervention * Type and dose: ivermectin 0.4 mg/kg, single dose * Route of administration: oral • Treatment details of control group * Placebo • Concomitant therapy: NA
Outcomes	• Primary study outcome * Clinical COVID-19 case diagnosis at 7, 14, 30, and 90 days. (confirmed by serological IgM and IgG anti-SARS-CoV-2 test at 14 days after initial symptoms)

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ISRCTN90437126 *(Continued)*

	• Relevant review outcomes planned
	  * Clinical status of COVID-19 using the WHO Clinical Progression Scale measured at 14 days after COVID-19 diagnosis
	  * Incidence of severe COVID-19 cases at 14 days after treatment
	  * Rate of adverse events within 7 days after treatment
	  * Hospitalization rate at 14 days
	• Additional study outcomes
	  * Clinical status of COVID-19 using the WHO Clinical Progression Scale measured at 30 days after COVID-19 diagnosis
	  * Incidence of severe COVID-19 cases at 30 days after treatment
	  * Hospitalization rate at 7, 30, and 90 days
	  * Deaths at 90 days
	  * Incidence of severe COVID-19 cases at 30 days after treatment

Notes	• Reason for awaiting classification: unclear if participants had had high-risk exposure (eligibility criteria for this review regarding prevention) • Recruitment status: recruiting • Prospective completion date: 30 June 2022 • Date last update posted: 31 March 2021 • Sponsor/funding: Federal University of Pernambuco, Clinical Research Institute Scinet

NCT04351347

Methods	• Trial design: open-label RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 300 • Setting: NR • Country: Egypt • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04351347 • Date of registration: 17 April 2020

Participants	• Inclusion criteria
	  * People with COVID-19
	• Exclusion criteria
	  * Allergy or adverse effects to treatment

Interventions	• Details of intervention
	  * Type and dose: ivermectin, no details on dosing and frequency scheme
	  * Route of administration: oral
	• Treatment details of control group
	  * Standard of care, no details provided
	• Concomitant therapy: NR

Outcomes	• Primary study outcome
	  * Number of participants with improvement or death within 1 month
	• Relevant review outcomes planned
	  * Mortality at 30 days
	• Additional study outcomes
	  * None

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NCT04351347 *(Continued)*

Notes	• Reason for awaiting classification: unclear if standard of care administered in ivermectin arm; unclear if RT-PCR confirmed diagnosis at enrolment; unclear healthcare setting • Recruitment status: recruiting • Prospective completion date: 1 December 2030 • Date last update posted: 10 March 2021 • Sponsor/funding: Tanta University

NCT04374019

Methods	• Trial design: open-label RCT with 5 parallel arms, unclear which comparisons are planned; besides ivermectin study arms include camostat mesilate, artemesia annua and artesunate • Type of record: trial register entry • Sample size: 240 • Setting: NR • Country: USA • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04374019 • Date of registration: 5 May 2020
Participants	• Inclusion criteria * Age ≥ 18 years * Laboratory-confirmed SARS-CoV-2 infection within the past 7 days or the presence of symptoms or physical examination signs providing high probability of COVID-19 disease * Must have adequate organ and marrow function measured within the last 6 months * Must have ≥ 1 of the following high-risk features or clinical deterioration: hypertension, diabetes mellitus, moderate-to-severe COPD, emphysema, cystic fibrosis, or asthma; people with cancer who have received any immunosuppressive drugs within 1 year from enrolment, sickle cell disease or thalassaemia, age ≥ 50 years, BMI ≥ 30, living in a nursing home or long-term facility, underlying serious heart condition as determined by the treating physician, immunocompromised person as defined by the treating physician or COVID-19 Telehealth Treatment Team • Exclusion criteria * Severe or life-threatening COVID-19 * Weight < 45 kg * Pregnant or breastfeeding women * Receiving dialysis or with creatinine clearance < 45 mL/minute * Existing Division of Microbiology and Infectious Diseases Toxicity Scale for Determining Severity of Adverse Events grade ≥ 3 hepatic failure * Previously documented moderate or severe retinopathy or macular degeneration * Uncontrolled seizure disorder * Prolonged QT, defined as QTc ≥ 470 mseconds for men and QTc ≥ 480 mseconds for women using Bazett's formula * Known allergy to artesunate, artemisia annua, hydroxychloroquine, macrolides, 4-aminoquinolines, camostat mesilate, or other agents to be used in the trial * Currently receiving any study medications for other indications * Concurrent use of medication that would cause drug–drug interactions * Psychiatric illness/social situations that would limit compliance

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NCT04374019 *(Continued)*

Interventions	• Details of intervention for relevant arms
	  * Type and dose: ivermectin 12 mg total daily dose (< 75 kg) or 15 mg total daily dose (> 75 kg), for 2 days
	  * Route of administration: oral
	• Treatment details of control group
	  * NR
	• Concomitant therapy: NR

Outcomes	• Primary study outcome
	  * Clinical deterioration at 14 days
	• Relevant review outcomes planned
	  * Progression to ICU care or ventilation at 28 days
	  * Rate of severe adverse events at 14 days
	• Additional study outcomes
	  * Mortality at 14 days
	  * Change in viral load at 40 days
	  * Rate of organ failure at 28 days
	  * Change in clinical status at 28 days
	  * Oxygen-free days at 28 days
	  * Ventilator-free days at 28 days
	  * ICU-free days at 28 days
	  * Hospital-free days at 28 days
	  * Participants meeting Hy's Law criteria at 28 days
	  * Liver function at 28 days
	  * Heart function at 28 days

Notes	• Reason for awaiting classification: unclear control arm; unclear healthcare setting • Recruitment status: recruiting • Prospective completion date: May 2021 • Date last update posted: 6 November 2020 • Sponsor/funding: Susanne Arnold

NCT04407130

Methods	• Trial design: double-blind RCT with 3 parallel arms, only 2 arms relevant; the third arm investigates ivermectin plus another active treatment (doxycycline) • Type of record: trial register entry • Sample size: 72 • Setting: inpatient • Country: Bangladesh • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04407130 • Date of registration: 29 May 2020

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NCT04407130 *(Continued)*

Participants	• Inclusion criteria * Bangladeshi aged 18–65 years admitted to any of the study hospitals * Men or women * At the enrolment having ≥ 1 of the following symptoms: temperature ≥ 37.5 °C, cough, or sore throat * SpO_2 > 94% * Duration of illness ≤ 7 days * No oxygen support on enrolment * Capable of swallowing oral medication * PCR positive for SARS-CoV-2 virus * Participant properly informed about the study and agreed to sign the informed consent form • Exclusion criteria * Allergy to ivermectin or doxycycline; or other contraindications to any of the study medications * History of chronic heart disease (ischaemic heart disease, heart failure, documented cardiomyopathy, etc.) * History of chronic liver disease (alanine transaminase value > 3 times normal value) * History of chronic kidney disease (creatinine for men > 1.3 mg/dL or > 115 µmol/L and for women > 1.2 mg/dL or > 106.1 µmol/L) * Pregnant or lactating women * Participated in any other clinical trial within last 4 weeks * Having received ivermectin/doxycycline within last 7 days
Interventions	• Details of intervention for relevant arms * Type and dose: ivermectin 0.2 mg/kg, once daily for 5 days * Route of administration: oral • Treatment details of control group * Placebo • Concomitant therapy: NA
Outcomes	• Primary study outcome * Virological clearance at 7 days * Remission of fever at 7 days * Remission of cough at 7 days • Relevant review outcomes planned * Virological clearance at 7 days * Duration of hospitalization within 14 days • Additional study outcomes * Participants requiring oxygen at 7 days * Participants failing to maintain SpO_2 > 93% despite oxygenation at 7 days * Number of days on oxygen support at 7 days * All-causes mortality at 14 days
Notes	• Reason for awaiting classification: study completed, but results not published yet • Recruitment status: completed • Prospective completion date: 20 November 2020 • Date last update posted: 4 February 2021 • Sponsor/funding: International Centre for Diarrhoeal Disease Research, Bangladesh

NCT04407507

Methods	• Trial design: clinical study of unclear design with 2 parallel arms

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NCT04407507 *(Continued)*

	• Type of publication: trial registry entry with posted results • Setting: outpatient • Recruitment dates: July 2020 to January 2021 • Country: Mexico • Language: English • Number of centres: NR, multicentred • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04407507 • Date of registration: 29 May 2020
Participants	• Number of participants (randomized/analyzed): 66/56; 66 participants analyzed for safety outcomes; unclear if participants were actually randomized • Age (mean): overall 39 (SD 14.19) years • Males, n: overall 18 (27.3%) • Severity of condition according to study definition: outpatients with mild or no symptoms • Severity of condition according to WHO scale: 1 to 3 • Co-morbidities: NR • Virus detection performed at baseline (test-positive at baseline): NR, but RT-PCR positivity defined as inclusion criterion • Inclusion criteria: diagnosis of acute severe respiratory syndrome due to SARS-CoV-2 coronavirus infection defined by RT-PCR; asymptomatic, or with mild symptoms who are taking outpatient treatment of the disease; signed informed consent • Exclusion criteria: severe disease COVID-19; positive to proof of infection by some other virus such as influenza H1N1, severe acute respiratory syndrome, etc.; recurrent urinary tract infections; ALT or AST > 5 times above its normal limits; pregnant or lactating; receiving antihypertensive medication verapamil, the immunosuppressant cyclosporin A or the antipsychotic trifluoperazine, or both; known allergy or hypersensitivity to dewormers; using an antioxidant supplement; history of filariasis, strongyloidiasis, scabies, river blindness, or any parasitic disease in the last 12 months

Interventions	• Details of intervention of relevant arms
	  * Type and dose: ivermectin 12 mg, once daily for 3 days
	  * Route of administration: oral
	• Treatment details of control group
	  * Placebo with standard of care
	• Concomitant therapy: standard of care including paracetamol administered in both study arms
	• Duration of follow-up: 21 days
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  * Participants with a disease control status defined as no disease progression to severe at 14 days
	• Relevant review outcomes reported
	  * Adverse events within 21 days
	  * Serious adverse events within 21 days
	  * Mortality at 21 days
	  * Need for invasive mechanical ventilation at 14 days
	• Additional study outcomes reported
	  * SARS-CoV-2 viral load at 5 and 14 days
	  * Presence and frequency of symptoms associated with the COVID-19 disease within 14 days

Notes	• Reason for awaiting classification: unclear study design; author request sent (even though the register entry and study protocol use the term randomization, the method of assignment described in the study protocol does not seem to fulfil randomization criteria); no response received from the author • Date of results first posted: 21 May 2021

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NCT04407507 *(Continued)*

- Sponsor/funding: Investigacion Biomedica para el Desarrollo de Farmacos S.A. de C.V.
- Information on ethics votum: no name of responsible ethics committee, reference number of proposal, or votum provided in publication; author request sent; no response received

NCT04716569

Methods	• Trial design: open-label RCT with parallel arms • Type of record: trial register entry • Sample size: 150 • Setting: NR • Country: Egypt • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04716569 • Date of registration: 20 January 2021

Participants	• Inclusion criteria
	  * People with early COVID-19
	  * Age ≥ 18 years
	• Exclusion criteria
	  * Children and pregnant women

Interventions	• Details of intervention
	  * Type and dose: ivermectin, no details on dosing scheme reported
	  * Route of administration: intranasal spray
	• Treatment details of control group
	  * Standard of care, details NR
	• Concomitant therapy: NR

Outcomes	• Primary study outcome
	  * Progress of COVID-19 symptoms (fever, cough, sore throat, myalgia, diarrhoea, shortness of breath) with radiological assessment and blood tests within 14 days of enrolment
	• Relevant review outcomes planned
	  * None
	• Additional study outcomes
	  * None

Notes	• Reason for awaiting classification: unclear confirmation of SARS-CoV-2 diagnosis at enrolment and unclear if standard of care administered in ivermectin arm • Recruitment status: recruiting • Prospective completion date: 20 March 2021 • Date last update posted: 17 March 2021 • Sponsor/funding: South Valley University

NCT04746365

Methods	• Trial design: double-blind RCT with 3 parallel arms, only 2 arms relevant; the third arm investigates hydroxychloroquine • Type of record: trial register entry • Sample size: 300

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NCT04746365 *(Continued)*

	• Setting: inpatients • Country: Egypt • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04746365 • Date of registration: 9 February 2021

Participants	• Inclusion criteria
	  * Participant (or legally authorized representative) provides written informed consent prior to initiation of any study procedures
	  * Understands and agrees to comply with planned study procedures
	  * Agrees to the collection of oropharyngeal swabs and venous blood per protocol
	  * Male or non-pregnant female adult age ≥ 18 years at enrolment
	  * Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other
	  * Severe cases according to WHO definition
	• Exclusion criteria
	  * ALT/AST > 5 times the ULN
	  * Mortality within 12 hours of admission
	  * Pregnancy
	  * Anticipated transfer to another hospital within 24 hours
	  * Allergy to any study medication commercial or public health assay in any specimen prior to randomization
	  * Mechanically ventilated on admission

Interventions	• Details of intervention for relevant arms:
	  * Type and dose: ivermectin 12 mg, thrice daily on day 0, 3, and 6
	  * Route of administration: oral
	• Treatment details of control group
	  * Unclear if placebo or standard of care
	• Concomitant therapy: NR

Outcomes	• Primary study outcome
	  * Reduction in the WHO Ordinal Scale of clinical status by ≥ 2 points at 14 days
	  * Time to discharge at 14 days
	• Relevant review outcomes planned
	  * Duration of hospitalization within 14 days
	  * Adverse events (grade 3 and 4) at 14 days
	  * Serious adverse events at 14 days
	• Additional study outcomes
	  * Mortality at 14 days

Notes	• Reason for awaiting classification: unclear control arm; also study completed, no results published yet • Recruitment status: completed • Prospective completion date: 6 February 2021 • Date last update posted: 9 February 2021 • Sponsor/funding: Elaraby Hospital

NCT04891250

Methods	• Trial design: double-blind RCT with 3 parallel arms

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NCT04891250 *(Continued)*

	• Type of record: trial register entry • Sample size: 800 • Setting: NR • Country: Zambia • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment and prevention • Trial registration number: NCT04891250 • Date of registration: 18 May 2021

Participants	• Inclusion criteria
	  * People diagnosed positive for SARS-CoV-2 by rRT-PCR with presence of a fever, cough, sore throat, or a combination
	• Exclusion criteria
	  * Allergic to ivermectin or potential for a drug–drug interaction with ivermectin
	  * Chronic illnesses (e.g. ischaemic heart disease, heart failure, documented cardiomyopathy, chronic kidney disease, chronic liver disease)
	  * Having received ivermectin in the last 7 days
	  * Pregnant or lactating women
	  * Participation in any other clinical trial within the last 1 month

Interventions	• Details of intervention
	  * Type and dose: ivermectin, no details on dosing or frequency scheme
	  * Route of administration: NR
	• Treatment details of control group
	  * No treatment except standard of care
	• Concomitant therapy: unclear

Outcomes	• Primary study outcome
	  * All-cause COVID-19 related mortality at 28 days
	  * COVID-19 infection within study duration
	• Relevant review outcomes planned
	  * All-cause COVID-19-related mortality at 28 days
	  * COVID-19 infection within study duration
	• Additional study outcomes
	  * Patient cure rate at 14–28 days
	  * Determine proportion who will develop severe disease and needing admission in addition to the above outcomes within 90 days

Notes	• Reason for awaiting classification: unclear description regarding intervention details, standard of care, inclusion criteria for prophylaxis substudy • Recruitment status: not yet recruiting • Prospective completion date: December 2022 • Date last update posted: 18 May 2021 • Sponsor/funding: Centre for Infectious Disease Research in Zambia, Ministry of Health and University of Zambia

Samaha 2021

Methods	• Trial design: clinical study of unclear design with 2 parallel arms • Type of record: journal publication and trial register entry • Sample size: 100

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Samaha 2021 *(Continued)*

	• Setting: outpatient • Country: Lebanon • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: ChiCTR2000033627 • Date of registration: 7 June 2020
Participants	• Inclusion criteria * Adults with positive PCR for COVID-19 (asymptomatic for the pilot intervention) * Bodyweight > 45 kg * Consent for voluntary participation • Exclusion criteria * People with end-stage heart failure * Recent cardiac intervention (< 2 months): coronary angioplasty, implantable cardioverter-defibrillator, coronary artery bypass graft, valvuloplasty or replacement * Pulmonary fibrosis or advanced COPD * End-stage kidney or liver disease * Pregnant or lactating women * People receiving immunosuppressive therapy * Active tuberculosis, active hepatitis * People requiring planned blood transfusion (thalassaemia major, aplastic anaemia)
Interventions	• Details of intervention * Type and dose: ivermectin 9 mg or 12 mg or 0.15 mg/kg (weight-adjusted), single dose * Route of administration: oral • Treatment details of control group (e.g. type, dose, route of administration) * No treatment except standard of care • Concomitant therapy: standard of care including supplements administered in both study arms
Outcomes	• Primary study outcome * Reduction of viral load and treating COVID-19 infection • Relevant review outcomes planned * Admission to hospital • Additional study outcomes * None
Notes	• Reason for awaiting classification: unclear study design and fulfilment of randomization criteria; author request sent (even though the register entry uses the term randomization, within the journal publication the detailed description of assignment to intervention is unclear ('stratified randomisation,' 'age-matched,' 'case-control;' additionally contradictory information on study period: protocol June–July, publication September–November); author responded, though without providing clarifying details on randomization method • Date of publication: 26 May 2021 • Sponsor/funding: Rayak Hospital, Lebanese University • Information on ethics votum: name of responsible ethics committee, reference number of proposal, and votum reported and provided by study author via personal communication

ALT: alanine aminotransferase; AST: aspartate aminotransferase; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; CT: computer tomography; ESR: erythrocyte sedimentation rate; GGT: gamma glutamyl transferase; ICU: intensive care unit; IgA: immunoglobulin A; IgM: immunoglobulin M; NR: not reported; PaO_2: partial pressure of oxygen; PCR: polymerase chain reaction; RCT: randomized controlled trial; RT-PCR: reverse transcription polymerase chain reaction; rRT-PCR: real-time reverse transcription polymerase chain reaction; SpO_2: oxygen saturation by pulse oximetry; ULN: upper limit of normal; WHO: World Health Organization.

