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Ivermectin for preventing and treating COVID-19 (Review)

Popp M, Reis S, Schießer S, Hausinger RI, Stegemann M, Metzendorf MI, Kranke P, Meybohm P, Skoetz N, Weibel S

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[Intervention Review]

Ivermectin for preventing and treating COVID-19

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ABSTRACT

Background

Ivermectin, an antiparasitic agent, 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 early stages of infection. Currently, evidence on ivermectin for prevention of SARS-CoV-2 infection and COVID-19 treatment is conflicting.

Objectives

To assess the efficacy and safety of ivermectin plus standard of care compared to standard of care plus/minus 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), WHO COVID-19 Global literature on coronavirus disease, and HTA database weekly to identify completed and ongoing trials without language restrictions to 16 December 2021. Additionally, we included trials with > 1000 participants up to April 2022.

Selection criteria

We included randomized controlled trials (RCTs) comparing ivermectin to standard of care, placebo, or another proven intervention for treatment of people with confirmed COVID-19 diagnosis, irrespective of disease severity or treatment setting, and for prevention of SARS-CoV-2 infection. Co-interventions had to be the same in both study arms.

For this review update, we reappraised eligible trials for research integrity: only RCTs prospectively registered in a trial registry according to WHO guidelines for clinical trial registration were eligible for inclusion.

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Data collection and analysis

We assessed RCTs for bias, using the Cochrane RoB 2 tool. We used GRADE to rate the certainty of evidence for outcomes in the following settings and populations: 1) to treat inpatients with moderate-to-severe COVID-19, 2) to treat outpatients with mild COVID-19 (outcomes: mortality, clinical worsening or improvement, (serious) adverse events, quality of life, and viral clearance), and 3) to prevent SARS-CoV-2 infection (outcomes: SARS-CoV-2 infection, development of COVID-19 symptoms, admission to hospital, mortality, adverse events and quality of life).

Main results

We excluded seven of the 14 trials included in the previous review version; six were not prospectively registered and one was non-randomized. This updated review includes 11 trials with 3409 participants investigating ivermectin plus standard of care compared to standard of care plus/minus placebo. No trial investigated ivermectin for prevention of infection or compared ivermectin to an intervention with proven efficacy. Five trials treated participants with moderate COVID-19 (inpatient settings); six treated mild COVID-19 (outpatient settings). Eight trials were double-blind and placebo-controlled, and three were open-label. We assessed around 50% of the trial results as low risk of bias.

We identified 31 ongoing trials. In addition, there are 28 potentially eligible trials without publication of results, or with disparities in the reporting of the methods and results, held in 'awaiting classification' until the trial authors clarify questions upon request.

Ivermectin for treating COVID-19 in inpatient settings with moderate-to-severe disease

We are uncertain whether ivermectin plus standard of care compared to standard of care plus/minus placebo reduces or increases all-cause mortality at 28 days (risk ratio (RR) 0.60, 95% confidence interval (CI) 0.14 to 2.51; 3 trials, 230 participants; very low-certainty evidence); or clinical worsening, assessed by participants with new need for invasive mechanical ventilation or death at day 28 (RR 0.82, 95% CI 0.33 to 2.04; 2 trials, 118 participants; very low-certainty evidence); or serious adverse events during the trial period (RR 1.55, 95% CI 0.07 to 35.89; 2 trials, 197 participants; very low-certainty evidence). Ivermectin plus standard of care compared to standard of care plus placebo may have little or no effect on clinical improvement, assessed by the number of participants discharged alive at day 28 (RR 1.03, 95% CI 0.78 to 1.35; 1 trial, 73 participants; low-certainty evidence); on any adverse events during the trial period (RR 1.04, 95% CI 0.61 to 1.79; 3 trials, 228 participants; low-certainty evidence); and on viral clearance at 7 days (RR 1.12, 95% CI 0.80 to 1.58; 3 trials, 231 participants; low-certainty evidence). No trial investigated quality of life at any time point.