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Characteristics of ongoing studies *[ordered by study ID]*

2020-001994-66/ES

Study name	Randomised clinical trial of ivermectin for treatment and prophylaxis of COVID-19

Methods	• Trial design: double-blind RCT with 2 parallel arms
	• Type of record: trial register entry
	• Sample size: 266
	• Setting
	  * Substudy treatment: outpatient
	  * Substudy prevention: after high-risk exposure
	• Country: Spain
	• Language: English
	• Number of centres: NR
	• Study purpose (treatment, prevention): treatment and prevention
	• Trial registration number: 2020-001994-66/ES
	• Date of registration: 8 May 2020

Participants	• Inclusion criteria
	  * Substudy treatment
	  ☐ Symptomatic (respiratory) participants with a positive RT-PCR test for COVID-19 and a clinical condition of < 5 days of evolution
	  ☐ Age ≥ 18 years
	  ☐ In women of childbearing age, negative pregnancy test and use of contraceptive method during the study period
	  ☐ Accept to take the medication and the complementary test procedures during the study, including analysis and nasal sampling
	  ☐ Able to provide informed consent (oral or written)
	  * Substudy prevention
	  ☐ Contacts of symptomatic (respiratory) people with a positive RT-PCR test for COVID-19 and a diagnosis of < 5 days of evolution
	  ☐ Of legal age
	  ☐ In women of childbearing age, negative pregnancy test and use of contraceptive method during the study period
	  ☐ Accept to take the medication and the complementary test procedures during the study, including analysis and nasal sampling
	  ☐ Able to provide informed consent (oral or written)

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- Exclusion criteria
  - Substudy treatment
    - ☐ Moderate or severe forms of infection requiring hospital admission
    - ☐ Respiratory distress with respiratory rate ≥ 30 breaths per minute, SaO_2 ≤ 93% at rest, PaO_2/FIO_2 ≤ 300 mmHg
    - ☐ Participants taking medications that may interfere with the study medication such as anticoagulants
    - ☐ Inability to take oral medication
    - ☐ Severe liver disorders (Child-Pugh C)
    - ☐ Impairment of severe renal function (with glomerular filtration rate ≤ 30 mL/minute/1.73 m^2) or requiring dialysis
    - ☐ Participants with coagulation disorders
    - ☐ Participants with severe neurological or mental impairment
    - ☐ Pregnant or lactating women
    - ☐ Unable to consent to the study protocol
    - ☐ People with known hypersensitivity to ivermectin
    - ☐ People who have been treated in any other study in the previous 30 days
    - ☐ Concomitant administration of enzyme inducers (such as carbamazepine) that could affect the effectiveness of the drug and those receiving CYP3A4 substrates (such as statins) due to the risk of increased toxicity
    - ☐ Any other contraindication according to the technical sheet for ivermectin
  - Substudy prevention
    - ☐ Participants taking medications that may interfere with study medication
    - ☐ Inability to take oral medication
    - ☐ Severe liver disorders (Child-Pugh C) or alcoholism
    - ☐ Impaired severe renal function (with glomerular filtration rate ≤ 30 mL/minute/1.73 m^2) or requiring dialysis
    - ☐ Participants with coagulation disorders
    - ☐ Participants with severe neurological or mental impairment
    - ☐ Pregnant or lactating women
    - ☐ Unable to consent to study protocol
    - ☐ People with known hypersensitivity to ivermectin
    - ☐ People who have been treated in any other study in the previous 30 days
    - ☐ Concomitant administration of enzyme inducers (such as carbamazepine) that could affect the effectiveness of the drug and those receiving CYP3A4 substrates (such as statins) due to the risk of increased toxicity
    - ☐ Any other contraindication according to the technical data sheet for Ivermectin

Interventions	• Details of intervention
	  * Type and dose: ivermectin 3 mg, no information on frequency scheme
	  * Route of administration: oral
	• Treatment details of control group
	  * Placebo
	• Concomitant therapy: NA

Outcomes	• Primary study outcome
	  * Substudy treatment: compare viral clearance in people with SARS-CoV-2 treated with ivermectin and placebo, time point unclear
	  * Substudy prevention: compare contagion rate between home contacts of people with COVID-19 receiving prophylaxis with ivermectin and placebo, time point unclear
	• Relevant review outcomes planned
	  * None

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	• Additional study outcomes
	  * Substudy treatment: compare clinical evolution and complications between people with COVID-19 receiving ivermectin and placebo
	  * Substudy prevention: compare clinical evolution and complications between home contacts of people with COVID-19 receiving ivermectin and placebo prophylaxis

Starting date	NR
Contact information	Fundació Assistencial Mútua Terrassa Passeig Olabarria s/n Valldoreix 08197 Spain tomas.perez.porcuna@gmail.com
Notes	• Recruitment status: NR • Prospective completion date: NR • Date last update posted: NR • Sponsor/funding: Fundació Assistencial Mútua Terrassa

ACTRN12620000982910

Study name	A randomized double-blind placebo-controlled trial of oral ivermectin for outpatient treatment of those at high risk for hospitalization due to COVID-19
Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 400 • Setting: outpatient • Country: Australia • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: ACTRN12620000982910 • Date of registration: 14 September 2020

Participants	• Inclusion criteria
	  * People aged ≥ 50 years who have tested positive for SARS-CoV-2 (by any NAAT/PCR-based testing system recognized by public health authorities) within the preceding 12 days
	  * Are still symptomatic or have not yet developed symptoms
	  * Have any of the following risk factors: take medication for hypertension, take medication (oral or injectable) for blood glucose control, take medication for heart disease, take medication (oral or inhaled) for lung disease, currently smoke
	  * Are residing in the community
	  * Have at their current place of residence (i.e. at the location they are maintained in isolation) communication facilities necessary for trial functioning, these are: reliable mobile or landline telephone (or both) access, reliable access to email
	  * Capable of giving informed consent which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol

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ACTRN12620000982910 *(Continued)*

	• Exclusion criteria * Duration of symptoms ≥ 10 days AND symptoms clearly getting better * Residents in an aged care facility (hostel or nursing home) or quarantine hotel * Not usually fully independent in activities of daily living and self-care including: washing, toileting, dressing, and dental care * Current residence outside logistical boundaries of the study as defined from time to time during recruitment * Self-reported severe liver disease or cirrhosis, or both * Use of warfarin * Known allergy to Ivermectin * Fit, seizure, or stroke in the last 6 months * Dementia of any type * Head injury requiring medical attention in the last 6 months * Concussion in the last 6 months * Current use of the following medications: verapamil, ciclosporin, cobicistat, ritonavir, ketoconazole, itraconazole, fusidic acid, erythromycin, clarithromycin * Current use or use within the last 3 months of the medication: amiodarone * Psychosocial illness which in the opinion of the investigative team would make successful trial completion (including follow-up data collection) unlikely, for example including: uncontrolled substance use, homelessness, poorly controlled mental state disorder * Inability to communicate in English to the level necessary to provide verbal consent and telephone call follow-up data * Current participation in another clinical drug trial for SARS-CoV-2
Interventions	• Details of intervention * Type and dose: ivermectin 0.2 mg/kg, single dose with the option of a second dose after 7 days * Route of administration: oral • Treatment details of control group * Placebo • Concomitant therapy: NA
Outcomes	• Primary study outcome * Proportions of participants progressing to hospitalization due to SARS-CoV-2 or death at 14 days • Relevant review outcomes planned * Proportions of participants progressing to hospitalization due to SARS-CoV-2 or death at 14 days * Hospitalization without death at 14 days * Proportions of participants progressing to admission to intensive care due to SARS-CoV-2 or death at 14 days * Proportions of participants progressing to requirement for intubation because of SARS-CoV-2 or death at 14 days * Duration of hospitalization of survivors within 14 days * Duration of outpatient symptoms at 14 days * Proportion of participants progressing to death at 28 days

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ACTRN12620000982910 *(Continued)*

	• Additional study outcomes * Proportions of participants progressing to hospitalization or death at 7, 21, and 28 days * Proportions of participants presenting to hospital with any of the following: clinical signs of respiratory distress (> 20 breaths per minute) or oximetry desaturation (≤ 94%) (or both), clinical or radiological signs of pneumonia at 7, 14, 21, and 28 days * Proportions of participants progressing to admission to intensive care due to SARS-CoV-2 or death at 7, 21, and 28 days * Proportions of participants progressing to requirement for intubation because of SARS-CoV-2 or death at 7, 21, and 28 days * Duration of hospitalization of survivors within 7, 21, and 28 days and up to 6 months * Duration of outpatient symptoms at 7, 21, and 28 days * Proportion of participants progressing to death at 7, 14, and 21 days and up to 6 months
Starting date	15 February 2021
Contact information	Dr Mark Stein Department of Diabetes and Endocrinology Royal Melbourne Hospital 300 Grattan Street Victoria, 3050 Australia msteintpep1@florey.edu.au
Notes	• Recruitment status: not yet recruiting • Prospective completion date: NR • Date last update posted: 27 January 2021 • Sponsor/funding: The Leona M and Harry B Helmsley Charitable Trust (USA)

CTRI/2020/05/025068

Study name	A phase IIB open label randomized controlled trial to evaluate the efficacy and safety of Ivermectin in reducing viral loads in patients with hematological disorders who are admitted with COVID 19 infection
Methods	• Trial design: open-label RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 50 • Setting: inpatient • Country: India • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: CTRI/2020/05/025068 • Date of registration: 7 May 2020
Participants	• Inclusion criteria * Age 1–65 years * Male or female * RT-PCR-confirmed COVID-19 diagnosis • Exclusion criteria * People with other viral infections

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CTRI/2020/05/025068 *(Continued)*

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.2 mg/kg, single dose
	  * Route of administration: oral
	• Treatment details of control group
	  * No treatment except standard of care
	• Concomitant therapy: standard of care defined as standard protocol for management of COVID-19 infection administered in both study arms

Outcomes	• Primary study outcome
	  * Viral load reduction in participants with haematological illnesses admitted with COVID-19 infection at 7 days
	• Relevant review outcomes planned
	  * None
	• Additional study outcomes
	  * To study the factors that affect viral load reduction
	  * To study if the reduction in viral load correlates with improvement in inflammatory parameters
	  * To study the incidence of serious adverse events and safety of this drug when used in haematological illnesses

Starting date	27 May 2020
Contact information	Biju George, Professor Christian Medical College Vellore Department of Haematology Vellore Tamil Nadu 632004 India biju@cmcvellore.ac.in
Notes	• Recruitment status: not yet recruiting • Prospective completion date: NR • Date last update posted: 27 May 2020 • Sponsor/funding: Christian Medical College Vellore

CTRI/2020/05/025224

Study name	Study to efficacy of Ivermectin in patients of COVID-19
Methods	• Trial design: open-label RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 50 • Setting: inpatient • Country: India • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: CTRI/2020/05/025224 • Date of registration: 18 May 2020

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CTRI/2020/05/025224 *(Continued)*

Participants	• Inclusion criteria * Adults (age 18–75 years) * Laboratory-confirmed SARS-CoV-2 infection * In the view of the responsible doctor, no contraindication to any of the study treatments * Hospitalized at R D Gardi Medical College, Ujjain Madhya Pradesh • Exclusion criteria * Anticipated transfer to another hospital, within 72 hours, which is not a study site * Known allergy to study medication or its components (non-medicinal ingredients) * Known HIV infection
Interventions	• Details of intervention * Type and dose: ivermectin 12 mg, once daily for 2 days * Route of administration: oral • Treatment details of control group * No treatment except standard of care • Concomitant therapy: standard of care according to hospital guidelines administered in both study arms
Outcomes	• Primary study outcome * Eradication of virus at 1, 3, and 5 days • Relevant review outcomes planned * Duration of hospitalisation • Additional study outcomes * Overall safety of study drug * Improvement in the abnormal laboratory values
Starting date	24 May 2020
Contact information	Dr Ashish Pathak R. D. Gardi Medical College Department of Pediatrics Agar Road, Surasa Ujjain MADHYA PRADESH 456006 India drashish.jpathak@gmail.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: NR • Date last update posted: 18 May 2020 • Sponsor/funding: R. D. Gardi Medical College

Garcia 2021

Study name	Randomized clinical trial to compare the efficacy of ivermectin versus placebo to negativize nasopharyngeal PCR in patients with early COVID-19 in Peru (SAINT-Peru): a structured summary of a study protocol for randomized controlled trial
Methods	• Trial design: triple-blind RCT with 2 parallel arms • Type of record: trial register entries and published protocol • Sample size: 186 • Setting: outpatient • Country: Peru

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Garcia 2021 *(Continued)*

	• Language: English • Number of centres: 2 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT046355943, PER-034-20 • Date of registration: 19 November 2020
Participants	• Inclusion criteria * COVID-19 symptomatology (cough, fever, anosmia, etc.) lasting < 96 hours, with a positive nasopharyngeal swab PCR test for SARS-CoV-2 * Age 18 years * No use of ivermectin in the month prior to the visit * No known history of ivermectin allergy * Capable to give informed consent * Not current use of CYP 3A4 or P-gp inhibitor drugs such as quinidine, amiodarone, diltiazem, spironolactone, verapamil, clarithromycin, erythromycin, itraconazole, ketoconazole, cyclosporin, tacrolimus, indinavir, ritonavir, cobicistat, or critical CYP3A4 substrate drugs such as warfarin • Exclusion criteria * COVID-19 pneumonia diagnosed by the attending physician (oxygen saturation < 95% or lung examination) * Positive pregnancy test for women at childbearing age * Positive IgG against SARS-CoV-2 by rapid diagnostic test at screening
Interventions	• Details of intervention * Type and dose: ivermectin 0.3 mg/kg, once daily for 3 days * Route of administration: oral • Treatment details of control group * Placebo • Concomitant therapy: NA
Outcomes	• Primary study outcome * Proportion of participants with a positive SARS-CoV-2 PCR from a nasopharyngeal swab 7 days after treatment • Relevant review outcomes planned * All-cause mortality at 21 days • Additional study outcomes * Mean viral load at baseline and on 4, 7, 14, and 21 days * Proportion of participants with fever and cough at days 4, 7, 14, and 21 days * Proportion of participants with a positive rapid diagnostic test at 21 days * Participants progressing to severe disease or death during the trial * Proportion of drug-related adverse events at 7 days * Seroconversion at 21 days * Levels of IgG, IgM, and IgA up to and at 21 days * Frequency of innate immune cells up to and at 7 days * Results from cytokine Human Magnetic 30-Plex Panel up to and at 21 days * Presence of intestinal helminths at baseline and at 14 days
Starting date	29 August 2020
Contact information	Hansel Mundaca, MD Hospital Nacional Cayetano Heredia Lima, Peru hansel.mundaca@upch.pe
Notes	• Recruitment status: recruiting

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Garcia 2021 *(Continued)*

- Prospective completion date: 30 April 2021
- Date last update posted: 18 March 2021
- Sponsor/funding: Universidad Peruana Cayetano Heredia

IRCT20111224008507N4

Study name	Double-blind placebo-controlled clinical trial of evaluating the effectiveness of Ivermectin in treatment of outpatients with COVID-19 in 2021
Methods	• Trial design: double-blind RCT with two parallel arms • Type of record: trial register entry • Sample size: 1000 • Setting: outpatient • Country: Iran • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: IRCT20111224008507N4 • Date of registration: 31 January 2021

Participants	• Inclusion criteria
	  * People with positive coronavirus rapid test or RT-PCR positive
	  * No need for hospitalization
	  * Weight > 15 kg
	  * Age > 5 years
	  * No treatment with antiviral drugs before and during the study
	  * Informed consent for inclusion
	• Exclusion criteria
	  * Underlying liver and kidney disease
	  * People with AIDS
	  * Pregnancy and lactation

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.4 mg/kg, once daily for 3 days
	  * Route of administration: oral
	• Treatment details of control group
	  * Placebo with standard of care
	• Concomitant therapy: standard of care according to national treatment protocol administered in both study arms

Outcomes	• Primary study outcome
	  * Clinical improvement
	  * Negative RT-PCR result at 6 days
	• Relevant review outcomes planned
	  * Drug adverse effects
	  * Negative RT-PCR result at 6 days
	• Additional study outcomes
	  * The main complaint's recovery time
	  * Need to be hospitalized, time point unclear
	  * Mortality, time point unclear

Starting date	19 February 2021

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IRCT20111224008507N4 *(Continued)*

Contact information	Dr Mohammad Sadegh Rezai Mazandaran University of Medical Sciences Boali Hospital, Pasdaran Blv. 485838477 Sari, Mazandaran Iran drmsrezaii@yahoo.com
Notes	• Recruitment status: recruiting • Prospective completion date: 22 August 2022 • Date last update posted: 6 March 2021 • Sponsor/funding: Mazandaran University of Medical Sciences

IRCT20111224008507N5

Study name	Double-blind placebo-controlled clinical trial of evaluating the effectiveness of Ivermectin in treatment of patients admitted with COVID-19 in 2021
Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 1000 • Setting: inpatient • Country: Iran • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: IRCT20111224008507N5 • Date of registration: 22 February 2021

Participants	• Inclusion criteria
	  * People with positive coronavirus rapid test or RT-PCR
	  * Age > 5 years
	  * Weight > 15 kg
	  * No treatment with antiviral drugs before and during the study
	  * Informed consent for participation
	• Exclusion criteria
	  * Underlying liver and kidney disease
	  * People with acquired immunodeficiency
	  * Pregnancy and lactation

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.4 mg/kg, once daily for 3 days
	  * Route of administration: oral
	• Treatment details of control group
	  * Placebo with standard of care
	• Concomitant therapy: standard of care according to national treatment protocol administered in both study arms

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IRCT20111224008507N5 *(Continued)*

Outcomes	• Primary study outcome
	  * Duration until reduction in persistent cough
	  * Negative RT-PCR result at 6 days
	  * Main complaint's recovery time
	  * Mortality, time point unclear
	  * Drug adverse effects (wheezing, itching, skin rash, oedema, and hypotension)
	  * Reduction in tachypnoea
	  * SaO_2 > 94%
	• Relevant review outcomes planned
	  * Drug adverse effects
	  * Negative RT-PCR result at 6 days
	• Additional study outcomes
	  * None

Starting date	19 February 2021
Contact information	Dr Mohammad Sadegh Rezai Mazandaran University of Medical Sciences Boali Hospital, Pasdaran Blv. 485838477 Sari, Mazandaran Iran drmsrezaii@yahoo.com
Notes	• Recruitment status: recruiting • Prospective completion date: 22 August 2022 • Date last update posted: 4 March 2021 • Sponsor/funding: Mazandaran University of Medical Sciences

IRCT20190624043993N2

Study name	Evaluation effects of the standard regimen along with ivermectin on treatment of corona virus type 2 pneumonia
Methods	• Trial design: open-label RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 50 • Setting: NR • Country: Iran • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: IRCT20190624043993N2 • Date of registration: 12 July 2020

Participants	• Inclusion criteria
	  * Definite (clinical and positive PCR) COVID-19 disease
	  * < 48 hours have passed since the onset of symptoms

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IRCT20190624043993N2 *(Continued)*

	• Exclusion criteria
	  * Underlying liver disease/hepatitis
	  * Underlying haematological disorders
	  * Seizures and encephalopathy
	  * Known allergies to ivermectin
	  * Pregnancy/lactation
	  * People who themselves or their legal guardians are reluctant to participate or continue clinical trials

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.15 mg/kg, once daily, unclear duration of intervention
	  * Route of administration: oral
	• Treatment details of control group
	  * No treatment except standard of care
	• Concomitant therapy: standard of care according to national guideline administered in both study arms

Outcomes	• Primary study outcome
	  * Clinical radiographic response at 7 and 14 days
	• Relevant review outcomes planned
	  * Virological response (PCR) at 7 days
	• Additional study outcomes
	  * None

Starting date	22 August 2020
Contact information	Foroud Shahbazi Kermanshah University of Medical Sciences Parastar Blve 1673-67145 Kermanshah Iran Foroud08@gmail.com
Notes	• Recruitment status: NR • Prospective completion date: 19 February 2021 • Date last update posted: 12 July 2020 • Sponsor/funding: Kermanshah University of Medical Sciences

IRCT20200404046937N4

Study name	Evaluating the efficacy and safety of Ivermectin in the treatment of COVID-19 patients: a double-blind randomized controlled trial, phase II
Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 60 • Setting: inpatient • Country: Iran • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: IRCT20200404046937N4

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IRCT20200404046937N4 *(Continued)*

	• Date of registration: 6 August 2020
Participants	• Inclusion criteria * Age ≥ 18 years * Laboratory PCR confirmed infection with COVID-19 * Hospitalized * Agreeing to participate in the study * Acceptance of non-participation in another study before the 28th day of the study • Exclusion criteria * People with a history of allergic reaction to ivermectin * Renal dysfunction * Liver dysfunction * Pregnancy or deciding to get pregnant or breastfeeding
Interventions	• Details of intervention * Type and dose: ivermectin 14 mg, every 12 hours for up to 3 doses * Route of administration: oral • Treatment details of control group * Placebo with standard of care • Concomitant therapy: standard of care defined as routine drugs of the disease administered in both study arms
Outcomes	• Primary study outcome * Viral diagnostic test at day 1 * Duration of hospitalization • Relevant review outcomes planned * Duration of hospitalization • Additional study outcomes * Fever, respiratory rate, dyspnoea, cough * Blood cell count, CRP * CT scan
Starting date	30 July 2020
Contact information	Mehran Varnasseri Ahvaz University of Medical Sciences Razi hospital Felestin Ave, Amanieh Ave Ahvaz, Khouzestan Iran drvarnasei.m@gmail.com
Notes	• Recruitment status: recruiting • Prospective completion date: 30 September 2021 • Date last update posted: 8 March 2021 • Sponsor/funding: Ahvaz University of Medical Sciences

NCT04403555

Study name	Ivermectin as a Novel Therapy in COVID-19 Treatment
Methods	• Trial design: open-label RCT with 2 parallel arms • Type of record: trial register entry

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NCT04403555 *(Continued)*

	• Sample size: 160 • Setting: inpatient • Country: Egypt • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04403555 • Date of registration: 27 May 2020

Participants	• Inclusion criteria
	  * Adult age 20–65 years with COVID-19 confirmed by pharyngeal swab PCR
	• Exclusion criteria
	  * Allergy or contraindication to the drugs used in the study
	  * Pregnant or lactating mothers
	  * People with cardiac problems

Interventions	• Details of intervention
	  * Type and dose: ivermectin 24 mg, for 3 days
	  * Route of administration: oral
	• Treatment details of control group
	  * No treatment except standard of care
	• Concomitant therapy: standard of care (no details provided) administered in both study arms

Outcomes	• Primary study outcome
	  * Number of deaths within 1 month
	• Relevant review outcomes planned
	  * Length of hospital stay at 30 days
	  * Need for mechanical ventilation at 30 days
	  * Mortality at 30 days
	• Additional study outcomes
	  * None

Starting date	1 June 2020
Contact information	Sherief Abd-Elsalam Tanta University Tanta 35111 Egypt sheriefabdelsalam@yahoo.com
Notes	• Recruitment status: recruiting • Prospective completion date: 30 April 2021 • Date last update posted: 3 December 2030 • Sponsor/funding: Tanta University

NCT04425707

Study name	Ivermectin In treatment of COVID 19 patients
Methods	• Trial design: open-label RCT with 3 parallel arms, only 2 arms relevant; the third arm investigates ivermectin without standard of care compared to standard of care which then equals an active comparator

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NCT04425707 *(Continued)*

	• Type of record: trial register entry • Sample size: 100 • Setting: inpatient • Country: Egypt • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04425707 • Date of registration: 11 June 2020

Participants	• Inclusion criteria
	  * Asymptomatic mild cases and moderate cases proven to be infected by COVID-19 by viral RNA swap
	  * Age ≥ 18 years
	• Exclusion criteria:
	  * Contraindications for the drug: hypersensitivity
	  * Any medications with possible drug interactions
	  * Severe cases
	  * Any malignant condition
	  * Pregnant females
	  * Breastfeeding women
	  * Receiving following medications: erdafitinib, lasmiditan, quinidine due to potential severe drug interaction

Interventions	• Details of intervention of relevant arms
	  * Type and dose: ivermectin, dosing and frequency NR
	  * Route of administration: oral
	• Treatment details of control group
	  * No treatment except standard of care
	• Concomitant therapy: standard of care (no details provided) administered in both study arms

Outcomes	• Primary study outcome
	  * NR
	• Relevant review outcomes planned
	  * None
	• Additional study outcomes
	  * Rate of viral clearance in comparison to other treatment protocols

Starting date	9 June 2020
Contact information	Dr Ehab Kamal General Director of Fever Hospitals Ministry of Health and Population Cairo Egypt
Notes	• Recruitment status: recruiting • Prospective completion date: 1 September 2020 • Date last update posted: 11 June 2020 • Sponsor/funding: Ministry of Health and Population, Egypt

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NCT04429711

Study name	Ivermectin vs. placebo for the treatment of patients with mild to moderate COVID-19
Methods	• Trial design: quadruple-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 100 • Setting: NR • Country: Israel • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04429711 • Date of registration: 12 June 2020

Participants	• Inclusion criteria
	  * Participants eligible for inclusion will include non-pregnant adult age > 18 years with molecular confirmation of COVID-19
	  * Participants will be eligible in a period of no longer than 72 hours after exposure
	• Exclusion criteria
	  * Severe infection (defined as need for invasive or non-invasive ventilator support, extracorporeal membrane oxygenation or shock requiring vasopressor support)
	  * Weight < 40 kg or > 100 kg
	  * Unable to take oral medication
	  * Known allergy to the drugs
	  * Pregnancy or breastfeeding
	  * Participating in another RCT for treatment of COVID-19

Interventions	• Details of intervention
	  * Type and dose: ivermectin 12–15 mg, once daily for 3 days
	  * Route of administration: oral
	• Treatment details of control group
	  * Placebo
	• Concomitant therapy: NA

Outcomes	• Primary study outcome
	  * Viral clearance at 6 days
	  * Viral shedding duration within 14 days
	  * Symptom clearance time within 14 days
	• Relevant review outcomes planned
	  * Viral clearance at 6 days
	  * Symptom clearance time within 14 days
	• Additional study outcomes
	  * None

Starting date	12 May 2020
Contact information	Eli Schwartz, Prof Sheba Medical Center Ramat-Gan Israel Eli.schwartz@sheba.health.gov.il
Notes	• Recruitment status: recruiting • Prospective completion date: 31 October 2020 • Date last update posted: 16 June 2020

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NCT04429711 *(Continued)*

- Sponsor/funding: Sheba Medical Center
- Online video with results is not an eligible publication format for this review

NCT04438850

Study name	COVidIVERmectin: ivermectin for treatment of COVID-19 (COVER)
Methods	• Trial design: triple-blind RCT with 3 parallel arms • Type of record: trial register entries • Sample size: 102 • Setting: outpatient • Country: Italy • Language: English • Number of centres: 5 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04438850 • Date of registration: 19 June 2020

Participants	• Inclusion criteria
	  * Age ≥ 18 years
	  * Positivity for SARS-CoV-2 (nasopharyngeal swabs) by RT-PCR
	  * Consent to participating in the study and to the processing of personal data
	  * COVID-19 Severity Score < 3
	  * Participant able to take oral drugs
	• Exclusion criteria
	  * Pregnant or lactating women (pregnancy test not required, if doubt person is excluded)
	  * People with known central nervous system diseases
	  * Lack of (or inability to provide) informed consent
	  * Receiving dialysis
	  * Any severe medical condition with a prognosis of < 6 months
	  * Receiving warfarin treatment
	  * Receiving antiviral treatment
	  * Receiving chloroquine phosphate or hydroxychloroquine

Interventions	• Details of intervention
	  * Type and dose:
	  ☐ Intervention 1: ivermectin 0.6 mg/kg, once daily for 5 days
	  ☐ Intervention 2: 1.2 mg/kg, once daily for 5 days
	  * Route of administration: oral
	• Treatment details of control group
	  * Placebo
	• Concomitant therapy: NA

Outcomes	• Primary study outcome
	  * Number of serious adverse drug reaction at 14 days
	  * Viral load at 7 days
	• Relevant review outcomes planned
	  * Number of serious adverse drug reaction at 14 days
	  * Proportion of participants with virological clearance at 14 days
	  * Hospitalization rate within 14 days

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NCT04438850 *(Continued)*

	• Additional study outcomes
	  * Trend over time of quantitative viral load at 7 and 14 days measured by quantitative, digital droplet PCR.
	  * Time to clinical resolution (for symptomatic participants) within 14 and 30 days
	  * Time from diagnosis to documented viral clearance within 14 and 30 days
	  * Proportion of participants with virological clearance at 30 days
	  * Severity score at 14 and 30 days
	  * Hospitalization rate within 30 days

Starting date	31 July 2020
Contact information	Zeno Bisoffi, PhD IRCCS Sacro Cuore Don Calabria hospital Negrar, Verona 37024 Italy zeno.bisoffi@sacrocuore.it
Notes	• Recruitment status: recruiting • Prospective completion date: September 2021 • Date last update posted: 17 May 2021 • Sponsor/funding: IRCCS Sacro Cuore Don Calabria di Negrar

NCT04445311

Study name	Ivermectin in treatment of COVID-19
Methods	• Trial design: open-label RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 100 • Setting: NR • Country: Egypt • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04445311 • Date of registration: 24 June 2020

Participants	• Inclusion criteria
	  * People with confirmed COVID-19 during period of the study aged > 18 years
	• Exclusion criteria
	  * Refuse to participate pregnancy or lactation hypersensitivity to ivermectin receive any drug with interaction with ivermectin

Interventions	• Details of intervention
	  * Type and dose: ivermectin for 3 days, no details on dosing scheme
	  * Route of administration: oral
	• Treatment details of control group
	  * No treatment except standard of care
	• Concomitant therapy: standard of care (no details provided) administered in both study arms

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NCT04445311 *(Continued)*

Outcomes	• Primary study outcome
	  * Time to be symptom free within 21 days
	• Relevant review outcomes planned
	  * Need for hospital admission within 21 days
	  * Need for mechanical ventilation within 21 days
	  * Length of stay within 30 days
	  * Mortality at 30 days
	• Additional study outcomes
	  * None

Starting date	31 May 2020
Contact information	Waheed Shouman, MD Zagazig University Sharkia 44519 Egypt shouman66@gmail.com
Notes	• Recruitment status: recruiting • Prospective completion date: 15 August 2020 • Date last update posted: 24 June 2020 • Sponsor/funding: Zagazig University

NCT04472585

Study name	Efficacy of subcutaneous ivermectin with or without zinc in COVID-19 patients (SIZI-COVID-PK)
Methods	• Trial design: RCT with 6 parallel arms, unclear blinding description • Type of record: trial register entry • Sample size: 180 • Setting: NR • Country: Pakistan • Language: English • Number of centres: 2 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04472585 • Date of registration: 15 July 2020

Participants	• Inclusion criteria
	  * People with positive nasopharyngeal RT-PCR SARS-CoV-2 test with mild-to-moderate disease
	  * Age ≥ 18 years
	  * Body mass index 18–28 kg/m^2
	• Exclusion criteria
	  * Allergy to any drug
	  * Co-morbidities: any pre-existing cardiac disease, pulmonary disease
	  * Arrhythmias
	  * Pregnancy
	  * RT-PCR performed > 3 days prior to enrolment

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NCT04472585 *(Continued)*

Interventions	• Details of intervention
	  * Type and dose
	  ☐ Intervention 1: ivermectin 0.2 mg/kg subcutaneous injection once every 48 hours
	  ☐ Intervention 2: ivermectin 0.2 mg/kg subcutaneous injection once every 48 hours with zinc sulphate
	  ☐ Intervention 3: ivermectin 0.2 mg/kg, oral once daily
	  ☐ Intervention 4: ivermectin 0.2 mg/kg, oral once daily with zinc sulphate
	  * Route of administration: subcutaneous or oral
	• Treatment details of control group
	  * Control for interventions 1 and 3: placebo injection and capsule
	  * Control for interventions 2 and 4: placebo with zinc sulphate
	• Concomitant therapy: standard of care administered in all study arms

Outcomes	• Primary study outcome
	  * Time needed to turn positive COVID-19 PCR to negative within 14 days
	  * Time taken for alleviation of symptoms within 14 days
	• Relevant review outcomes planned
	  * Morality at 30 days
	• Additional study outcomes
	  * Time needed to make participants clinically well within 14 days

Starting date	14 November 2020
Contact information	Shoaib Ashraf, PhD Harvard University Boston USA sashraf@mgh.harvard.edu
Notes	• Recruitment status: recruiting • Prospective completion date: 30 October 2021 • Date last update posted: 17 February 2021 • Sponsor/funding: Sohaib Ashraf

NCT04510233

Study name	Ivermectin nasal spray for COVID19 patients
Methods	• Trial design: open-label RCT with 3 parallel arms • Type of record: trial register entry • Sample size: 60 • Setting: NR • Country: Egypt • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04510233 • Date of registration: 12 August 2020
Participants	• Inclusion criteria * People of mild-to-moderate severity who are confirmed to be positive for SARS-CoV-2

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NCT04510233 *(Continued)*

	• Exclusion criteria * People with severe form of COVID-19 or those who are on ventilatory support or those with cytokine storm

Interventions	• Details of intervention
	  * Type and dose
	  ☐ Intervention 1: ivermectin nasal spray 1 mL in each nostril, twice daily
	  ☐ Intervention 2: ivermectin 6 mg, 3 times daily for 3 days
	  * Route of administration: intranasal or oral
	• Treatment details of control group
	  * No treatment except standard of care
	• Concomitant therapy
	  * Standard of care including oxygen supplement administered in all study arms

Outcomes	• Primary study outcome
	  * Negative PCR result of SARS-Cov-2 RNA in people with COVID-19 at 14 days
	• Relevant review outcomes planned
	  * Negative PCR result of SARS-Cov-2 RNA in people with COVID-19 at 14 days
	• Additional study outcomes
	  * None

Starting date	September 2020
Contact information	Kamal Okasha, PhD Tanta University Tanta 35111 Egypt okasha70@yahoo.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: October 2020 • Date last update posted: 12 August 2020 • Sponsor/funding: Tanta University

NCT04527211

Study name	Effectiveness and safety of ivermectin for the prevention of COVID-19 infection in Colombian health personnel (IveprofCovid19)
Methods	• Trial design: quadruple-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 550 • Setting: after high-risk exposure • Country: Columbia • Language: English • Number of centres: NR, multicentred • Study purpose (treatment, prevention): prevention • Trial registration number: NCT04527211 • Date of registration: 26 August 2020

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NCT04527211 *(Continued)*

Participants	• Inclusion criteria
	  * People aged > 18 years of either sex who work as healthcare workers, laboriously active during the recruitment of the study in health services that do not screen for the exclusion of acutely ill people
	  * People who have not presented general symptoms such as general discomfort, fever, cough, dyspnoea, or muscle pain in the last week
	  * People with negative COVID-19 serological antibody diagnostic tests
	• Exclusion criteria
	  * People considered as a resolved case of COVID-19 infection, according to guidelines from the Colombian National Institute of Health
	  * Health personnel with social distancing due to close contact without personal protective equipment with people with confirmed infection, or who are taking any medication as possible prophylaxis for COVID-19 (e.g. chloroquine, hydroxychloroquine, azithromycin)
	  * Health workers who have permits or temporary withdrawal from their hospital work for > 1 week during the first month of the study
	  * Known allergy to ivermectin
	  * Pregnant or breastfeeding women
	  * Body mass index < 18.5 and > 35

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.2 mg/kg, once weekly for 7 weeks
	  * Route of administration: oral
	• Treatment details of control group
	  * Placebo
	• Concomitant therapy: NA

Outcomes	• Primary study outcome
	  * Clinical development of COVID-19 disease during the 7-week intervention period
	• Relevant review outcomes planned
	  * None
	• Additional study outcomes
	  * Seroconversion at 8 weeks
	  * Hospitalization requirement within 8 weeks
	  * Intensive care unit requirement within 8 weeks
	  * Safety of the intervention within 8 weeks

Starting date	7 September 2020
Contact information	Dr Eduar D Echeverri Pontificia Universidad Javeriana Valle Del Cauca 760501 Cali Colombia dr.echeverri@gmail.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 16 December 2020 • Date last update posted: 26 August 2020 • Sponsor/funding: Javeriana University

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NCT04602507

Study name	Ivermectin in adults with severe COVID-19
Methods	• Trial design: quadruple-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 100 • Setting: inpatient • Country: Columbia • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04602507 • Date of registration: 26 October 2020
Participants	• Inclusion criteria * Age > 18 years * Confirmed diagnosis of SARS-CoV-2 by PCR * Diagnosis of severe pneumonia according to criteria of the National Institute of Health and the Colombian Consensus (suspected respiratory infection, organ failure, arterial SaO_2 in room air < 90%, or respiratory rate > 30 breaths/minute) or diagnosis of acute respiratory distress syndrome according to criteria of the National Institute of Health and the Colombian Consensus (clinical findings, bilateral radiographic infiltrates, oxygenation deficit: mild: 200 mmHg < PaO_2/FiO_2 < 300 mmHg; moderate: 100 mmHg < PaO_2/FiO_2 < 200 mmHg and, severe: PaO_2/FiO_2 < 100 mmHg) * < 14 days since the onset of symptoms * Hospitalized in a general internal medicine ward, special care unit, or those designated for managing people with COVID-19 • Exclusion criteria * Pregnant or lactating women * Use of ivermectin in the 2 weeks before admission to the clinic * Diseases affecting the blood–brain barrier (meningitis, encephalocranial trauma, acute subarachnoid haemorrhage) * Limited understanding of explanations and consent, defined by the investigating physician * People with HIV/AIDS * Participation in another clinical trial
Interventions	• Details of intervention * Type and dose: ivermectin 0.4 mg/kg, single dose * Route of administration: oral • Treatment details of control group * Placebo with standard of care • Concomitant therapy: standard of care (details NR) administered in both study arms
Outcomes	• Primary study outcome * Cumulative incidence of ICU admission within 21 days • Relevant review outcomes planned * Cumulative incidence of ICU admission within 21 days * Duration of hospitalization within 28 days * Mortality at 21 days * Adverse effects of ivermectin within 21 days • Additional study outcomes * ICU length of stay within 28 days * Length of stay in ventilator time within 28 days

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NCT04602507 *(Continued)*

Starting date	7 December 2020
Contact information	Federico Rodríguez-Vega, MD Clinica CES Medellín, Antioquia 050001 Colombia federicorodriguez@clinicaces.edu.co
Notes	• Recruitment status: recruiting • Prospective completion date: March 2021 • Date last update posted: 10 December 2020 • Sponsor/funding: CES University

NCT04673214

Study name	Evaluation of prognostic modification in COVID-19 patients in early intervention treatment
Methods	• Trial design: single-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 62 • Setting: outpatient • Country: Mexico • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04673214 • Date of registration: 17 December 2020

Participants	• Inclusion criteria
	  * Eligible for Family Medicine Unit No.20 and Family Medicine Unit No.13 belonging to the North DF of the IMSS
	  * Men and women
	  * Age > 18 years
	  * Compliance with the operational definition COVID-19 and confirmatory test of PCR positive within the first days of the illness (that are evaluated in first level of medical attention)
	  * Comorbidities such as type 2 diabetes mellitus, systemic arterial hypertension, overweight, or obesity
	  * Agree to sign an informed consent
	  * Related to video call: that the Family Medicine Unit No.20 and the Family Medicine Unit No.13 belonging to the North DF of the IMSS have the installation of electronic equipment for Internet use
	• Exclusion criteria
	  * People with severe COVID-19 (sent immediately to second level of care, hospital)
	  * Any personal pathological history of haematological diseases
	  * Allergy to macrolides (azithromycin) and ivermectin

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.2 mg/kg, once daily for 2 days
	  * Route of administration: oral
	• Treatment details of control group
	  * No treatment except standard of care

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NCT04673214 *(Continued)*

	• Concomitant therapy * Standard of care including azithromycin, ribaroxaban and paracetamol administered in both study arms

Outcomes	• Primary study outcome
	  * Estimate clinical symptoms by days of follow-up in participants with COVID-19 under treatment with azithromycin/ivermectin/ribaroxaban/paracetamol vs azithromycin/ribaroxaban/paracetamol followed by video call for 14 days from Family Medicine Unit 13 and Family Medicine Unit 20
	• Relevant review outcomes planned
	  * Adverse drug reactions
	• Additional study outcomes
	  * None

Starting date	16 December 2020
Contact information	Gilberto Cruz Arteaga Coordinación de Investigación en Salud Distrito Federal 02000 Mexico gilberto.cruz@imss.gob.mx
Notes	• Recruitment status: recruiting • Prospective completion date: 12 February 2021 • Date last update posted: 22 December 2020 • Sponsor/funding: Gilberto Cruz Arteaga, Coordinación de Investigación en Salud, Mexico

NCT04703205

Study name	Study in COvid-19 Patients With iveRmectin (CORVETTE-01)
Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of record: trial register entries • Sample size: 240 • Setting: outpatient • Country: Japan • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04703205 • Date of registration: 11 January 2021

Participants	• Inclusion criteria
	  * Diagnosed with COVID-19 (including asymptomatic) by PCR test (SARS-CoV-2 nucleic acid detection) within 3 days before the qualification test
	  * SaO_2 in room air ≥ 95%
	  * Age ≥ 20 years at time of obtaining consent
	  * Weight ≥ 40 kg at time of qualification test
	  * Understanding the content of this clinical trial and can obtain written consent to participate in the clinical trial
	• Exclusion criteria
	  * Pregnant or breastfeeding women, or unwilling to prevent pregnancy by medically appropriate means for up to 7 days after study drug administration. Medically appropriate contraception means using a combination of ≥ 2 of the following: not having sexual intercourse, taking