Ivermectin for treating COVID-19 in outpatient settings with asymptomatic or mild disease

Ivermectin plus standard of care compared to standard of care plus/minus placebo probably has little or no effect on all-cause mortality at day 28 (RR 0.77, 95% CI 0.47 to 1.25; 6 trials, 2860 participants; moderate-certainty evidence) and little or no effect on quality of life, measured with the PROMIS Global-10 scale (physical component mean difference (MD) 0.00, 95% CI -0.98 to 0.98; and mental component MD 0.00, 95% CI -1.08 to 1.08; 1358 participants; high-certainty evidence). Ivermectin may have little or no effect on clinical worsening, assessed by admission to hospital or death within 28 days (RR 1.09, 95% CI 0.20 to 6.02; 2 trials, 590 participants; low-certainty evidence); on clinical improvement, assessed by the number of participants with all initial symptoms resolved up to 14 days (RR 0.90, 95% CI 0.60 to 1.36; 2 trials, 478 participants; low-certainty evidence); on serious adverse events (RR 2.27, 95% CI 0.62 to 8.31; 5 trials, 1502 participants; low-certainty evidence); on any adverse events during the trial period (RR 1.24, 95% CI 0.87 to 1.76; 5 trials, 1502 participants; low-certainty evidence); and on viral clearance at day 7 compared to placebo (RR 1.01, 95% CI 0.69 to 1.48; 2 trials, 331 participants; low-certainty evidence). None of the trials reporting duration of symptoms were eligible for meta-analysis.

Authors' conclusions

For outpatients, there is currently low- to high-certainty evidence that ivermectin has no beneficial effect for people with COVID-19. Based on the very low-certainty evidence for inpatients, we are still uncertain whether ivermectin prevents death or clinical worsening or increases serious adverse events, while there is low-certainty evidence that it has no beneficial effect regarding clinical improvement, viral clearance and adverse events. No evidence is available on ivermectin to prevent SARS-CoV-2 infection. In this update, certainty of evidence increased through higher quality trials including more participants. According to this review's living approach, we will continually update our search.

PLAIN LANGUAGE SUMMARY

Ivermectin for preventing and treating COVID-19

Is ivermectin effective for COVID-19?

Key messages

We found no evidence to support the use of ivermectin for treating COVID-19 or preventing SARS-CoV-2 infection. The evidence base improved slightly in this update, but is still limited.

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

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What is ivermectin?

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

Medical regulators have not approved ivermectin for COVID-19.

What did we want to find out?

We wanted to update our knowledge of whether ivermectin reduces death, illness, and length of infection in people with COVID-19, or is useful in prevention of the infection. We included trials comparing the medicine to placebo (dummy treatment), usual care, or treatments for COVID-19 that are known to work to some extent, such as dexamethasone. We excluded trials comparing ivermectin to other medicines that do not work, like hydroxychloroquine, or whose effectiveness against COVID-19 is uncertain.

We evaluated the effects of ivermectin in infected people on:

– people dying;
– whether people's COVID-19 got better or worse;
– quality of life;
– serious and non-serious unwanted effects;
– viral clearance.

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

What did we do?

We searched for randomized controlled trials that investigated ivermectin to prevent or treat COVID-19. People treated in hospital or as outpatients had to have laboratory-confirmed COVID-19.

In this update, we also investigated the trustworthiness of the trials and only included them if they fulfilled clear ethical and scientific criteria.

We compared and summarized the results of the trials and rated our confidence in the evidence, based on common criteria such as trial methods and sizes.

What did we find?

We excluded seven of the 14 trials included in the previous review as these trials did not fulfil the expected ethical and scientific criteria. Together with four new trials, we included 11 trials with 3409 participants that investigated ivermectin combined with any usual care compared to the same usual care or placebo.

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

No trial investigated ivermectin to prevent SARS-CoV-2 infection.

We also found 31 ongoing trials, and an additional 28 trials still requiring clarification from the authors or not yet published.

Main results

Treating people in hospital with COVID-19

We do not know whether ivermectin compared with placebo or usual care 28 days after treatment:

– leads to more or fewer deaths (3 trials, 230 people);
– worsens or improves patients' condition, assessed by need for ventilation or death (2 trials, 118 people);
– increases or reduces serious unwanted events (2 trials, 197 people).