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NCT04703205 *(Continued)*

	surgical sterilization such as vasectomy or intrauterine device, taking oral contraceptive, using condoms * Severe liver damage (AST or ALT at the time of qualification test is > 3 times the upper limit of institutional standard and total bilirubin is > 2 times upper limit of institutional standard value), renal disorder (estimated glomerular filtration rate of eligibility test value ≤ 30 mL/minute/1.73m^2) * Hypersensitivity to ivermectin * History of severe drug allergies such as Stevens-Johnson syndrome, toxic epidermal necrolysis * Received prespecified prohibited medication within the past month (within the past 6 months for biologicals), or those who need to use prespecified prohibited medication during the clinical trial period * Participating in other clinical trials or who have participated in other clinical trials within 30 days before obtaining consent * Person considered unsuitable for this clinical trial by the principal investigator
Interventions	• Details of intervention * Type and dose: ivermectin 0.2 mg/kg, single dose * Route of administration: oral • Treatment details of control group * Placebo • Concomitant therapy: NA
Outcomes	• Primary study outcome * Period until the COVID-19 PCR test (SARS-CoV-2 nucleic acid detection) becomes negative within 14 days • Relevant review outcomes planned * None • Additional study outcomes * None
Starting date	16 September 2020
Contact information	Kunihiro K Yamaoka, PhD Kitasato University Sagamihara Kanagawa Japan yamaoka@med.kitasato-u.ac.jp
Notes	• Recruitment status: recruiting • Prospective completion date: 30 September 2021 • Date last update posted: 8 March 2021 • Sponsor/funding: Kitasato University

NCT04712279

Study name	The (HD)IVACOV Trial (The High-Dose IVermectin Against COVID-19 Trial)
Methods	• Trial design: triple-blind RCT with 3 parallel arms • Type of record: trial register entry • Sample size: 294 • Setting: outpatient • Country: Brazil • Language: English

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NCT04712279 *(Continued)*

	• Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04712279 • Date of registration: 15 January 2021
Participants	• Inclusion criteria * Age ≥ 18 years * Laboratory-confirmed positive SARS-CoV-2 RT-PCR test within 7 days prior to randomization * Clinical status on the COVID-19 Ordinal Scale 1–3 * Participant (or legally authorized representative) gives written informed consent prior to performing any study procedures * Participant (or legally authorized representative) agree that they will not participate in another COVID-19 trial during this study • Exclusion criteria * Enrolled in a study to investigate a treatment for COVID-19 * Require oxygen use, hospitalization, or mechanical ventilation * Tachycardia (heart rate > 150 beats per minute) or hypotension (systolic/diastolic blood pressure < 90/60 mmHg) * Allergic to the investigational product or similar drugs (or any excipients) * QTcF > 450 msecond * Uncontrolled medical conditions that could compromise participation in the study – uncontrolled hypertension (systolic/diastolic blood pressure > 220/120 mmHg), uncontrolled hypothyroidism (thyroid-stimulating hormone > 10 IU/L), uncontrolled diabetes mellitus (glycosylated haemoglobin > 12%) * ALT or AST > 5 times the upper limit of normal * Estimated glomerular filtration rate < 30 mL/minute or requiring dialysis * Person (or legally authorized representative) unwilling or unable to provide informed consent
Interventions	• Details of intervention * Type and dose ☐ Intervention 1: ivermectin 0.6 mg/kg, once daily for 5 days ☐ Intervention 2: ivermectin 1 mg/kg, once daily for 5 days * Route of administration: NR • Treatment details of control group * Placebo with standard of care • Concomitant therapy: standard of care including hydroxychloroquine administered in both study arms
Outcomes	• Primary study outcome * WHO Clinical Progression Scale at 14 days • Relevant review outcomes planned: * Proportion of deaths at 28 days * Overall duration of clinical manifestations within 14 days

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NCT04712279 *(Continued)*

- Additional study outcomes:
  * WHO COVID-19 Ordinal Scale for Clinical Improvement at 7 days
    - ☐ Proportion of participants needing oxygen use within 28 days
    - ☐ Proportion of participants needing high-flow oxygen therapy or non-invasive ventilation within 28 days
    - ☐ Proportion of hospitalizations at 28 days
    - ☐ Proportion of mechanical ventilation use at 28 days
    - ☐ Duration of hospitalization within 28 days
  * Time-to-recovery within 28 days
  * Viral load at 5 days
  * Positivity rate of RT-PCR SARS-CoV-2 (qualitative analysis) at 5 days
  * Duration of fatigue, ansomia within 14 days
  * Proportion of participants needing additional drugs or interventions within 28 days
  * Proportion of pressors use at 28 days
  * Proportion of post-COVID mental, physical, and overall symptoms at 30, 60, and 90 days
  * Duration of new oxygen use within 28 days
  * Duration of mechanical ventilation within 28 days
  * Proportion of increased ultrasensitive CRP, erythrocyte sedimentation rate, eosinophils at 1, 3, and 7 days
  * Proportion of increased D-dimer at 7 days
  * Disease duration

Starting date	25 January 2021
Contact information	Flavio A Cadegiani, MD, PhD Corpometria Institute +55 61 99650.6111 flavio.cadegiani@gmail.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 20 April 2021 • Date last update posted: 15 January 2021 • Sponsor/funding: Corpometria Institute

NCT04727424

Study name	Repurposed approved therapies for outpatient treatment of patients with early-onset COVID-19 and mild symptoms
Methods	• Trial design: quadruple-blind RCT with 4 parallel arms, only 2 arms relevant; the third arm investigates fluvoxamine, the fourth arm investigates metformin • Type of record: trial register entry • Sample size: 2724 • Setting: outpatient • Country: Brazil • Language: English • Number of centres: 6 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04727424 • Date of registration: 27 January 2021

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NCT04727424 *(Continued)*

Participants	• Inclusion criteria * Age > 18 years with the ability to provide free and informed consent * Acute influenza-like symptoms < 7 days * At least 1 enhancement factor ☐ Age > 50 years ☐ Diabetes mellitus requiring oral medication or insulin ☐ Systemic arterial hypertension requiring at least 1 oral medication for blood pressure control ☐ Known cardiovascular diseases (heart failure, congenital heart disease, valvar heart valve disease, coronary artery disease, cardiomyopathies) ☐ Symptomatic lung disease (emphysema, chronic bronchitis) ☐ People with symptomatic asthma requiring chronic use of agents for control of symptoms ☐ Smoking ☐ Obesity, defined as body mass index > 30 kg /m^2 bodyweight ☐ Received transplant ☐ Stage IV chronic kidney disease or receiving dialysis ☐ Immunosuppressed/using corticosteroid therapy (equivalent to prednisone ≥ 10 mg/day) or immunosuppressive therapy, or both) ☐ History of cancer in the last 5 years or undergoing treatment of a current cancer ☐ Chronic renal disease KDIGO (Kidney Disease Improving Global Outcomes) IV or end-stage renal disease on chronic ambulatory renal replacement therapy * Positive rapid test for SARS-CoV-2 antigen performed on occasion of the screening or with a positive SARS-CoV-2 diagnostic test within 7 days of the onset of symptoms. * Willingness to use the proposed investigative treatment and follow the protocol-related procedures foreseen in the research

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NCT04727424 *(Continued)*

- Exclusion criteria
  * Negative SARS-CoV-2 test
  * Influenza-like symptom onset ≥ 8 days
  * People with COVID-19 being referred for hospitalization
  * History of SARS-CoV-2 vaccine shot
  * Acute respiratory conditions due to other causes
  * Dyspnoea secondary to other acute and chronic respiratory causes or infections (e.g. decompensated COPD, acute bronchitis, pneumonia, primary pulmonary arterial hypertension)
  * Acute influenza-like condition presenting with ≥ 1 of the criteria below:
    ☐ Respiratory rate > 28 breaths/minute
    ☐ SaO_2 < 90% or < 93% in nasal oxygen therapy at 10 L/minute
    ☐ PaO_2/FIO_2 < 300 mmHg
  * Using serotonin reception inhibitors (donepezil, sertraline)
  * Use of the following medications in the last 14 days
    ☐ Monoamine oxide inhibitors: phenelzine, tranylcypromine, selegiline, isocarboxazide, moclobemide
    ☐ Use of iodinated contrasts during start of treatment through D14
    ☐ Use of antiretroviral agents
  * Severe psychiatric disorders or major uncontrolled depression or controlled with any of the prohibited drugs above
  * Pregnant or breastfeeding women
  * History of severe ventricular cardiac arrhythmia (ventricular tachycardia, people with ventricular fibrillation recovered) or long QT syndrome
  * History of diabetic ketoacidosis or clinical condition that maintains persistent acidosis
  * Surgical procedure or use of contrast designed to occur during treatment or up to 4 days after the last dose of the study medication
  * Current daily or uncontrolled alcoholism
  * History of seizures in the last month or uncontrolled medical condition
  * Clinical history of liver cirrhosis or Child-Pugh C classification
  * Known severe degenerative neurological diseases or serious mental disorders
  * Inability of the patient or representative to give consent or adhere to the procedures proposed in the protocol
  * Known hypersensitivity or intolerance to fluvoxamine, ivermectin or metformin
  * Inability to take oral or sublingual medications
  * Inability to follow protocol-related procedures

Interventions

- Details of intervention for relevant arms
  * Type and dose: ivermectin 6 mg, once daily for 3 days
  * Route of administration: oral
- Treatment details of control group
  * Placebo
- Concomitant therapy: NA

Outcomes

- Primary study outcome
  * Evaluation of emergency department visits and observation unit stay > 6 hours
  * Hospitalization due to COVID-19 progression within 28 days
- Relevant review outcomes planned
  * Adverse events at 28 days

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NCT04727424 *(Continued)*

	• Additional study outcomes * Change in viral load at 3 and 7 days * Time to > 50% clinical symptoms changes (self-reported) within 28 days * Number of days with respiratory symptoms since randomization within 28 days * All-cause and COVID-19 related hospitalizations within 28 days * All-cause mortality at 28 days * Cardiovascular death, respiratory death at 28 days * Health and functioning after COVID-19 disease at 14 and 28 days * WHO scale for clinical improvement at 28 days * Adherence of study drug within 10 days
Starting date	19 January 2021 CARDRESEARCH – Cardiologia Assistencial e de Pesquisa Belo Horizonte, Minas Gerais 30150240 Brazil
Contact information	Gilmar Reis, MD, PhD
Notes	• Recruitment status: recruiting • Prospective completion date: 1 March 2022 • Date last update posted: 24 March 2021 • Sponsor/funding: CARDRESEARCH – Cardiologia Assistencial e de Pesquisa

NCT04729140

Study name	An outpatient clinical trial using ivermectin and doxycycline in COVID-19 positive patients at high risk to prevent COVID-19 related hospitalization
Methods	• Trial design: double-blind RCT with 3 parallel arms, only 2 arms relevant; the third arm investigates doxycycline • Type of record: trial register entry • Sample size: 150 • Setting: outpatient • Country: USA • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04729140 • Date of registration: 28 January 2021

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NCT04729140 *(Continued)*

Participants	• Inclusion criteria
	  * Age ≥ 18 years
	  * Willing and able to provide verbal/telephonic/personal or computer-based informed consent
	  * Experiencing symptoms of COVID-19 illness and tested positive for SARS-CoV-2 with PCR, NAAT, or antigen testing
	  * Residents in a nursing home or long-term care facility
	  * Immunocompromised state, including solid organ transplant, HIV infection, other immune deficiency, immunosuppressant medication including systemic corticosteroids
	  * Chronic lung disease, including COPD, moderate-to-severe asthma, cystic fibrosis, pulmonary fibrosis
	  * Cardiovascular disease
	  * Cancer
	  * Hypertension
	  * Obesity (body mass index ≥ 30 kg/m^2)
	  * Diabetes mellitus
	  * Chronic kidney disease
	  * Chronic liver disease
	  * Cerebrovascular disease
	  * Neurological disorders including dementia
	  * Tobacco use disorders
	  * Haematological disorders, including sickle cell disease and thalassaemia
	• Exclusion criteria
	  * Age < 18 years
	  * Received any COVID vaccine within the last 30 days
	  * Contraindications to ivermectin or doxycycline
	  * History of seizure disorder or epilepsy
	  * History of myocardial infarction within last month
	  * Already receiving ivermectin or doxycycline for treatment of any other disease or disorder
	  * Allergies to ivermectin or doxycycline including angio-oedema, severe asthma, exfoliative dermatitis, Steven Johnson syndrome, or psoriasis
	  * History of angio-oedema, exfoliative dermatitis, Steven Johnson syndrome, psoriasis
	  * Currently pregnant or planning to conceive
	  * Breastfeeding
	  * History of prior *Clostridium difficile* infection

Interventions	• Details of intervention for relevant arms
	  * Type and dose: ivermectin 0.2 mg/kg, once daily for 2 days
	  * Route of administration: oral
	• Treatment details of control group
	  * Placebo
	• Concomitant therapy: NA

Outcomes	• Primary study outcome
	  * Decreased admission rate to the hospital secondary to respiratory illness related to COVID-19 within 5 weeks
	• Relevant review outcomes planned
	  * Mortality at 5 weeks

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NCT04729140 *(Continued)*

	• Additional study outcomes
	  * Decrease in total duration of symptoms secondary to respiratory illness related to COVID-19 within 5 weeks
	  * Assessment of various blood biomarkers (e.g. cytokines, glucose, electrolytes, CRP, liver enzymes, etc.) within 2 weeks
	  * Measurement of participants with new onset of various physical and psychological symptoms secondary to respiratory illness related to COVID-19 within 5 weeks

Starting date	28 December 2020
Contact information	Werther Marciales, MD MAX HEALTH, Subsero Health 2055 Wood Street, Suite 100 Sarasota, Florida, 34237 US werther40@msn.com
Notes	• Recruitment status: recruiting • Prospective completion date: 28 March 2021 • Date last update posted: 1 April 2021 • Sponsor/funding: Max Health, Subsero Health

NCT04834115

Study name	Efficacy of ivermectin in outpatients with non-severe COVID-19
Methods	• Trial design: triple-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 400 • Setting: outpatient • Country: Paraguay • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04834115 • Date of registration: 6 April 2021

Participants	• Inclusion criteria
	  * Positive diagnostic RT-qPCR or antigen test for SARS-CoV-2
	  * Symptomatic people with up to 8 days from the onset of symptoms
	  * Asymptomatic cases with up to 5 days of positive test for SARS-CoV-2
	  * Agreement to participate by signing the informed consent form

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NCT04834115 *(Continued)*

	• Exclusion criteria
	  * Severity criteria defined in the Coronavirus Disease Epidemiological and Laboratory Surveillance Guide (Version 3/11/2020)
	  * Pregnant or breastfeeding women
	  * Women of childbearing age and without commitment to use contraceptive methods during the study
	  * Inability to complete the study
	  * Current treatment with drugs known to interact with ivermectin
	  * Known intolerance to ivermectin, its derivate, or any of its excipients
	  * Known Child-Pugh C liver disease
	  * Prior ivermectin consumption in the 10 days prior to study entry

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.2 mg/kg, single dose
	  * Route of administration: oral
	• Treatment details of control group
	  * Placebo
	• Concomitant therapy: NA

Outcomes	• Primary study outcome
	  * Proportion of participants with hospitalization criteria at 30 days
	• Relevant review outcomes planned
	  * Proportion of participants with ivermectin adverse events within 30 days
	• Additional study outcomes
	  * Proportion of participants with COVID-19 signs and symptoms up to 14 days
	  * Proportion of cohabitants who had COVID-19 after the index case up to 30 days
	  * Quantitative levels of IgG for SARS-CoV-2 measured by enzyme-linked immunosorbent assay

Starting date	17 November 2020
Contact information	Gabriela Avila, MD, MSc, PhD Facultad de Ciencias Médicas - Universidad Nacional de Asunción Asunción 111421 Paraguay mavila@med.una.py
Notes	• Recruitment status: recruiting • Prospective completion date: 30 May 2021 • Date last update posted: 6 April 2020 • Sponsor/funding: Universidad Nacional de Asunción

NCT04836299

Study name	Clinical trial to "Study the Efficacy and Therapeutic Safety of Ivermectin: (SAINTBO)"
Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 90 • Setting: inpatient • Country: Bolivia • Language: English • Number of centres: 1

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NCT04836299 *(Continued)*

	• Study purpose (treatment, prevention): treatment • Trial registration number: NCT04836299 • Date of registration: 8 April 2021
Participants	• Inclusion criteria * Confirmed case of COVID-19 in national reference hospitals – COVID sentinel hospitals. * Men and women aged 18–75 years inclusive * Supply of signed and dated informed consent form * Declared availability to comply with all study procedures and availability for duration of the study * In good general health with mild or moderate symptoms during the first week of disease evolution (onset of symptoms maximum 7 days before recruitment) * Ability to take oral medications and be willing to adhere to the medication consumption regimen prescribed in the study * Must, in the opinion of the principal investigator, be able to comply with all requirements of the clinical trial (including home monitoring during isolation) * Able and willing to comply with the requirements of the protocol. Voluntarily signed informed consent obtained prior to any proceeding related to the trial • Exclusion criteria * History of ivermectin allergy * Hypersensitivity to any component of ivermectin or the excipients of the brand to be used * COVID-19 pneumonia: diagnosed by the treating physician or identified on a chest x-ray * Fever or cough present > 48 hours * IgG positive against SARS-CoV-2 by a rapid diagnostic test * Recent travel history to *Loa loa* endemic countries (Angola, Cameroon, Central African Republic, Chad, the Democratic Republic of the Congo, Ethiopia, Equatorial Guinea, Gabon, Republic of the Congo, Nigeria, and Sudan) * Current use of quinidine, amiodarone, diltiazem, spironolactone, verapamil, clarithromycin, erythromycin, itraconazole, ketoconazole, ciclosporin, tacrolimus, indinavir, ritonavir, or cobicistat * Use of critical drugs such as warfarin
Interventions	• Details of intervention * Type and dose: ivermectin 0.6 mg/kg, single dose * Route of administration: oral • Treatment details of control group * Placebo • Concomitant therapy: NA
Outcomes	• Primary study outcome * Evolution of viral load within 3 days * Clinical remission at 28 days • Relevant review outcomes planned * Clinical signs of toxicity or adverse effects within 28 days * Need for supplemental oxygen at 28 days * Need for mechanical ventilation at 21 days • Additional study outcomes * Hospital stay within 3 months
Starting date	8 May 2021
Contact information	Jorge L Aviles, MPH Universidad Mayor de San Simón Cochabamba Bolivia

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NCT04836299 *(Continued)*

Notes	• Recruitment status: not yet recruiting • Prospective completion date: 5 December 2021 • Date last update posted: 8 April 2021 • Sponsor/funding: Universidad Mayor de San Simón

NCT04885530

Study name	ACTIV-6: COVID-19 study of repurposed medications
Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 15,000 • Setting: outpatient • Country: USA • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04885530 • Date of registration: 13 May 2021

Participants	• Inclusion criteria
	  * Completed informed consent
	  * Age ≥ 30 years
	  * Confirmed SARS-CoV-2 infection by any authorized or approved PCR or antigen test collected within 10 days of screening
	  * ≥ 2 current symptoms of acute infection for ≤ 7 days. Symptoms include the following: fatigue, dyspnoea, fever, cough, nausea, vomiting, diarrhoea, body aches, chills, headache, sore throat, nasal symptoms, new loss of sense of taste or smell
	• Exclusion criteria
	  * Prior diagnosis of COVID-19 infection (> 10 days from screening)
	  * Current or recent (within 10 days of screening) hospitalization
	  * Known allergy/sensitivity or any hypersensitivity to components of the study drug or placebo
	  * Known contraindication(s) to study drug including prohibited concomitant medications

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.3–0.4 mg/kg, once daily for 3 days
	  * Route of administration: oral
	• Treatment details of control group
	  * Placebo
	• Concomitant therapy: NA

Outcomes	• Primary study outcome
	  * Number of hospitalizations measured by participant reports up to 14 days
	  * Number of deaths measured by participant reports up to 14 days
	  * Number of symptoms measured by participant reports up to 14 days
	• Relevant review outcomes planned
	  * Number of hospitalizations measured by patient reports up to 14 days
	  * Number of deaths measured by patient reports up to 28 days