Ivermectin compared with placebo or usual care 28 days after treatment, may make little or no difference to:

– improving patients' condition, assessed by discharge from hospital (1 trial, 73 people);
– non-serious unwanted events (3 trials, 228 participants).

Seven days after treatment, ivermectin may make little or no difference to reduction of negative COVID-19 tests (3 trials, 231 participants) compared with placebo or usual care.

Treating outpatients with COVID-19

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Ivermectin compared with placebo or usual care 28 days after treatment, probably makes little or no difference to people dying (6 trials, 2860 people).

Ivermectin compared with placebo or usual care 28 days after treatment, makes little or no difference to quality of life (1 trial, 1358 people).

Ivermectin compared with placebo or usual care 28 days after treatment, may make little or no difference to:

– worsening patients' condition, assessed by admission to hospital or death (2 trials, 590 people);
– serious unwanted events (5 trials, 1502 people);
– non-serious unwanted events (5 trials, 1502 participants);
– improving people's COVID-19 symptoms in the 14 days after treatment (2 trials, 478 people);
– number of people with negative COVID-19 tests 7 days after treatment (2 trials, 331 people).

What are the limitations of the evidence?

Our confidence in the evidence, especially for outpatients, improved since the last review version, because we could look at more participants included in high-quality trials. Although we are quite certain regarding our results on risk of people dying and quality of life, the confidence in the evidence is still low for many other outpatient and inpatient outcomes because there were only few events measured. The methods differed between trials, and they did not report everything we were interested in, such as relevant outcomes.

How up to date is this evidence?

The systematic literature search is up to date to 16 December 2021. Additionally, we included trials with > 1000 participants up to April 2022.

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SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings table 1

Ivermectin for treating COVID-19 in inpatient settings with moderate to severe disease

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

Setting: inpatients

Intervention: ivermectin plus standard of care

Comparison: standard of care plus/minus placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with standard of care plus/minus placebo	Risk with ivermectin				
All-cause mortality at day 28	73 per 1000	44 per 1000 (10 to 183)	**RR 0.60** (0.14 to 2.51)	230 (3 RCTs)	⊕○○○ **Very low**[a]	We are uncertain whether ivermectin reduces or increases all-cause mortality at day 28.
Worsening of clinical status: participants with new need for invasive mechanical ventilation or death at day 28	154 per 1000	126 per 1000 (51 to 314)	**RR 0.82** (0.33 to 2.04)	118 (2 RCTs)	⊕○○○ **Very low**[a]	We are uncertain whether ivermectin reduces or increases clinical worsening, assessed by the need for invasive mechanical ventilation or death at day 28.
Improvement of clinical status: participants discharged alive at day 28	730 per 1000	752 per 1000 (569 to 986)	**RR 1.03** (0.78 to 1.35)	73 (1 RCT)	⊕⊕○○ **Low**[b]	Ivermectin may have little or no effect on clinical improvement, assessed by the number of participants discharged alive at day 28.
QoL at longest follow-up available	NA	NA	NA	NA	NA	No trials reported QoL at any time point.
Serious adverse events during the trial period	5 per 1000	8 per 1000 (0 to 179)	**RR 1.55** (0.07 to 35.89)	197 (2 RCTs)	⊕○○○ **Very low**[a]	We are uncertain whether ivermectin increases or reduces serious adverse events during the trial period.

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Any adverse events during the trial period	183 per 1000	190 per 1000 (112 to 328)	**RR 1.04** (0.61 to 1.79)	228 (3 RCTs)	⊕⊕○○ **Low**[b]	Ivermectin may have little or no effect on any adverse events during the trial period.
Viral clearance at day 7	370 per 1000	414 per 1000 (293 to 585)	**RR 1.12** (0.80 to 1.58)	231 (3 RCTs)	⊕⊕○○ **Low**[b]	Ivermectin may have little or no effect on viral clearance at day 7.

*__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; **NA**: not available; **QoL**: quality of life; **RCT:** randomized controlled trial; **RR:** risk ratio.

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, very few events, and wide CI.

[b]Downgraded one level for serious risk of bias and one level for serious imprecision due to few participants and wide CI.

Summary of findings 2. Summary of findings table 2

Ivermectin for treating COVID-19 in outpatient settings with asymptomatic or mild disease

Patient or population: all trials contributing results to the summary of findings table included people with mild disease (WHO scale 1 to 3)[§]

Setting: outpatients

Intervention: ivermectin plus standard of care

Comparison: standard of care plus/minus placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with standard of care	Risk with ivermectin				

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	plus/minus placebo					
All-cause mortality at day 28	27 per 1000	21 per 1000 (13 to 34)	**RR 0.77** (0.47 to 1.25)	2860 (6 RCTs)	⊕⊕⊕○ **Moderate**[a]	Ivermectin probably has little or no effect on all-cause mortality at day 28.
Worsening of clinical status: admission to hospital or death within 28 days	74 per 1000	81 per 1000 (15 to 445)	**RR 1.09** (0.20 to 6.02)	590 (2 RCTs)	⊕⊕○○ **Low**[b]	Ivermectin may have little or no effect on clinical admission to hospital or death within 28 days.
Improvement of clinical status: all initial symptoms resolved (asymptomatic) at day 14	591 per 1000	532 per 1000 (355 to 804)	**RR 0.90** (0.60 to 1.36)	478 (2 RCTs)	⊕⊕○○ **Low**[c]	Ivermectin may have little or no effect on clinical improvement, assessed by the number of participants with all initial symptoms resolved up to 14 days.
Improvement of clinical status: time to symptom resolution	NA	NA	NA	NA	NA[d]	No trial reported data for time to symptom resolution suitable for meta-analysis.
QoL (physical component) at up to 28 days, measured on the PROMIS Global-10 scale and normalized to values from 16.2, low QoL, to 67.2, maximum QoL	The mean score on a numerical quality of life scale was 49.6 points with a SD of 10.4 points	The mean score on a numerical quality of life scale was 49.6 points with a SD of 7.8 points	**MD 0.00** (-0.98 to 0.98) points	1358 (1 RCT)	⊕⊕⊕⊕ **High**	Ivermectin has little or no effect on QoL (PROMIS Global-10 physical component) at up to 28 days.
QoL (mental component) at up to 28 days, measured on the PROMIS Global-10 scale and normalized to values from 21.2, low QoL, to 67.6, maximum QoL	The mean score on a numerical quality of life scale was 52.5 points with a SD of 9 points	The mean score on a numerical quality of life scale was 52.5 points with a SD of 11.2 points	**MD 0.00** (-1.08 to 1.08) points	1358 (1 RCT)	⊕⊕⊕⊕ **High**	Ivermectin has little or no effect on QoL (PROMIS Global-10 mental component) at up to 28 days.
Serious adverse events during the trial period	4 per 1000	9 per 1000 (2 to 33)	**RR 2.27** (0.62 to 8.31)	1502 (5 RCTs)	⊕⊕○○ **Low**[e]	Ivermectin may have little or no effect on serious adverse events during the trial period.
Any adverse events during the trial period	320 per 1000	397 per 1000 (278 to 563)	**RR 1.24** (0.87 to 1.76)	1502 (5 RCTs)	⊕⊕○○ **Low**[f]	Ivermectin may have little or no effect on any adverse events during the trial period.
Viral clearance at day 7	237 per 1000	240 per 1000 (164 to 351)	**RR 1.01** (0.69 to 1.48)	331 (2 RCTs)	⊕⊕○○ **Low**[g]	Ivermectin may have little or no effect on viral clearance at day 7.

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*__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; **NA**: not available; **RCT:** randomized controlled trial; **RR:** risk ratio; **SD**: standard deviation; **QoL**: quality of life; §One contributing trial included people at WHO scale 2 to 4, but was considered an outpatient trial (WHO 2 to 3) based on the trial author's statement (majority of participants were ambulatory and well during admission, hospitalization mostly for isolation and close monitoring only in case of high risk of disease progression based on public health policy at the time of trial).