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NCT04885530 *(Continued)*

	• Additional study outcomes * Change in COVID Clinical Progression Scale up to 28 days * Number of hospitalizations measured by participant reports up to 28 days * Number of symptom resolutions measured by participant reports up to 28 days * Change in quality of life measured by the PROMIS-29 at 7, 14, 28, and 29 days * Composite score of hospitalizations, urgent care visits, and emergency department visits measured by participant reports up to 28 days
Starting date	May 2021
Contact information	Allison DeLong Duke Clinical Research Institute Durham 27701 North Carolina USA allison.hayes@duke.edu
Notes	• Recruitment status: not yet recruiting • Prospective completion date: March 2023 • Date last update posted: 13 May 2021 • Sponsor/funding: Susanna Naggie, National Center for Advancing Translational Science (NCATS), Vanderbilt University Medical Center

NCT04886362

Study name	Ivermectina Colombia (IVERCOL)
Methods	• Trial design: quadruple-blin RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 966 • Setting: outpatient • Country: Colombia • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04886362 • Date of registration: 14 May 2021
Participants	• Inclusion criteria * Age ≥ 18 years * Positive antigen test or RT-PCR for SARS-CoV-2 * < 7 days from symptoms onset * Indication for outpatient management * Mild disease according to the official guide "Pneumonia Diagnosis and Treatment Scheme for Novel Coronavirus Infection (Trial Version 8):" People with mild symptoms, with or without radiological signs of pneumonia, with oxygen saturation > 90% * Able to provide consent to participate

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NCT04886362 *(Continued)*

	• Exclusion criteria * People who at the time of admission require hospitalization or supplemental oxygen, or both * History of allergy to ivermectin * Medical history of liver disease * Belong to another clinical trial evaluating the efficacy of an investigational drug against COVID-19 * Immunosuppression or HIV, acute or chronic kidney failure, current neoplasia * Current use of warfarin, erdafitinib, or quinidine * Received vaccination for SARS-CoV-2 * Ivermectin consumption prior to inclusion in the research protocol * Not accepting of the conditions of home care and monitoring * Desists from participating in the study * Pregnancy or breastfeeding women
Interventions	• Details of intervention * Type and dose: ivermectin 0.6 mg/kg, twice daily for 5 days * Route of administration: oral • Treatment details of control group * Placebo • Concomitant therapy: NA
Outcomes	• Primary study outcome * Composite outcome, first outcome that occurs in each participant during 28 days ☐ Hypoxaemia (oxygen saturation ≤ 90%) and need for supplemental oxygen in home care programme or ☐ Need for hospitalization includes general bed or ICU or ☐ Death from any cause • Relevant review outcomes planned * Number and type of serious and non-serious adverse events within 28 days • Additional study outcomes * Proportion of participants with ≥ 4 points on the WHO scale at 28 days * Number of days with supplemental oxygen requirement at 28 days * Number of days on ICU management at 28 days * Number of days with endotracheal intubation at 28 days * Number of days of hospitalization at 28 days
Starting date	July 2021
Contact information	Juan Carlos Chacón Jimenez, MD ceivercol@suramericana.com.co
Notes	• Recruitment status: not yet recruiting • Prospective completion date: September 2021 • Date last update posted: 14 May 2021 • Sponsor/funding: Ayudas Diagnosticas Sura S.A.S.

NCT04894721

Study name	Prophylaxis for COVID-19: ivermectin in close contacts of COVID-19 cases (IVERNEX-TUC)
Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 750

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NCT04894721 *(Continued)*

	• Setting: after high-risk exposure • Country: Argentina • Language: English • Number of centres: NR • Study purpose (treatment, prevention): prevention • Trial registration number: NCT04894721 • Date of registration: 20 May 2021

Participants	• Inclusion criteria
	  * Age > 18 years
	  * Women of childbearing age with negative pregnancy test
	  * In close contact group or epidemiological nexus of a positive COVID-19 case
	  * Able to understand and grant informed consent
	  * RT-PCR with a negative result
	• Exclusion criteria
	  * Hypersensitivity or allergy to any component of the drug under evaluation
	  * Age < 18 years
	  * Use of immunosuppressants (including systemic corticosteroids) in last 30 days
	  * Pregnant or lactating
	  * Other acute infectious diseases
	  * Autoimmune disease or chronic decompensated diseases, or both
	  * Received a vaccine for COVID-19 (1 or 2 doses) or who have received ivermectin (prior to 30 days of the study) or who are participating in another COVID-19 prophylaxis study

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.6 mg/kg, once daily at 1 and 7 days
	  * Route of administration: oral
	• Treatment details of control group
	  * Placebo
	• Concomitant therapy: standard biosecurity care used in both study arms

Outcomes	• Primary study outcome
	  * Number of participants diagnosed with COVID-19 at 14 days
	• Relevant review outcomes planned
	  * Number of participants diagnosed with COVID-19 at 14 days
	• Additional study outcomes
	  * Contagion risk within 2 weeks
	  * Prophylactic effect associated with patient's pre-existing comorbidity

Starting date	20 March 2021
Contact information	Maria Peral, PhD SI.PRO.SA, Ministerio de Salud Pública Tucumán 4000 Argentina mperal@fm.unt.edu.ar
Notes	• Recruitment status: recruiting • Prospective completion date: 30 May 2021 • Date last update posted: 20 May 2021 • Sponsor/funding: Ministry of Public Health, Argentina

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PACTR202102588777597

Study name	Ivermectin Treatment Trial (ITT)

Methods	• Trial design: open-label RCT with 2 parallel arms
	• Type of record: trial register entry
	• Sample size: 240
	• Setting:
	  * Substudy treatment: inpatient
	  * Substudy prevention: after high-risk exposure
	• Country: Nigeria
	• Language: English
	• Number of centres: 2
	• Study purpose (treatment, prevention): treatment and prevention
	• Trial registration number: PACTR202102588777597
	• Date of registration: 12 February 2021

Participants	• Inclusion criteria
	  * Substudy treatment
	  ☐ Provide written informed consent prior to initiation of any study procedures
	  ☐ Understand and agree to comply with planned study procedures
	  ☐ Agree to the collection of oropharyngeal swabs and venous blood per protocol
	  ☐ Adults aged ≥ 18 years at enrolment
	  ☐ Laboratory-confirmed SARS-CoV-2 infection as determined by RT-PCR in any specimen no more than 72 hours prior to randomisation
	  * Substudy prevention
	  ☐ Household contacts of adults with laboratory-positive COVID-19
	• Exclusion criteria
	  * Substudy treatment
	  ☐ American Society of Anaesthesiologists class ≥ 3
	  ☐ Stage 4 severe chronic kidney disease or requiring dialysis (estimated glomerular filtration rate < 30)
	  ☐ Pregnant or breastfeeding
	  ☐ Anticipated transfer to another facility which is not a study site within 72 hours
	  ☐ Haematological diseases (glucose-6-phosphate dehydrogenase deficiency)
	  ☐ Chronic liver and kidney disease and reaching end-stage
	  ☐ Arrhythmia and chronic heart disease
	  ☐ Retinal disease or hearing loss
	  ☐ Mental illness
	  ☐ Skin disorders (including rash, dermatitis, psoriasis)
	  ☐ Allergy to ivermectin or its analogues
	  * Substudy prevention
	  ☐ NR

Interventions	• Details of intervention
	  * Type and dose: ivermectin 0.2 mg/kg, once daily at 1 and 3 days
	  * Route of administration: oral
	• Treatment details of control group
	  * No treatment except standard of care
	• Concomitant therapy: standard of care including co-amoxiclav, zinc, calcium, vitamin C and D administered in both study arms

Outcomes	• Primary study outcome
	  * Substudy treatment: mortality at 7 days
	  * Substudy prevention: NR

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PACTR202102588777597 *(Continued)*

	• Relevant review outcomes planned
	  * SARS-CoV-2 clearance at 4 and 6 days
	• Additional study outcomes
	  * Substudy treatment: resolution of symptoms assessed by clinical status and daily National Early Warning Score until discharge and at 7 days; SARS-CoV-2 clearance at 1 day
	  * Substudy prevention: NR

Starting date	3 February 2021
Contact information	Akin Osibogun Lagos Nigeria akinosibogun@yahoo.co.uk
Notes	• Recruitment status: recruiting • Prospective completion date: 3 March 2022 • Date last update posted: 12 February 2021 • Sponsor/funding: Lagos State Ministry of Health

PACTR202102848675636

Study name	Double blind, community-based, randomized controlled trial on the use of ivermectin as post exposure chemo-prophylaxis for COVID-19 among high risk individuals in Lagos (IVERPEPCOV) COVID-19
Methods	• Trial design: double-blind RCT with 6 parallel arms • Type of record: trial register entry • Sample size: 2000 • Setting: after high-risk exposure • Country: Nigeria • Language: English • Number of centres: 2 • Study purpose (treatment, prevention): prevention • Trial registration number: PACTR202102848675636 • Date of registration: 11 February 2021

Participants	• Inclusion criteria
	  * Provision of signed and dated informed consent form
	  * Stated willingness to comply with all study procedures and availability for the duration of the study
	  * Men or women, aged 18–85 years
	  * Close contacts (6 m with no personal protective equipment) to confirmed RT-PCR-positive individual
	  * Ability to take oral medication and be willing to adhere to the study regimen
	  * Women of reproductive potential: negative pregnancy test and last menstrual period date
	  * Agreement to adhere to Lifestyle Considerations throughout study duration

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PACTR202102848675636 *(Continued)*

	• Exclusion criteria
	  * Current use of cytochrome P4 enzyme inducers such as azole group of oral antifungal medication (ketoconazole, itraconazole), warfarin
	  * Non-exposure to people with COVID-19
	  * Refuse to give informed consent
	  * Pregnant and lactating women
	  * Known hypersensitivity to ivermectin
	  * Have had treatment with any investigational drug within 2 weeks prior to randomization
	  * Children, stigmatized population, institutionalized people
	  * Previously diagnosed and recovered from COVID-19
	  * Severely ill people such as those on ventilators, hepatic or renal impairment, or unconscious
	  * People receiving drugs that can have serious interactions with the trial drug including barbiturates (e.g. asphennobarbital, butalbital), benzodiazepines (e.g. clonazepam, lorazepam), sodium oxybate (gamma-hydroxybutyrate), valproic acid and herbal medicines
	• Treatment with another investigational drug

Interventions	• Details of intervention
	  * Type and dose
	  ☐ Intervention 1: ivermectin 0.2 mg/kg, once weekly for 4 weeks
	  ☐ Intervention 2: ivermectin 0.2 mg/kg, alternate week for 2 doses
	  ☐ Intervention 3: ivermectin 0.2 mg/kg, once monthly for 3 months
	  * Route of administration: oral
	• Treatment details of control group
	  * 3 placebo regimens according to each intervention arm
	• Concomitant therapy
	  * NA

Outcomes	• Primary study outcome
	  * Number developing COVID-19 clinical disease at 14 days, subsequently confirmed by RT-PCR
	• Relevant review outcomes planned
	  * Number developing COVID-19 clinical disease at 14 days, subsequently confirmed by RT-PCR
	  * Number with serious adverse outcome within the study period
	• Additional study outcomes
	  * Number developing severe or critical COVID-19

Starting date	1 March 2021
Contact information	Olufemi Babalola Department of Surgery Bingham University Karu Lagos Nigeria bablo57@gmail.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 31 October 2021 • Date last update posted: 11 February 2021 • Sponsor/funding: Federal Government of Nigeria

Vallejos 2020

Study name	Ivermectin to prevent hospitalizations in COVID-19 (IVERCORCOVID19)

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Vallejos 2020 *(Continued)*

Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 500 • Setting: outpatient • Country: Argentina • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04529525 • Date of registration: 27 August 2020
Participants	• Inclusion criteria * Age > 18 years who reside in the province of Corrientes at the time of diagnosis * Confirmed diagnosis of COVID-19 by PCR test for detection of SARS-CoV-2 in the last 48 hours * Women of childbearing age, using a contraceptive method of proven efficacy and safety (barrier, hormonal, or permanent contraceptives) for ≥ 3 months prior to inclusion in the present study and for the entire duration of the study and until at least 30 days after the end of study. A woman will be considered to have no reproductive capacity if she is postmenopausal (≥ 2 years without her menstrual cycles) or if she has undergone surgical sterilization (≥ 1 month before the time of inviting her to participate in this study) * Weight at inclusion > 48 kg * Signed informed consent for participation • Exclusion criteria * Pregnant or breastfeeding women * Known allergy to ivermectin or some of the components of ivermectin tablets or placebo * Current use of home oxygen * That require hospitalization due to COVID-19 at the time of diagnosis or history of hospitalization for COVID-19 * Presence of malabsorptive syndrome * Presence of any other concomitant acute infectious disease * History of severe liver disease, e.g. liver cirrhosis * Need or use of antiviral drugs at the time of admission for another viral pathology other than COVID-19 * Need or use of hydroxychloroquine or chloroquine * Use of ivermectin up to 7 days prior to randomization * Receiving dialysis or required dialysis in the last 2 months or who plan to in the next 2 months * Current participation or in the last 30 days in a research study that has included the administration of a drug
Interventions	• Details of intervention * Type and dose: ivermectin 12–24 mg (weight-adjusted), twice within 24 hours * Route of administration: oral • Treatment details of control group: * Placebo • Concomitant therapy * NA
Outcomes	• Primary study outcome * Percentage of hospitalization of medical cause in people with COVID-19 at 30 days (in average) • Relevant review outcomes planned * Negative swab at 3 (SD 1) days and 12 (SD 2) days after entering the study * Incidence of treatment-emergent adverse events at 30 days (in average)

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Vallejos 2020 *(Continued)*

	• Additional study outcomes * Time to hospitalization * Time to invasive mechanical ventilation support * Percentage of use of invasive mechanical ventilation support at 30 days (in average) * Percentage of dialysis in each arm at 30 days (in average)
Starting date	19 August 2020
Contact information	Dr Julio Vallejos Ministry of Public Health of the Province of Corrientes Corrientes 3400 Argentina juliovallejos@funcacorr.org.ar
Notes	• Recruitment status: recruiting • Prospective completion date: 15 March 2021 • Date last update posted: 16 February 2021 • Sponsor/funding: Instituto de Cardiología de Corrientes

ALT: alanine aminotransferase; AST: aspartate aminotransferase; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; CT: computer tomography; ICU: intensive care unit; IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; NA: not available; NAAT: nucleic acid amplification test; NR: not reported; PaO_2/FIO_2: partial pressure of oxygen/fraction of inspired oxygen; PCR: polymerase chain reaction; RCT: randomized controlled trial; RNA: ribonucleic acid; RT-PCR: reverse transcription polymerase chain reaction; RT-qPCR: reverse transcription quantitative polymerase chain reaction; SaO_2: oxygen saturation; SD: standard deviation; WHO: World Health Organization.

RISK OF BIAS

Legend: ✓ Low risk of bias ✗ High risk of bias ~ Some concerns

Risk of bias for analysis 1.1 All-cause mortality up to 28 days (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.1.1 Moderate disease (WHO 4 to 5)						
Gonzalez 2021	~	~	✓	✓	~	~
Kirti 2021	✓	~	✓	✓	✓	~

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Risk of bias for analysis 1.2 Worsening of clinical status – need for invasive mechanical ventilation up to 28 days (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.2.1 Moderate disease (WHO 4 to 5)						
Gonzalez 2021	~	~	✓	✓	~	~
Kirti 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 1.3 Worsening of clinical status – need for oxygen up to 28 days (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.3.1 Moderate disease (WHO 4 to 5)						
Ahmed 2020	~	~	✓	✓	~	~

Risk of bias for analysis 1.4 Improvement of clinical status – participants discharged without respiratory deterioration or death at 28 days (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.4.1 Moderate disease (WHO 4 to 5)						
Gonzalez 2021	~	~	✓	✓	~	~

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Risk of bias for analysis 1.5 Any adverse events within 28 days (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.5.1 Moderate disease (WHO 4 to 5)						
Mohan 2021	✓	✓	✓	~	~	~

Risk of bias for analysis 1.6 Any adverse events within 28 days (secondary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.6.1 Moderate disease (WHO 4 to 5)						
Krolewiecki 2020	✓	✓	✓	✗	✓	✗
Mohan 2021	✓	✓	✓	~	~	~
Pott-Junior 2021	✓	✓	✓	✗	~	✗
Shah Bukhari 2021	~	~	✗	✗	~	✗

Risk of bias for analysis 1.7 Serious adverse events within 28 days (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.7.1 Moderate disease (WHO 4 to 5)						
Krolewiecki 2020	✓	✓	✓	~	~	~
Mohan 2021	✓	✓	✓	~	✓	~

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Risk of bias for analysis 1.8 Serious adverse events within 28 days (secondary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.8.1 Moderate disease (WHO 4 to 5)						
Ahmed 2020	~	~	✓	✗	~	✗
Krolewiecki 2020	✓	✓	✓	~	~	~
Mohan 2021	✓	✓	✓	~	✓	~

Risk of bias for analysis 1.9 Admission to intensive care unit (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.9.1 Moderate disease (WHO 4 to 5)						
Kirti 2021	✓	~	✓	✓	✓	~
Pott-Junior 2021	✓	✓	✓	✓	~	~

Risk of bias for analysis 1.10 Duration of hospitalization (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.10.1 Moderate disease (WHO 4 to 5)						
Ahmed 2020	~	~	✓	✓	~	~

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Risk of bias for analysis 1.11 Viral clearance at 3 days (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.11.1 Moderate disease (WHO 4 to 5)						
Ahmed 2020	~	~	✓	✓	~	~
Mohan 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.12 Viral clearance at 3 days (secondary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.12.1 Moderate disease (WHO 4 to 5)						
Ahmed 2020	~	~	✓	✓	~	~
Kishoria 2020	~	~	✗	✓	~	✗
Mohan 2021	✓	✓	✓	✓	✓	✓
Shah Bukhari 2021	~	~	✗	✓	✗	✗

Risk of bias for analysis 1.13 Viral clearance at 7 days (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.13.1 Moderate disease (WHO 4 to 5)						
Ahmed 2020	~	~	✓	✓	~	~
Mohan 2021	✓	✓	✓	✓	✓	✓

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Risk of bias for analysis 1.14 Viral clearance at 7 days (secondary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.14.1 Moderate disease (WHO 4 to 5)						
Ahmed 2020	~	~	✓	✓	~	~
Kirti 2021	✓	~	✗	✓	✓	✗
Mohan 2021	✓	✓	✓	✓	✓	✓
Pott-Junior 2021	✓	✗	✓	✓	~	✗

Risk of bias for analysis 1.15 Viral clearance at 14 days (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.15.1 Moderate disease (WHO 4 to 5)						
Ahmed 2020	~	~	✓	✓	~	~

Risk of bias for analysis 1.16 Viral clearance at 14 days (secondary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.16.1 Moderate to severe disease (WHO 4 to 9)						
Ahmed 2020	~	~	✓	✓	~	~
Okumuş 2021	✗	✗	✗	✓	~	✗

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Risk of bias for analysis 2.1 All-cause mortality up to 28 days (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chaccour 2021	✓	✓	✓	✓	✓	✓
López-Medina 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 2.2 Worsening of clinical status – need for invasive mechanical ventilation up to 14 days (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
López-Medina 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 2.3 Worsening of clinical status – need for non-invasive mechanical ventilation or high flow up to 14 days (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
López-Medina 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 2.4 Symptom resolution – number of participants with symptoms resolved up to 14 days (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
López-Medina 2021	✓	~	✓	✓	✓	~

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Risk of bias for analysis 2.5 Duration to symptom resolution (secondary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Podder 2020	✗	~	✗	✗	~	✗

Risk of bias for analysis 2.6 Any adverse events within 28 days (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chaccour 2021	✓	✓	✓	✓	✓	✓
López-Medina 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 2.7 Serious adverse events within 28 days (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chaccour 2021	✓	✓	✓	~	~	~
López-Medina 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 2.8 Viral clearance at 7 days (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chaccour 2021	✓	✓	✓	✓	✓	✓

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Risk of bias for analysis 2.9 Viral clearance at 14 days (secondary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Podder 2020	✗	~	✗	✓	~	✗

Risk of bias for analysis 3.1 Development of clinical COVID-19 symptoms (secondary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Shoumann 2021	~	✓	~	✗	✓	✗