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 imprecision due to wide CI.
[b]Downgraded one level for serious inconsistency (I^2 = 44%) and one level for serious imprecision due to few events and wide CI.
[c]Downgraded one level for serious risk of bias and one level for serious inconsistency (I^2 = 57%).
[d]Two trials reported the median duration of symptom resolution for ivermectin versus placebo: one study reported 12 days (interquartile range (IQR) 9 to 13 days) in the placebo group versus 10 days (IQR 9 to 13 days) in the ivermectin group, the second study reported 14 days (IQR 11 to 14 days) for both groups.
[e]Downgraded one level for serious risk of bias and one level for serious imprecision due to very few events and wide CI.
[f]Downgraded one level for serious risk of bias (exclusion of one unblinded study with high risk of bias revealed an effect estimate of RR 1.07 (0.84 to 1.36), indicating no difference between ivermectin and placebo) and one level for serious inconsistency (I^2 = 80%).
[g]Downgraded one level for serious risk of bias and one level for serious imprecision due to wide CI.

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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 the World Health Organization (WHO) declared COVID-19 a pandemic. By January 2022, over 360 million cases were confirmed, including over 5.6 million deaths (WHO 2020a; WHO 2022a).

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 population characteristics, the case-mix of infected and deceased individuals, other local factors, and changes during the ongoing outbreak. With > 70% in-hospital mortality for people receiving ventilation (Karagiannidis 2020), 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 worldwide case-fatality ratio is estimated at 1.5%, with large statistical fluctuations (< 0.1% in Iceland up to almost 20% in Yemen; status January 2022) (Dong 2020). However, these varying rates should not be interpreted as markers for the quality of health care (Karagiannidis 2020), or the characteristics of different virus variants. Variations in case-fatality ratios may be explained by the mean age of a population or of those infected, national vaccination rates, quality and extent of local testing 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 sensitivity ranging from 70% to 98%, depending on pretest probability (Watson 2020). Offering lower sensitivity but greater practicality and accessibility, antigen tests are the primary instrument for COVID-19 diagnosis, especially in point-of-care testing (WHO 2020b).

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). The global vaccination campaign progresses, with 11.8 billion doses administered by May 2022 (Ritchie 2022), making a huge contribution in fighting the pandemic. However, global inequity ensures that not every region of the world has unlimited access to the vaccination. Therefore, the most effective, while ubiquitously available measures to control the virus spreading, are still non-pharmaceutical interventions, including physical distancing, wearing a face mask (especially when distancing cannot be maintained), ventilating rooms, avoiding crowds and close contact, regularly cleaning hands, and coughing into a bent elbow or tissue (WHO 2022b). Research on prophylaxis of SARS-CoV-2 infection and treatment of COVID-19 continues to be carried out globally. 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 the Americas, parts of Asia, and Africa.

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* (Campbell 1983). Ivermectin was introduced for medical use in 1982 and is effective against endoparasites such as *Onchocerca volvulus* and other helminths, as well as ectoparasites such as mites causing scabies and lice. The mode of action is based on binding to specific cell membrane channels that only occur in invertebrates (Campbell 1983; Dourmishev 2005; Panahi 2015). Ivermectin is on the WHO List of Essential Medicines for its high effectiveness against human endoparasite and ectoparasite infestations (WHO 2019).

In animals and humans, ivermectin is easily absorbed by the mucosa if taken orally, or by the skin if used 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 (Dourmishev 2005; González-Canga 2008; Panahi 2015). Ivermectin is widely used in veterinary medicine, and is an essential drug for treating human parasitic diseases, such as onchocerciasis, lymphatic filariasis, strongyloidiasis, and scabies globally (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 indications and doses, ivermectin is generally well tolerated. Adverse effects include weakness, drowsiness, diarrhoea, nausea, and vomiting. In addition, ivermectin can cause fever and rash (González-Canga 2008). Rare serious adverse effects can occur, such as vision problems, neurotoxicity, and liver damage. Those side effects seem to arise partially from ivermectin initiating the rapid death of parasites, especially when used for treatment of endoparasites, leading to hyperinflammation and anaphylactic reactions. Considering this pathomechanism, those effects should not occur in the treatment of viruses. However, the US Food and Drug Administration (FDA) has registered those toxic side effects in people using ivermectin in high doses for the treatment of COVID-19 (FDA 2020; González-Canga 2008).

How the intervention might work

One in vitro study showed that ivermectin can inhibit replication of 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

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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 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 viral diseases. Only one of these had published results (Yamasmith 2018). In this small, single-centre trial 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 a RNA virus closely related to SARS-CoV-1. In 2020, ivermectin gained much 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. This observation has led to ivermectin being suggested as a potential antiviral agent that could prevent infection with SARS-CoV-2 completely or at least the progression to severe COVID-19. 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, some COVID-19 clinical trials were initiated to investigate the prophylactic and therapeutic effects of ivermectin.

Why it is important to do this review

Globally, the numbers of new COVID-19 cases and deaths continue to increase with a substantial impact on healthcare systems. Vaccination remains a key response to address ongoing circulation and reduce the impact of emerging variants of concern. Despite efforts towards full vaccination uptake, pharmaceutical treatment interventions remain a mainstay in the management of COVID-19. So far, the drug treatments shown to be effective against COVID-19, and which are recommended in international guidelines, target SARS-CoV-2 itself or the immune response to the infection; for example dexamethasone, IL-6 inhibitors, JAK-inhibitors or monoclonal antibodies (Ghosn 2021; Kreuzberger 2021; Wagner 2021; NIH 2021; WHO 2021b).

Ivermectin is an inexpensive and widely-used medicine in humans and animals, 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, countries of Central and South America and Asia. In South America in particular, people began liberally self-medicating with ivermectin, and the drug has become part of public health policies without reliable scientific data; in May 2020, Bolivian health officials recommended ivermectin for the treatment of COVID-19 without supplying evidence, and municipalities promoted the drug as a preventive measure (Rodríguez-Mega 2020). Due to growing interest in ivermectin and increasing hospitalizations for toxic side effects, the FDA discouraged the use of ivermectin to treat or prevent COVID-19, and warned people not to self-medicate with formulations intended for animals (FDA 2020; Temple 2021).

The growing research interest in ivermectin has led to the registration of numerous clinical trials in registries worldwide. As of 27 January 2022, there were 83 trials registered on ClinicalTrials.gov (clinicaltrials.gov/) investigating ivermectin for COVID-19 in various settings.

Several trials 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 trials indicate no effect or even a negative effect on disease progression. Many trials are already summarized in existing systematic reviews, meta-analyses, and guidelines (Bryant 2021a; Izcovich 2021; NIH 2021). It should be kept in mind that several meta-analyses and reviews have been retracted, or their updates show major methodologic inconsistencies (Hill 2021b; Kory 2021). Additionally, many of the original trials have been retracted or have not been published in peer-reviewed journals, being 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 trials, 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 unreliable due to methodological inaccuracies and insufficient quality (Popp 2021d).

As of January 2022, the efficacy and safety of ivermectin for COVID-19 treatment and prophylaxis of SARS-CoV-2 infection are still subject to debate. The most recent guideline from the Association of Scientific Medical Societies in Germany (AWMF) stands by its recommendation against the use of ivermectin as antiviral treatment (German AWMF Guideline 2021a), while the Peruvian ministry of health removed its previous positive recommendation for the use of ivermectin entirely from its guideline (The Guardian 2021b). In February 2021, the US National Institutes of Health (NIH) revised its 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 the drug should 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 of SARS-CoV-2 infection and treatment of COVID-19. As this review (Popp 2021b), and the other reviews of the Cochrane Living Systematic Reviews Series on different interventions for COVID-19 (Ansems 2021; Kreuzberger

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2021; Mikolajewska 2021; Popp 2021c; Stroehlein 2021; Wagner 2021) are living systematic reviews during the COVID-19 pandemic, specific adaptions related to the research question, including participants, interventions, comparators, outcomes, and methods were necessary for this update. We have transparently reported relevant protocol changes between the review and update in the section Differences between protocol and review.