Risk of bias for analysis 3.2 Any adverse events within 14 days (secondary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Shoumann 2021	~	✓	~	✗	~	✗

Risk of bias for analysis 3.3 All-cause mortality up to 28 days (primary analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Shoumann 2021	~	✓	~	✓	~	~

DATA AND ANALYSES

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Comparison 1. Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in the inpatient setting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality up to 28 days (primary analysis)	2	185	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.14, 2.51]
1.1.1 Moderate disease (WHO 4 to 5)	2	185	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.14, 2.51]
1.2 Worsening of clinical status – need for invasive mechanical ventilation up to 28 days (primary analysis)	2	185	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.11, 2.59]
1.2.1 Moderate disease (WHO 4 to 5)	2	185	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.11, 2.59]
1.3 Worsening of clinical status – need for oxygen up to 28 days (primary analysis)	1	45	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3.1 Moderate disease (WHO 4 to 5)	1	45	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.4 Improvement of clinical status – participants discharged without respiratory deterioration or death at 28 days (primary analysis)	1	73	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.78, 1.35]
1.4.1 Moderate disease (WHO 4 to 5)	1	73	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.78, 1.35]
1.5 Any adverse events within 28 days (primary analysis)	1	152	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.50, 2.97]
1.5.1 Moderate disease (WHO 4 to 5)	1	152	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.50, 2.97]
1.6 Any adverse events within 28 days (secondary analysis)	4	314	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.61, 1.79]
1.6.1 Moderate disease (WHO 4 to 5)	4	314	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.61, 1.79]
1.7 Serious adverse events within 28 days (primary analysis)	2	197	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.07, 35.89]
1.7.1 Moderate disease (WHO 4 to 5)	2	197	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.07, 35.89]
1.8 Serious adverse events within 28 days (secondary analysis)	3	242	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.07, 35.89]
1.8.1 Moderate disease (WHO 4 to 5)	3	242	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.07, 35.89]
1.9 Admission to intensive care unit (primary analysis)	2	143	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.11, 2.51]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9.1 Moderate disease (WHO 4 to 5)	2	143	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.11, 2.51]
1.10 Duration of hospitalization (primary analysis)	1	45	Mean Difference (IV, Random, 95% CI)	-0.10 [-2.43, 2.23]
1.10.1 Moderate disease (WHO 4 to 5)	1	45	Mean Difference (IV, Random, 95% CI)	-0.10 [-2.43, 2.23]
1.11 Viral clearance at 3 days (primary analysis)	2	170	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.45, 2.32]
1.11.1 Moderate disease (WHO 4 to 5)	2	170	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.45, 2.32]
1.12 Viral clearance at 3 days (secondary analysis)	4	288	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.59, 5.04]
1.12.1 Moderate disease (WHO 4 to 5)	4	288	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.59, 5.04]
1.13 Viral clearance at 7 days (primary analysis)	2	159	Risk Ratio (M-H, Random, 95% CI)	1.82 [0.51, 6.48]
1.13.1 Moderate disease (WHO 4 to 5)	2	159	Risk Ratio (M-H, Random, 95% CI)	1.82 [0.51, 6.48]
1.14 Viral clearance at 7 days (secondary analysis)	4	265	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.76, 1.86]
1.14.1 Moderate disease (WHO 4 to 5)	4	265	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.76, 1.86]
1.15 Viral clearance at 14 days (primary analysis)	1	45	Risk Ratio (M-H, Random, 95% CI)	1.97 [1.13, 3.45]
1.15.1 Moderate disease (WHO 4 to 5)	1	45	Risk Ratio (M-H, Random, 95% CI)	1.97 [1.13, 3.45]
1.16 Viral clearance at 14 days (secondary analysis)	2	69	Risk Ratio (M-H, Random, 95% CI)	2.07 [1.28, 3.33]
1.16.1 Moderate to severe disease (WHO 4 to 9)	2	69	Risk Ratio (M-H, Random, 95% CI)	2.07 [1.28, 3.33]

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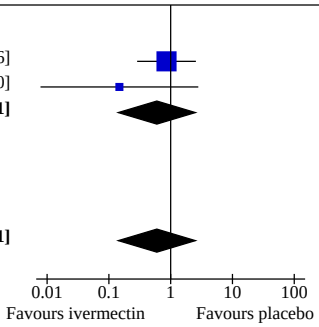
Analysis 1.1. Comparison 1: Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in the inpatient setting, Outcome 1: All-cause mortality up to 28 days (primary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
1.1.1 Moderate disease (WHO 4 to 5)												
Gonzalez 2021 (1)	5	36	6	37	79.5%	0.86 [0.29 , 2.56]	?	?	+	+	?	?
Kirti 2021 (2)	0	55	3	57	20.5%	0.15 [0.01 , 2.80]	+	?	+	+	+	?
Subtotal (95% CI)		**91**		**94**	**100.0%**	**0.60 [0.14 , 2.51]**						
Total events:	5		9									
Heterogeneity: Tau² = 0.36; Chi² = 1.28, df = 1 (P = 0.26); I² = 22%												
Test for overall effect: Z = 0.70 (P = 0.48)												
Total (95% CI)		**91**		**94**	**100.0%**	**0.60 [0.14 , 2.51]**						
Total events:	5		9									
Heterogeneity: Tau² = 0.36; Chi² = 1.28, df = 1 (P = 0.26); I² = 22%												
Test for overall effect: Z = 0.70 (P = 0.48)												
Test for subgroup differences: Not applicable												



Footnotes

(1) Time point (28 days), participants (WHO 5), intervention (ivermectin 12 mg or 18 mg daily for 5 days), comparator (placebo)

(2) Time point (28 days), participants (WHO 4 to 5), intervention (ivermectin 12 mg daily for 2 days), comparator (placebo)

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: All-cause mortality up to 28 days (primary analysis)

(C) Bias due to missing outcome data: All-cause mortality up to 28 days (primary analysis)

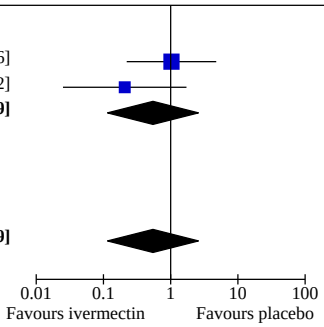
(D) Bias in measurement of the outcome: All-cause mortality up to 28 days (primary analysis)

(E) Bias in selection of the reported result: All-cause mortality up to 28 days (primary analysis)

(F) Overall bias: All-cause mortality up to 28 days (primary analysis)

Analysis 1.2. Comparison 1: Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in the inpatient setting, Outcome 2: Worsening of clinical status – need for invasive mechanical ventilation up to 28 days (primary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
1.2.1 Moderate disease (WHO 4 to 5)												
Gonzalez 2021 (1)	3	36	3	37	60.4%	1.03 [0.22 , 4.76]	?	?	+	+	?	?
Kirti 2021 (2)	1	55	5	57	39.6%	0.21 [0.03 , 1.72]	+	?	+	+	+	?
Subtotal (95% CI)		**91**		**94**	**100.0%**	**0.55 [0.11 , 2.59]**						
Total events:	4		8									
Heterogeneity: Tau² = 0.44; Chi² = 1.49, df = 1 (P = 0.22); I² = 33%												
Test for overall effect: Z = 0.76 (P = 0.45)												
Total (95% CI)		**91**		**94**	**100.0%**	**0.55 [0.11 , 2.59]**						
Total events:	4		8									
Heterogeneity: Tau² = 0.44; Chi² = 1.49, df = 1 (P = 0.22); I² = 33%												
Test for overall effect: Z = 0.76 (P = 0.45)												
Test for subgroup differences: Not applicable												



Footnotes

(1) Time point (28 days), participants (WHO 5), intervention (ivermectin 12 mg or 18 mg daily for 5 days), comparator (placebo)

(2) Time point (28 days), participants (WHO 4 to 5), intervention (ivermectin 12 mg daily for 2 days), comparator (placebo)

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Worsening of clinical status – need for invasive mechanical ventilation up to 28 days (primary analysis)

(C) Bias due to missing outcome data: Worsening of clinical status – need for invasive mechanical ventilation up to 28 days (primary analysis)

(D) Bias in measurement of the outcome: Worsening of clinical status – need for invasive mechanical ventilation up to 28 days (primary analysis)

(E) Bias in selection of the reported result: Worsening of clinical status – need for invasive mechanical ventilation up to 28 days (primary analysis)

(F) Overall bias: Worsening of clinical status – need for invasive mechanical ventilation up to 28 days (primary analysis)

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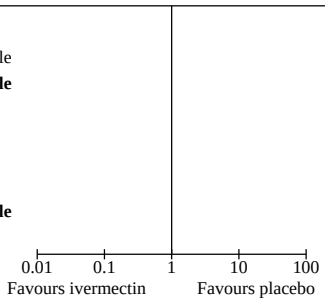
Analysis 1.3. Comparison 1: Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in the inpatient setting, Outcome 3: Worsening of clinical status – need for oxygen up to 28 days (primary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
1.3.1 Moderate disease (WHO 4 to 5)												
Ahmed 2020 (1)	0	22	0	23		Not estimable	?	?	+	+	?	?
Subtotal (95% CI)		**22**		**23**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
Total (95% CI)		**22**		**23**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
Test for subgroup differences: Not applicable												



Footnotes

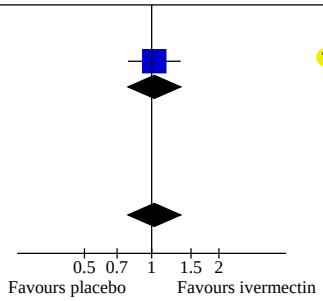
(1) Time point (14 days), participants (WHO 4), intervention (ivermectin 12 mg daily for 5 days), comparator (placebo)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Worsening of clinical status – need for oxygen up to 28 days (primary analysis)
(C) Bias due to missing outcome data: Worsening of clinical status – need for oxygen up to 28 days (primary analysis)
(D) Bias in measurement of the outcome: Worsening of clinical status – need for oxygen up to 28 days (primary analysis)
(E) Bias in selection of the reported result: Worsening of clinical status – need for oxygen up to 28 days (primary analysis)
(F) Overall bias: Worsening of clinical status – need for oxygen up to 28 days (primary analysis)

Analysis 1.4. Comparison 1: Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in the inpatient setting, Outcome 4: Improvement of clinical status – participants discharged without respiratory deterioration or death at 28 days (primary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
1.4.1 Moderate disease (WHO 4 to 5)												
Gonzalez 2021 (1)	27	36	27	37	100.0%	1.03 [0.78 , 1.35]	?	?	+	+	?	?
Subtotal (95% CI)		**36**		**37**	**100.0%**	**1.03 [0.78 , 1.35]**						
Total events:	27		27									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.20 (P = 0.84)												
Total (95% CI)		**36**		**37**	**100.0%**	**1.03 [0.78 , 1.35]**						
Total events:	27		27									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.20 (P = 0.84)												
Test for subgroup differences: Not applicable												



Footnotes

(1) Time point (28 days), participants (WHO 5), intervention (ivermectin 12 mg or 18 mg daily for 5 days), comparator (placebo)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Improvement of clinical status – participants discharged without respiratory deterioration or death at 28 days (primary an
(C) Bias due to missing outcome data: Improvement of clinical status – participants discharged without respiratory deterioration or death at 28 days (primary analysis)
(D) Bias in measurement of the outcome: Improvement of clinical status – participants discharged without respiratory deterioration or death at 28 days (primary analysis)
(E) Bias in selection of the reported result: Improvement of clinical status – participants discharged without respiratory deterioration or death at 28 days (primary analysis)
(F) Overall bias: Improvement of clinical status – participants discharged without respiratory deterioration or death at 28 days (primary analysis)

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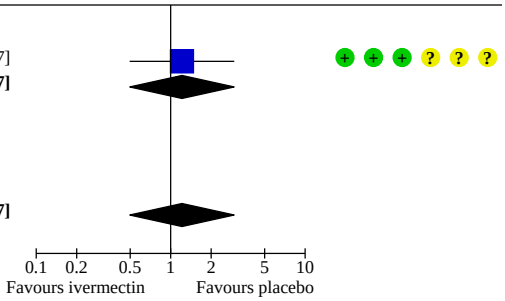
Analysis 1.5. Comparison 1: Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in the inpatient setting, Outcome 5: Any adverse events within 28 days (primary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Moderate disease (WHO 4 to 5)						
Mohan 2021 (1)	14	100	6	52	100.0%	1.21 [0.50 , 2.97]
Subtotal (95% CI)		**100**		**52**	**100.0%**	**1.21 [0.50 , 2.97]**
Total events:	14		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.42 (P = 0.67)						
Total (95% CI)		**100**		**52**	**100.0%**	**1.21 [0.50 , 2.97]**
Total events:	14		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.42 (P = 0.67)						
Test for subgroup differences: Not applicable						



Footnotes

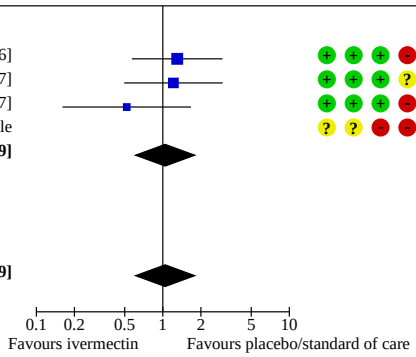
(1) Time point (14 days), participants (WHO 4 to 5 incl. asymptomatic people), intervention (ivermectin 12 mg and 24 mg, single dose), comparator (placebo)

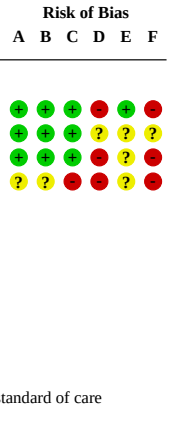
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Any adverse events within 28 days (primary analysis)
(C) Bias due to missing outcome data: Any adverse events within 28 days (primary analysis)
(D) Bias in measurement of the outcome: Any adverse events within 28 days (primary analysis)
(E) Bias in selection of the reported result: Any adverse events within 28 days (primary analysis)
(F) Overall bias: Any adverse events within 28 days (primary analysis)

Analysis 1.6. Comparison 1: Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in the inpatient setting, Outcome 6: Any adverse events within 28 days (secondary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo/standard of care Events	Placebo/standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Moderate disease (WHO 4 to 5)						
Krolewiecki 2020 (1)	13	30	5	15	42.7%	1.30 [0.57 , 2.96]
Mohan 2021 (2)	14	100	6	52	36.1%	1.21 [0.50 , 2.97]
Pott-Junior 2021 (3)	7	27	2	4	21.2%	0.52 [0.16 , 1.67]
Shah Bukhari 2021 (4)	0	41	0	45		Not estimable
Subtotal (95% CI)		**198**		**116**	**100.0%**	**1.04 [0.61 , 1.79]**
Total events:	34		13			
Heterogeneity: Tau² = 0.00; Chi² = 1.81, df = 2 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.15 (P = 0.88)						
Total (95% CI)		**198**		**116**	**100.0%**	**1.04 [0.61 , 1.79]**
Total events:	34		13			
Heterogeneity: Tau² = 0.00; Chi² = 1.81, df = 2 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.15 (P = 0.88)						
Test for subgroup differences: Not applicable						





Footnotes

(1) Time point (30 days), participants (WHO 4 to 5), intervention (ivermectin 0.6 mg/kg/day, 3 mg or 6 mg daily for 5 days), comparator (standard of care)
(2) Time point (14 days), participants (WHO 4 to 5 incl. asymptomatic people), intervention (ivermectin 12 mg and 24 mg, single dose, oral), comparator (placebo)
(3) Time point (28 days), participants (unclear, min. WHO 4, 20% WHO 5), intervention (ivermectin 0.1 mg/kg, 0.2 mg/kg, and 0.4 mg/kg over 72 h), comparator (standard of care)
(4) Time point (28 days), participants (WHO 4 to 5), intervention (ivermectin 12 mg, single dose), comparator (standard of care)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Any adverse events within 28 days (secondary analysis)
(C) Bias due to missing outcome data: Any adverse events within 28 days (secondary analysis)
(D) Bias in measurement of the outcome: Any adverse events within 28 days (secondary analysis)
(E) Bias in selection of the reported result: Any adverse events within 28 days (secondary analysis)
(F) Overall bias: Any adverse events within 28 days (secondary analysis)

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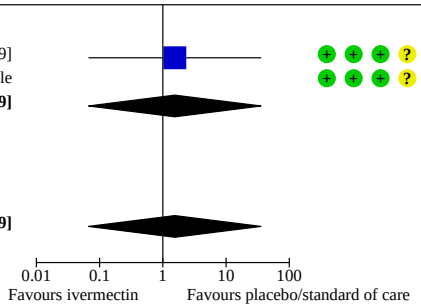
Analysis 1.7. Comparison 1: Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in the inpatient setting, Outcome 7: Serious adverse events within 28 days (primary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo/standard of care Events	Placebo/standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
1.7.1 Moderate disease (WHO 4 to 5)												
Krolewiecki 2020 (1)	1	30	0	15	100.0%	1.55 [0.07 , 35.89]	+	+	+	?	?	?
Mohan 2021 (2)	0	100	0	52		Not estimable	+	+	+	?	+	?
Subtotal (95% CI)		**130**		**67**	**100.0%**	**1.55 [0.07 , 35.89]**						
Total events:	1		0									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.27 (P = 0.79)												
Total (95% CI)		**130**		**67**	**100.0%**	**1.55 [0.07 , 35.89]**						
Total events:	1		0									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.27 (P = 0.79)												
Test for subgroup differences: Not applicable												



Footnotes

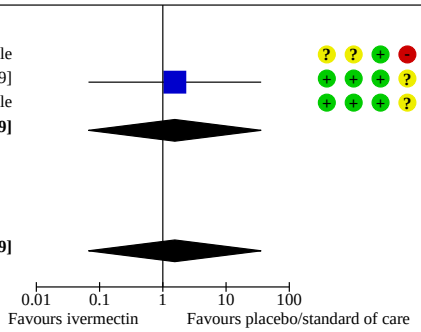
(1) Time point (30 days), participants (WHO 4 to 5), intervention (ivermectin 0.6 mg/kg/day, 3 mg or 6 mg daily for 5 days), comparator (standard of care)
(2) Time point (14 days), participants (WHO 4 to 5 incl. asymptomatic people), intervention (ivermectin 12 mg and 24 mg, single dose), comparator (placebo)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Serious adverse events within 28 days (primary analysis)
(C) Bias due to missing outcome data: Serious adverse events within 28 days (primary analysis)
(D) Bias in measurement of the outcome: Serious adverse events within 28 days (primary analysis)
(E) Bias in selection of the reported result: Serious adverse events within 28 days (primary analysis)
(F) Overall bias: Serious adverse events within 28 days (primary analysis)

Analysis 1.8. Comparison 1: Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in the inpatient setting, Outcome 8: Serious adverse events within 28 days (secondary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo/standard of care Events	Placebo/standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
1.8.1 Moderate disease (WHO 4 to 5)												
Ahmed 2020 (1)	0	22	0	23		Not estimable	?	?	+	-	?	-
Krolewiecki 2020 (2)	1	30	0	15	100.0%	1.55 [0.07 , 35.89]	+	+	+	?	?	?
Mohan 2021 (3)	0	100	0	52		Not estimable	+	+	+	?	+	?
Subtotal (95% CI)		**152**		**90**	**100.0%**	**1.55 [0.07 , 35.89]**						
Total events:	1		0									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.27 (P = 0.79)												
Total (95% CI)		**152**		**90**	**100.0%**	**1.55 [0.07 , 35.89]**						
Total events:	1		0									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.27 (P = 0.79)												
Test for subgroup differences: Not applicable												



Footnotes

(1) Time point (14 days), participants (WHO 4), intervention (ivermectin 12 mg daily for 5 days), comparator (placebo)
(2) Time point (30 days), participants (WHO 4 to 5), intervention (ivermectin 0.6 mg/kg/day, 3 mg or 6 mg daily for 5 days), comparator (standard of care)
(3) Time point (14 days), participants (WHO 4 to 5 incl. asymptomatic people), intervention (ivermectin 12 mg and 24 mg, single dose), comparator (placebo)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Serious adverse events within 28 days (secondary analysis)
(C) Bias due to missing outcome data: Serious adverse events within 28 days (secondary analysis)
(D) Bias in measurement of the outcome: Serious adverse events within 28 days (secondary analysis)
(E) Bias in selection of the reported result: Serious adverse events within 28 days (secondary analysis)
(F) Overall bias: Serious adverse events within 28 days (secondary analysis)

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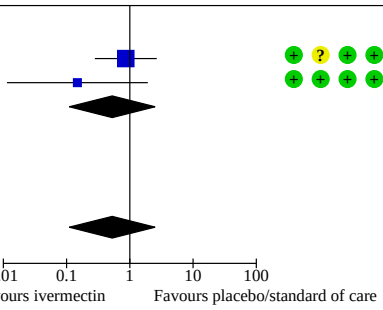
Analysis 1.9. Comparison 1: Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in the inpatient setting, Outcome 9: Admission to intensive care unit (primary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo/standard of care Events	Placebo/standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
1.9.1 Moderate disease (WHO 4 to 5)							
Kirti 2021 (1)	5	55	6	57	71.9%	0.86 [0.28 , 2.67]	+ ? + + + ?
Pott-Junior 2021 (2)	1	27	1	4	28.1%	0.15 [0.01 , 1.93]	+ + + + ? ?
Subtotal (95% CI)		**82**		**61**	**100.0%**	**0.53 [0.11 , 2.51]**	
Total events:	6		7				
Heterogeneity: Tau² = 0.55; Chi² = 1.54, df = 1 (P = 0.21); I² = 35%							
Test for overall effect: Z = 0.80 (P = 0.42)							
Total (95% CI)		**82**		**61**	**100.0%**	**0.53 [0.11 , 2.51]**	
Total events:	6		7				
Heterogeneity: Tau² = 0.55; Chi² = 1.54, df = 1 (P = 0.21); I² = 35%							
Test for overall effect: Z = 0.80 (P = 0.42)							
Test for subgroup differences: Not applicable							



Footnotes

(1) Time point (28 days), participants (WHO 4 to 5), intervention (ivermectin 12 mg daily for 2 days), comparator (placebo)

(2) Time point (28 days), participants (unclear, min. WHO 4, 20% WHO 5), intervention (ivermectin 0.1 mg/kg, 0.2 mg/kg, and 0.4 mg/kg over 72 hours), comparator (standard of care)

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Admission to intensive care unit (primary analysis)

(C) Bias due to missing outcome data: Admission to intensive care unit (primary analysis)

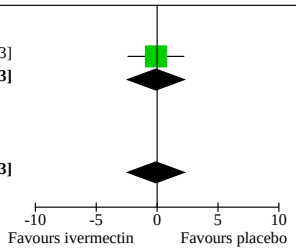
(D) Bias in measurement of the outcome: Admission to intensive care unit (primary analysis)

(E) Bias in selection of the reported result: Admission to intensive care unit (primary analysis)

(F) Overall bias: Admission to intensive care unit (primary analysis)

Analysis 1.10. Comparison 1: Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in the inpatient setting, Outcome 10: Duration of hospitalization (primary analysis)

Study or Subgroup	Ivermectin Mean	Ivermectin SD	Ivermectin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
1.10.1 Moderate disease (WHO 4 to 5)									
Ahmed 2020 (1)	9.6	4.7364	22	9.7	3.0063	23	100.0%	-0.10 [-2.43 , 2.23]	? ? + + ? ?
Subtotal (95% CI)			**22**			**23**	**100.0%**	**-0.10 [-2.43 , 2.23]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.08 (P = 0.93)									
Total (95% CI)			**22**			**23**	**100.0%**	**-0.10 [-2.43 , 2.23]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.08 (P = 0.93)									
Test for subgroup differences: Not applicable									



Footnotes

(1) Participants (WHO 4), intervention (ivermectin 12 mg daily for 5 days), comparator (placebo)

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Duration of hospitalization (primary analysis)

(C) Bias due to missing outcome data: Duration of hospitalization (primary analysis)

(D) Bias in measurement of the outcome: Duration of hospitalization (primary analysis)

(E) Bias in selection of the reported result: Duration of hospitalization (primary analysis)

(F) Overall bias: Duration of hospitalization (primary analysis)

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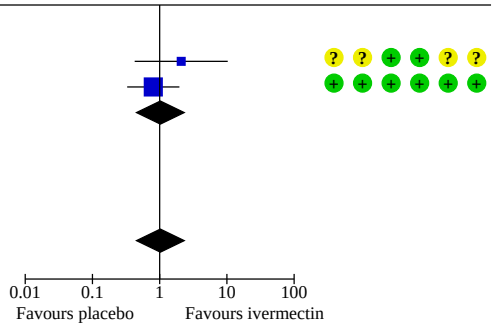
Analysis 1.11. Comparison 1: Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in the inpatient setting, Outcome 11: Viral clearance at 3 days (primary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 Moderate disease (WHO 4 to 5)						
Ahmed 2020 (1)	4	22	2	23	25.3%	2.09 [0.42 , 10.29]
Mohan 2021 (2)	10	80	7	45	74.7%	0.80 [0.33 , 1.96]
Subtotal (95% CI)		**102**		**68**	**100.0%**	**1.02 [0.45 , 2.32]**
Total events:	14		9			
Heterogeneity: Tau² = 0.02; Chi² = 1.06, df = 1 (P = 0.30); I² = 5%						
Test for overall effect: Z = 0.06 (P = 0.96)						
Total (95% CI)		**102**		**68**	**100.0%**	**1.02 [0.45 , 2.32]**
Total events:	14		9			
Heterogeneity: Tau² = 0.02; Chi² = 1.06, df = 1 (P = 0.30); I² = 5%						
Test for overall effect: Z = 0.06 (P = 0.96)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Time point (3 days), participants (WHO 4), intervention (ivermectin 12 mg daily for 5 days), comparator (placebo)

(2) Time point (3 days), participants (WHO 4 to 5 incl. asymptomatic people), intervention (ivermectin 12 mg and 24 mg, single dose), comparator (placebo)

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Viral clearance at 3 days (primary analysis)

(C) Bias due to missing outcome data: Viral clearance at 3 days (primary analysis)

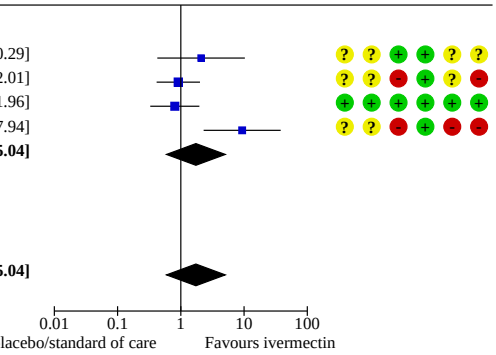
(D) Bias in measurement of the outcome: Viral clearance at 3 days (primary analysis)

(E) Bias in selection of the reported result: Viral clearance at 3 days (primary analysis)

(F) Overall bias: Viral clearance at 3 days (primary analysis)

Analysis 1.12. Comparison 1: Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in the inpatient setting, Outcome 12: Viral clearance at 3 days (secondary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo/standard of care Events	Placebo/standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Moderate disease (WHO 4 to 5)						
Ahmed 2020 (1)	4	22	2	23	19.8%	2.09 [0.42 , 10.29]
Kishoria 2020 (2)	8	19	6	13	29.7%	0.91 [0.41 , 2.01]
Mohan 2021 (3)	10	80	7	45	28.4%	0.80 [0.33 , 1.96]
Shah Bukhari 2021 (4)	17	41	2	45	22.0%	9.33 [2.29 , 37.94]
Subtotal (95% CI)		**162**		**126**	**100.0%**	**1.73 [0.59 , 5.04]**
Total events:	39		17			
Heterogeneity: Tau² = 0.84; Chi² = 11.21, df = 3 (P = 0.01); I² = 73%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Total (95% CI)		**162**		**126**	**100.0%**	**1.73 [0.59 , 5.04]**
Total events:	39		17			
Heterogeneity: Tau² = 0.84; Chi² = 11.21, df = 3 (P = 0.01); I² = 73%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Time point (3 days), participants (WHO 4), intervention (ivermectin 12 mg daily for 5 days), comparator (placebo)

(2) Time point (3 days), participants (WHO 4 incl. asymptomatic people), intervention (ivermectin 12 mg , single dose), comparator (standard of care)

(3) Time point (3 days), participants (WHO 4 to 5 incl. asymptomatic people), intervention (ivermectin 12 mg and 24 mg, single dose), comparator (placebo)

(4) Time point (3 days), participants (WHO 4 to 5), intervention (ivermectin 12 mg, single dose), comparator (standard of care)

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Viral clearance at 3 days (secondary analysis)

(C) Bias due to missing outcome data: Viral clearance at 3 days (secondary analysis)

(D) Bias in measurement of the outcome: Viral clearance at 3 days (secondary analysis)

(E) Bias in selection of the reported result: Viral clearance at 3 days (secondary analysis)

(F) Overall bias: Viral clearance at 3 days (secondary analysis)

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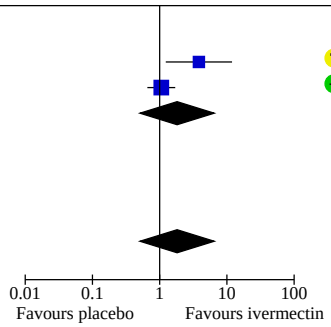
Analysis 1.13. Comparison 1: Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in the inpatient setting, Outcome 13: Viral clearance at 7 days (primary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
1.13.1 Moderate disease (WHO 4 to 5)												
Ahmed 2020 (1)	11	22	3	23	42.0%	3.83 [1.23 , 11.93]	?	?	+	+	?	?
Mohan 2021 (2)	29	72	16	42	58.0%	1.06 [0.66 , 1.70]	+	+	+	+	+	+
Subtotal (95% CI)		**94**		**65**	**100.0%**	**1.82 [0.51 , 6.48]**						
Total events:	40		19									
Heterogeneity: Tau² = 0.67; Chi² = 4.38, df = 1 (P = 0.04); I² = 77%												
Test for overall effect: Z = 0.92 (P = 0.36)												
Total (95% CI)		**94**		**65**	**100.0%**	**1.82 [0.51 , 6.48]**						
Total events:	40		19									
Heterogeneity: Tau² = 0.67; Chi² = 4.38, df = 1 (P = 0.04); I² = 77%												
Test for overall effect: Z = 0.92 (P = 0.36)												
Test for subgroup differences: Not applicable												



Footnotes

(1) Time point (7 days), participants (WHO 4), intervention (ivermectin 12 mg daily for 5 days), comparator (placebo)

(2) Time point (7 days), participants (WHO 4 to 5 incl. asymptomatic people), intervention (ivermectin 12 mg and 24 mg, single dose), comparator (placebo)

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Viral clearance at 7 days (primary analysis)

(C) Bias due to missing outcome data: Viral clearance at 7 days (primary analysis)

(D) Bias in measurement of the outcome: Viral clearance at 7 days (primary analysis)

(E) Bias in selection of the reported result: Viral clearance at 7 days (primary analysis)

(F) Overall bias: Viral clearance at 7 days (primary analysis)

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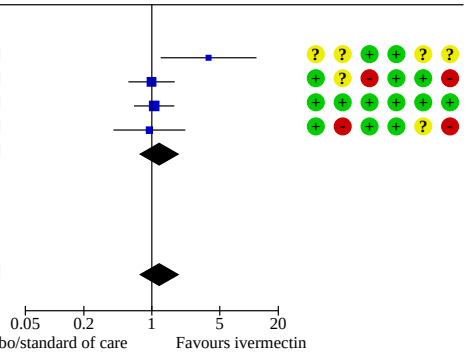
Analysis 1.14. Comparison 1: Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in the inpatient setting, Outcome 14: Viral clearance at 7 days (secondary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo/standard of care Events	Placebo/standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 Moderate disease (WHO 4 to 5)						
Ahmed 2020 (1)	11	22	3	23	12.5%	3.83 [1.23 , 11.93]
Kirti 2021 (2)	13	32	18	44	32.1%	0.99 [0.57 , 1.72]
Mohan 2021 (3)	29	72	16	42	36.3%	1.06 [0.66 , 1.70]
Pott-Junior 2021 (4)	17	27	2	3	19.2%	0.94 [0.40 , 2.21]
Subtotal (95% CI)		**153**		**112**	**100.0%**	**1.19 [0.76 , 1.86]**
Total events:	70		39			
Heterogeneity: Tau² = 0.08; Chi² = 5.14, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 0.76 (P = 0.45)						
Total (95% CI)		**153**		**112**	**100.0%**	**1.19 [0.76 , 1.86]**
Total events:	70		39			
Heterogeneity: Tau² = 0.08; Chi² = 5.14, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 0.76 (P = 0.45)						
Test for subgroup differences: Not applicable						



Footnotes

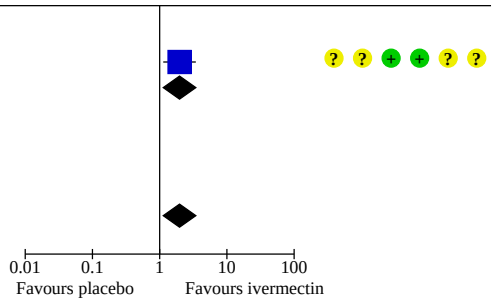
(1) Time point (7 days), participants (WHO 4), intervention (ivermectin 12 mg daily for 5 days), comparator (placebo)
(2) Time point (6 days), participants (WHO 4 to 5), intervention (ivermectin 12 mg daily for 2 days), comparator (placebo)
(3) Time point (7 days), participants (WHO 4 to 5 incl, asymptomatic people), intervention (ivermectin 12 mg and 24 mg, single dose), comparator (placebo)
(4) Time point (7 days), participants (unclear, min. WHO 4, 20% WHO 5), intervention (ivermectin 0.1 mg/kg, 0.2 mg/kg, and 0.4 mg/kg over 72 hours), comparator (standard of care)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Viral clearance at 7 days (secondary analysis)
(C) Bias due to missing outcome data: Viral clearance at 7 days (secondary analysis)
(D) Bias in measurement of the outcome: Viral clearance at 7 days (secondary analysis)
(E) Bias in selection of the reported result: Viral clearance at 7 days (secondary analysis)
(F) Overall bias: Viral clearance at 7 days (secondary analysis)

Analysis 1.15. Comparison 1: Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in the inpatient setting, Outcome 15: Viral clearance at 14 days (primary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 Moderate disease (WHO 4 to 5)						
Ahmed 2020 (1)	17	22	9	23	100.0%	1.97 [1.13 , 3.45]
Subtotal (95% CI)		**22**		**23**	**100.0%**	**1.97 [1.13 , 3.45]**
Total events:	17		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.39 (P = 0.02)						
Total (95% CI)		**22**		**23**	**100.0%**	**1.97 [1.13 , 3.45]**
Total events:	17		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.39 (P = 0.02)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Time point (14 days), participants (WHO 4), intervention (ivermectin 12 mg daily for 5 days), comparator (placebo)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Viral clearance at 14 days (primary analysis)
(C) Bias due to missing outcome data: Viral clearance at 14 days (primary analysis)
(D) Bias in measurement of the outcome: Viral clearance at 14 days (primary analysis)
(E) Bias in selection of the reported result: Viral clearance at 14 days (primary analysis)
(F) Overall bias: Viral clearance at 14 days (primary analysis)

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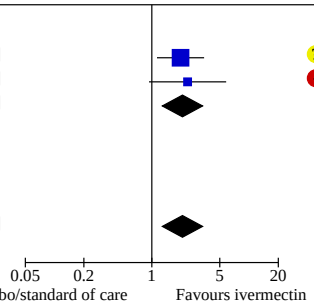
Analysis 1.16. Comparison 1: Ivermectin compared to placebo or standard of care for people with moderate-to-severe COVID-19 treated in the inpatient setting, Outcome 16: Viral clearance at 14 days (secondary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo/standard of care Events	Placebo/standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
1.16.1 Moderate to severe disease (WHO 4 to 9)												
Ahmed 2020 (1)	17	22	9	23	72.8%	1.97 [1.13 , 3.45]	?	?	+	+	?	?
Okumuş 2021 (2)	14	16	3	8	27.2%	2.33 [0.94 , 5.82]	-	-	-	+	?	-
Subtotal (95% CI)		**38**		**31**	**100.0%**	**2.07 [1.28 , 3.33]**						
Total events:	31		12									
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%												
Test for overall effect: Z = 2.99 (P = 0.003)												
Total (95% CI)		**38**		**31**	**100.0%**	**2.07 [1.28 , 3.33]**						
Total events:	31		12									
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%												
Test for overall effect: Z = 2.99 (P = 0.003)												
Test for subgroup differences: Not applicable												



Footnotes

(1) Time point (14 days), participants (WHO 4), intervention (ivermectin 12 mg daily for 5 days), comparator (placebo)
(2) Time point (10 days), participants (WHO 4 to 9), intervention (ivermectin 0.2 mg/kg daily for 5 days), comparator (standard of care)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Viral clearance at 14 days (secondary analysis)
(C) Bias due to missing outcome data: Viral clearance at 14 days (secondary analysis)
(D) Bias in measurement of the outcome: Viral clearance at 14 days (secondary analysis)
(E) Bias in selection of the reported result: Viral clearance at 14 days (secondary analysis)
(F) Overall bias: Viral clearance at 14 days (secondary analysis)

Comparison 2. Ivermectin compared to placebo or standard of care for people with mild COVID-19 treated in the outpatient setting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality up to 28 days (primary analysis)	2	422	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.05]
2.2 Worsening of clinical status – need for invasive mechanical ventilation up to 14 days (primary analysis)	1	398	Risk Ratio (M-H, Random, 95% CI)	2.97 [0.12, 72.47]
2.3 Worsening of clinical status – need for non-invasive mechanical ventilation or high flow up to 14 days (primary analysis)	1	398	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.4 Symptom resolution – number of participants with symptoms resolved up to 14 days (primary analysis)	1	398	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.89, 1.21]
2.5 Duration to symptom resolution (secondary analysis)	1	62	Mean Difference (IV, Random, 95% CI)	-1.02 [-2.76, 0.72]
2.6 Any adverse events within 28 days (primary analysis)	2	422	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.86, 1.05]
2.7 Serious adverse events within 28 days (primary analysis)	2	422	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.14, 6.96]

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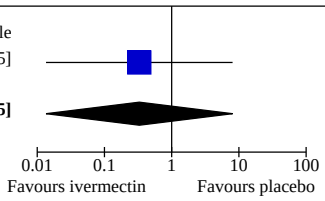
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.8 Viral clearance at 7 days (primary analysis)	1	24	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 67.06]
2.9 Viral clearance at 14 days (secondary analysis)	1	40	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.79, 1.13]

Analysis 2.1. Comparison 2: Ivermectin compared to placebo or standard of care for people with mild COVID-19 treated in the outpatient setting, Outcome 1: All-cause mortality up to 28 days (primary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Chaccour 2021 (1)	0	12	0	12		Not estimable	+	+	+	+	+	+
López-Medina 2021 (2)	0	200	1	198	100.0%	0.33 [0.01 , 8.05]	+	?	+	+	+	?
Total (95% CI)		**212**		**210**	**100.0%**	**0.33 [0.01 , 8.05]**						
Total events:	0		1									

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Footnotes
(1) Time point (28 days), participants (WHO 2 to 3), intervention (ivermectin 0.4 mg/kg, single dose), comparator (placebo)
(2) Time point (21 days), participants (WHO 2 to 5, < 1% participants at WHO 4 and 5), intervention (ivermectin 0.3 mg/kg daily for 5 days), comparator (placebo)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: All-cause mortality up to 28 days (primary analysis)
(C) Bias due to missing outcome data: All-cause mortality up to 28 days (primary analysis)
(D) Bias in measurement of the outcome: All-cause mortality up to 28 days (primary analysis)
(E) Bias in selection of the reported result: All-cause mortality up to 28 days (primary analysis)
(F) Overall bias: All-cause mortality up to 28 days (primary analysis)

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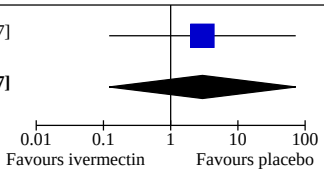
Analysis 2.2. Comparison 2: Ivermectin compared to placebo or standard of care for people with mild COVID-19 treated in the outpatient setting, Outcome 2: Worsening of clinical status – need for invasive mechanical ventilation up to 14 days (primary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
López-Medina 2021 (1)	1	200	0	198	100.0%	2.97 [0.12 , 72.47]	+	?	+	+	+	?
Total (95% CI)		**200**		**198**	**100.0%**	**2.97 [0.12 , 72.47]**						
Total events:	1		0									

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable



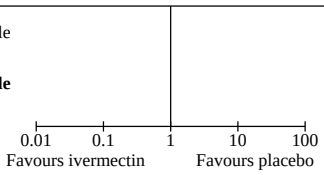
Footnotes
(1) Time point (15 days), participants (WHO 2 to 5, < 1% participants at WHO 4 and 5), intervention (ivermectin 0.3 mg/kg daily for 5 days), comparator (placebo)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Worsening of clinical status – need for invasive mechanical ventilation up to 14 days (primary analysis)
(C) Bias due to missing outcome data: Worsening of clinical status – need for invasive mechanical ventilation up to 14 days (primary analysis)
(D) Bias in measurement of the outcome: Worsening of clinical status – need for invasive mechanical ventilation up to 14 days (primary analysis)
(E) Bias in selection of the reported result: Worsening of clinical status – need for invasive mechanical ventilation up to 14 days (primary analysis)
(F) Overall bias: Worsening of clinical status – need for invasive mechanical ventilation up to 14 days (primary analysis)

Analysis 2.3. Comparison 2: Ivermectin compared to placebo or standard of care for people with mild COVID-19 treated in the outpatient setting, Outcome 3: Worsening of clinical status – need for non-invasive mechanical ventilation or high flow up to 14 days (primary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
López-Medina 2021 (1)	0	200	0	198		Not estimable	+	?	+	+	+	?
Total (95% CI)		**200**		**198**		**Not estimable**						
Total events:	0		0									

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Footnotes
(1) Time point (15 days), participants (WHO 2 to 5, < 1% participants at WHO 4 and 5), intervention (ivermectin 0.3 mg/kg daily for 5 days), comparator (placebo)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Worsening of clinical status – need for non-invasive mechanical ventilation or high flow up to 14 days (primary analysis)
(C) Bias due to missing outcome data: Worsening of clinical status – need for non-invasive mechanical ventilation or high flow up to 14 days (primary analysis)
(D) Bias in measurement of the outcome: Worsening of clinical status – need for non-invasive mechanical ventilation or high flow up to 14 days (primary analysis)
(E) Bias in selection of the reported result: Worsening of clinical status – need for non-invasive mechanical ventilation or high flow up to 14 days (primary analysis)
(F) Overall bias: Worsening of clinical status – need for non-invasive mechanical ventilation or high flow up to 14 days (primary analysis)

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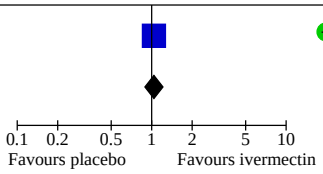
Analysis 2.4. Comparison 2: Ivermectin compared to placebo or standard of care for people with mild COVID-19 treated in the outpatient setting, Outcome 4: Symptom resolution – number of participants with symptoms resolved up to 14 days (primary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
López-Medina 2021 (1)	126	200	120	198	100.0%	1.04 [0.89 , 1.21]	+	?	+	+	+	?
Total (95% CI)		**200**		**198**	**100.0%**	**1.04 [0.89 , 1.21]**						
Total events:	126		120									

Heterogeneity: Not applicable
Test for overall effect: Z = 0.49 (P = 0.62)
Test for subgroup differences: Not applicable



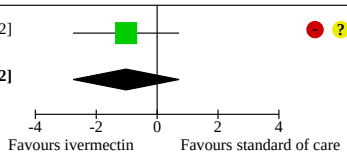
Footnotes
(1) Time point (15 days), participants (WHO 2 to 5, < 1% participants at WHO 4 and 5), intervention (ivermectin 0.3 mg/kg daily for 5 days), comparator (placebo)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Symptom resolution – number of participants with symptoms resolved up to 14 days (primary analysis)
(C) Bias due to missing outcome data: Symptom resolution – number of participants with symptoms resolved up to 14 days (primary analysis)
(D) Bias in measurement of the outcome: Symptom resolution – number of participants with symptoms resolved up to 14 days (primary analysis)
(E) Bias in selection of the reported result: Symptom resolution – number of participants with symptoms resolved up to 14 days (primary analysis)
(F) Overall bias: Symptom resolution – number of participants with symptoms resolved up to 14 days (primary analysis)

Analysis 2.5. Comparison 2: Ivermectin compared to placebo or standard of care for people with mild COVID-19 treated in the outpatient setting, Outcome 5: Duration to symptom resolution (secondary analysis)

Study or Subgroup	Ivermectin Mean	Ivermectin SD	Ivermectin Total	Standard of care Mean	Standard of care SD	Standard of care Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Podder 2020 (1)	5.31	2.48	32	6.33	4.23	30	100.0%	-1.02 [-2.76 , 0.72]	-	?	-	-	?	-
Total (95% CI)			**32**			**30**	**100.0%**	**-1.02 [-2.76 , 0.72]**						

Heterogeneity: Not applicable
Test for overall effect: Z = 1.15 (P = 0.25)
Test for subgroup differences: Not applicable



Footnotes
(1) Follow-up until symptom resolution, participants (WHO 2 to 3), intervention (ivermectin 0.2 mg/kg, single dose), comparator (standard of care)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Duration to symptom resolution (secondary analysis)
(C) Bias due to missing outcome data: Duration to symptom resolution (secondary analysis)
(D) Bias in measurement of the outcome: Duration to symptom resolution (secondary analysis)
(E) Bias in selection of the reported result: Duration to symptom resolution (secondary analysis)
(F) Overall bias: Duration to symptom resolution (secondary analysis)

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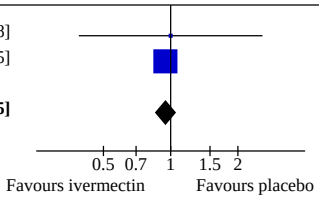
Analysis 2.6. Comparison 2: Ivermectin compared to placebo or standard of care for people with mild COVID-19 treated in the outpatient setting, Outcome 6: Any adverse events within 28 days (primary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Chaccour 2021 (1)	5	12	5	12	1.1%	1.00 [0.39 , 2.58]	+	+	+	+	+	+
López-Medina 2021 (2)	154	200	161	198	98.9%	0.95 [0.86 , 1.05]	+	?	+	+	+	?
Total (95% CI)		**212**		**210**	**100.0%**	**0.95 [0.86 , 1.05]**						
Total events:	159		166									

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.05 (P = 0.29)
Test for subgroup differences: Not applicable



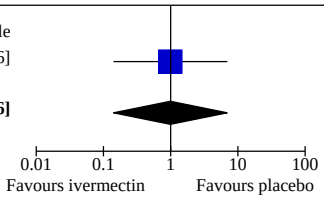
Footnotes
(1) Time point (28 days), participants (WHO 2 to 3), intervention (ivermectin 0.4 mg/kg, single dose), comparator (placebo)
(2) Time point (21 days), participants (WHO 2 to 5, < 1% participants at WHO 4 and 5), intervention (ivermectin 0.3 mg/kg daily for 5 days), comparator (placebo)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Any adverse events within 28 days (primary analysis)
(C) Bias due to missing outcome data: Any adverse events within 28 days (primary analysis)
(D) Bias in measurement of the outcome: Any adverse events within 28 days (primary analysis)
(E) Bias in selection of the reported result: Any adverse events within 28 days (primary analysis)
(F) Overall bias: Any adverse events within 28 days (primary analysis)

Analysis 2.7. Comparison 2: Ivermectin compared to placebo or standard of care for people with mild COVID-19 treated in the outpatient setting, Outcome 7: Serious adverse events within 28 days (primary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Chaccour 2021 (1)	0	12	0	12		Not estimable	+	+	+	?	?	?
López-Medina 2021 (2)	2	200	2	198	100.0%	0.99 [0.14 , 6.96]	+	?	+	+	+	?
Total (95% CI)		**212**		**210**	**100.0%**	**0.99 [0.14 , 6.96]**						
Total events:	2		2									

Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)
Test for subgroup differences: Not applicable



Footnotes
(1) Time point (28 days), participants (WHO 2 to 3), intervention (ivermectin 0.4 mg/kg, single dose), comparator (placebo)
(2) Time point (21 days), participants (WHO 2 to 5 , < 1% participants at WHO 4 and 5), intervention (ivermectin 0.3 mg/kg daily for 5 days), comparator (placebo)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Serious adverse events within 28 days (primary analysis)
(C) Bias due to missing outcome data: Serious adverse events within 28 days (primary analysis)
(D) Bias in measurement of the outcome: Serious adverse events within 28 days (primary analysis)
(E) Bias in selection of the reported result: Serious adverse events within 28 days (primary analysis)
(F) Overall bias: Serious adverse events within 28 days (primary analysis)

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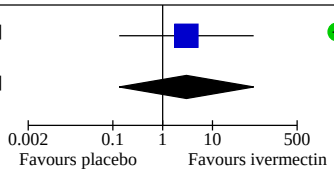
Analysis 2.8. Comparison 2: Ivermectin compared to placebo or standard of care for people with mild COVID-19 treated in the outpatient setting, Outcome 8: Viral clearance at 7 days (primary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Chaccour 2021 (1)	1	12	0	12	100.0%	3.00 [0.13 , 67.06]	+	+	+	+	+	+
Total (95% CI)		**12**		**12**	**100.0%**	**3.00 [0.13 , 67.06]**						
Total events:	1		0									

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



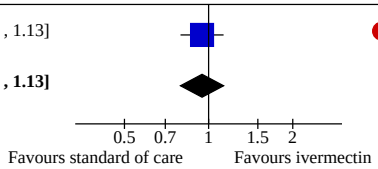
Footnotes
(1) Measured by E-gene clearance, time point (7 days), participants (WHO 2 to 3), intervention (ivermectin 0.4 mg/kg, single dose), comparator (placebo)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Viral clearance at 7 days (primary analysis)
(C) Bias due to missing outcome data: Viral clearance at 7 days (primary analysis)
(D) Bias in measurement of the outcome: Viral clearance at 7 days (primary analysis)
(E) Bias in selection of the reported result: Viral clearance at 7 days (primary analysis)
(F) Overall bias: Viral clearance at 7 days (primary analysis)

Analysis 2.9. Comparison 2: Ivermectin compared to placebo or standard of care for people with mild COVID-19 treated in the outpatient setting, Outcome 9: Viral clearance at 14 days (secondary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Standard of care Events	Standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Podder 2020 (1)	18	20	19	20	100.0%	0.95 [0.79 , 1.13]	-	?	-	+	?	-
Total (95% CI)		**20**		**20**	**100.0%**	**0.95 [0.79 , 1.13]**						
Total events:	18		19									

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable



Footnotes
(1) Time point (10 days), participants (WHO 2 to 3), intervention (ivermectin 0.2 mg/kg, single dose), comparator (standard of care)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Viral clearance at 14 days (secondary analysis)
(C) Bias due to missing outcome data: Viral clearance at 14 days (secondary analysis)
(D) Bias in measurement of the outcome: Viral clearance at 14 days (secondary analysis)
(E) Bias in selection of the reported result: Viral clearance at 14 days (secondary analysis)
(F) Overall bias: Viral clearance at 14 days (secondary analysis)

Comparison 3. Ivermectin compared to no treatment for prevention of SARS-CoV-2 infection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Development of clinical COVID-19 symptoms (secondary analysis)	1	304	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.08, 0.21]
3.2 Any adverse events within 14 days (secondary analysis)	1	304	Risk Ratio (M-H, Random, 95% CI)	11.50 [0.68, 193.21]

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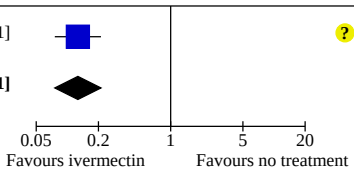
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 All-cause mortality up to 28 days (primary analysis)	1	304	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 3.1. Comparison 3: Ivermectin compared to no treatment for prevention of SARS-CoV-2 infection, Outcome 1: Development of clinical COVID-19 symptoms (secondary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Shoumann 2021 (1)	15	203	59	101	100.0%	0.13 [0.08 , 0.21]	?	+	?	-	+	-
Total (95% CI)		**203**		**101**	**100.0%**	**0.13 [0.08 , 0.21]**						
Total events:	15		59									

Heterogeneity: Not applicable
Test for overall effect: Z = 7.88 (P < 0.00001)
Test for subgroup differences: Not applicable



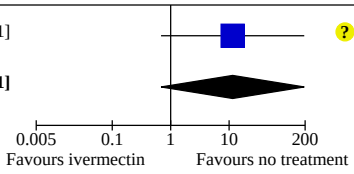
Footnotes
(1) Time point (14 days), participants (WHO 0), intervention (ivermectin 0.2–0.3 mg/kg, 2 doses at day 1 and 3), comparator (no treatment)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Development of clinical COVID-19 symptoms (secondary analysis)
(C) Bias due to missing outcome data: Development of clinical COVID-19 symptoms (secondary analysis)
(D) Bias in measurement of the outcome: Development of clinical COVID-19 symptoms (secondary analysis)
(E) Bias in selection of the reported result: Development of clinical COVID-19 symptoms (secondary analysis)
(F) Overall bias: Development of clinical COVID-19 symptoms (secondary analysis)

Analysis 3.2. Comparison 3: Ivermectin compared to no treatment for prevention of SARS-CoV-2 infection, Outcome 2: Any adverse events within 14 days (secondary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Shoumann 2021 (1)	11	203	0	101	100.0%	11.50 [0.68 , 193.21]	?	+	?	-	?	-
Total (95% CI)		**203**		**101**	**100.0%**	**11.50 [0.68 , 193.21]**						
Total events:	11		0									

Heterogeneity: Not applicable
Test for overall effect: Z = 1.70 (P = 0.09)
Test for subgroup differences: Not applicable



Footnotes
(1) Time point (14 days), participants (WHO 0), intervention (ivermectin 0.2–0.3 mg/kg, 2 doses at day 1 and 3), comparator (no treatment)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Any adverse events within 14 days (secondary analysis)
(C) Bias due to missing outcome data: Any adverse events within 14 days (secondary analysis)
(D) Bias in measurement of the outcome: Any adverse events within 14 days (secondary analysis)
(E) Bias in selection of the reported result: Any adverse events within 14 days (secondary analysis)
(F) Overall bias: Any adverse events within 14 days (secondary analysis)

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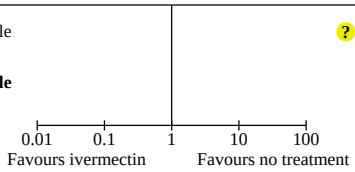
Analysis 3.3. Comparison 3: Ivermectin compared to no treatment for prevention of SARS-CoV-2 infection, Outcome 3: All-cause mortality up to 28 days (primary analysis)

Study or Subgroup	Ivermectin Events	Ivermectin Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Shoumann 2021 (1)	0	203	0	101		Not estimable	?	+	?	+	?	?
Total (95% CI)		**203**		**101**		**Not estimable**						
Total events:	0		0									

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Footnotes
(1) Time point (14 days), participants (WHO 0), intervention (ivermectin 0.2–0.3 mg/kg, 2 doses at day 1 and 3), comparator (no treatment)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: All-cause mortality up to 28 days (primary analysis)
(C) Bias due to missing outcome data: All-cause mortality up to 28 days (primary analysis)
(D) Bias in measurement of the outcome: All-cause mortality up to 28 days (primary analysis)
(E) Bias in selection of the reported result: All-cause mortality up to 28 days (primary analysis)
(F) Overall bias: All-cause mortality up to 28 days (primary analysis)

APPENDICES

Appendix 1. Search strategies

Cochrane COVID-19 Study Register

Search string: ivermectin* OR stromectol* OR mectizan* OR "MK 933" OR MK933 OR eqvalan* OR soolantra* OR sklice* OR stromectal* OR ivomec*

Study characteristics:
1) "Intervention assignment": “Randomised” OR
2) "Study type": "Interventional" AND "Study design": "Parallel/Crossover" AND "Unclear"
= 119 references

Web of Science Clarivate (Advanced search)

#1. TI=(ivermectin* OR stromectol* OR mectizan* OR "MK 933" OR MK933 OR eqvalan* OR soolantra* OR sklice* OR stromectal* OR ivomec*) OR AB=(ivermectin* OR stromectol* OR mectizan* OR "MK 933" OR MK933 OR eqvalan* OR soolantra* OR sklice* OR stromectal* OR ivomec*)

#2. TI=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR"SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2") OR AB=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR"SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

#3. #1 AND #2
Indexes=SCI-EXPANDED, ESCI Timespan=2020-2021
= 160 references

medRxiv (Advanced search)

for abstract or title "ivermectin AND randomized" (match all words)
for abstract or title "ivermectin AND randomised" (match all words)

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for abstract or title "ivermectin AND randomly" (match all words)
for abstract or title "ivermectin AND groups" (match all words)
= 35 references

Research Square

Abstract: ivermectin
Manually selected relevant references on ResearchSquare based on Title/Abstract
= 12 references

HISTORY

Protocol first published: Issue 4, 2021

CONTRIBUTIONS OF AUTHORS

MP: conception of the review; design of the review; search and selection of studies for inclusion in the review; collection of data for the review; assessment of the risk of bias in the included studies; analysis of data; assessment of the certainty in the body of evidence; interpretation of data, and writing of the review.

MS: conception of the review; design of the review; interpretation of data; writing and proofreading of the review.

MIM: search strategy design and writing of the review.

SG: interpretation of data; writing and proofreading of the review.

PK: conception of the review; design of the review; interpretation of data; proofreading of the review.

PM: conception of the review; design of the review; interpretation of data; proofreading of the review.

NS: conception of the review; design of the review; interpretation of data; proofreading of the review.

SW: conception of the review; design of the review; co-ordination of the review; search and selection of studies for inclusion in the review; collection of data for the review; assessment of the risk of bias in the included studies; analysis of data; assessment of the certainty in the body of evidence; interpretation of data, and writing of the review.

DECLARATIONS OF INTEREST

MP: funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the CEOsys project, which was paid to the institution).

MS: none.

MIM: none.

SG: none.

PK: none.

PM: none.

NS: none.

SW: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the CEOsys project, which was paid to the institution).

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Internal sources

- University Hospital Wuerzburg, Germany

  Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, University Hospital Wuerzburg

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- Liverpool School of Tropical Medicine, UK

External sources

- Federal Ministry of Education and Research, Germany

  NaFoUniMedCovid19 (funding number: 01KX2021); part of the project "CEOsys"
- Foreign, Commonwealth, and Development Office (FCDO), UK

  Project number 300342-104

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review differs from the protocol for the following aspects (Popp 2021).

1. We introduced 'patients discharged without respiratory deterioration or death at 28 days' that was reported by one study as a new primary outcome in the category 'improvement of clinical status' (inpatient setting) (Gonzalez 2021). This outcome was considered clinically useful.
2. We added the following paragraph to the 'type of participants section' to clarify how we handled studies including a mixed population with confirmed and suspected COVID-19 diagnosis: "If studies included participants with a confirmed or suspected COVID-19 diagnosis, we used only the data for the patient population with confirmed COVID-19 diagnosis. In cases, where data were not reported separately for people with confirmed or suspected COVID-19 diagnosis, we excluded the study." We considered this specification clinically relevant since it would be a loss of evidence to exclude data on people positive for SARS-CoV-2.
3. Since we found no eligible trials that reported on 'serious adverse events' and 'adverse events' in an outpatient setting within 14 days, we changed the eligible time point for both of those outcomes from 'within 14 days' to 'within 28 days,' which two studies provided and was considered clinically useful (Chaccour 2021; López-Medina 2021).
4. We added a paragraph to the methods section 'Methods for future updates.' The living systematic review approach was included in this review from the beginning as part of the CEOsys project.

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