OBJECTIVES

To assess the efficacy and safety of ivermectin plus standard of care compared to standard of care plus/minus 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 trial 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 trials registers, and abstract publications. We applied no restrictions on the language of publication of the articles. All trials, especially preprint articles that have not been peer-reviewed, must have reported robust and valid data on trial design, participants' characteristics, interventions, and outcomes, to be eligible for inclusion.

For research integrity, we further assessed all trials meeting eligibility criteria using a tool developed by our group to deal with problematic trials (see Selection of studies).

Types of participants

Treatment of COVID-19

We included trials 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 trials 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 trial.

Prevention of SARS-CoV-2 infection

We included trials 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 and the vaccination status in included participants. A history of SARS-CoV-2 infection or vaccination was not an exclusion criterion.

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

Types of interventions

We considered all doses and regimens of ivermectin eligible and pooled them for the analysis. We considered and categorized dosing schemes into low (≤ 0.2 mg/kg orally, single dose) and high doses (> 0.2 mg/kg orally, single dose or with higher frequency). We plan to analyse different doses in subgroup analyses, if sufficient trials are available for review updates.

We compared ivermectin plus standard of care to standard of care plus/minus placebo. Co-interventions (standard of care) must have been comparable between the trial arms.

We planned to compare ivermectin to any other active pharmacological comparator with proven efficacy for prevention or treatment of COVID-19. Proven interventions were defined as those recommended by the WHO living guideline (Agarwal 2020). As of 8 December 2021, strong recommendations for dexamethasone and for IL-6 receptor blockers (tocilizumab and sarilumab) in critically ill COVID-19 patients, and conditional recommendations for casirivimab and imdevimab for COVID-19 patients with high risk of severe disease and for critically-ill patients with seronegative status were available (Agarwal 2020). For patients that qualify for a proven active intervention, it would be unethical to further conduct trials that use placebo only. In contrast, trials using comparators (e.g. azithromycin, Popp 2021c) with proven ineffectiveness may confound the assessment of the efficacy or safety of ivermectin, and therefore we excluded such trials. 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 (Popp 2021c; Singh 2021). From those comparisons, no reliable evidence can be obtained.

Trials 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 plus standard of care versus standard of care plus/minus placebo; and
- ivermectin versus active pharmacological intervention with proven efficacy (no trials available for the current review version).

Types of outcome measures

We evaluated core outcomes in accordance with the Core Outcome Measures in Effectiveness Trials (COMET) Initiative for COVID-19 patients (COMET 2020; Marshall 2020), and additional outcomes that have been prioritized by consumer representatives and the German guideline panel for inpatient therapy of people with COVID-19 (German AWMF Guideline 2021a) and for outpatient therapy (German AWMF Guideline 2021b). The current outcome set

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differed between previous protocols and reviews and the current review. Changes to the outcomes were necessary due to the risk of competing events associated with the original outcome set. We added outcomes for inpatients and outpatients that aim to simultaneously capture all participants of the population with clinical worsening and all participants with clinical improvement. This was possible by using composite outcomes, e.g. combining new need for invasive mechanical ventilation and death as clinical worsening for inpatients, and combining admission to hospital and death for outpatients. This adjusted outcome set should allow evidence on ivermectin to become more unambiguous and patient-relevant.

We analysed 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 trials 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 trials in the Characteristics of included studies table.

Ivermectin for treating COVID-19 in inpatient settings with moderate to severe disease

- All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge
- Clinical status at day 28, day 60, and up to the longest follow-up, including:
  - worsening of clinical status
    - participants with new need for invasive mechanical ventilation or death
    - participants with need for ICU admission or death
  - improvement of clinical status
    - participants discharged alive. Participants should be discharged without clinical deterioration or death.
- Quality of life, including fatigue and neurological status, assessed with standardized scales e.g. WHOQOL-100) at up to 7 days; up to 28 days, and longest follow-up available
- Serious adverse events during the trial period, defined as number of participants with any event
- Adverse events (any grade) during the trial period, defined as number of participants with any event
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, and at day 3, 7, and 14

Ivermectin for treating COVID-19 in outpatient settings with asymptomatic or mild disease

- All-cause mortality at day 28, day 60, time-to-event, and up to the longest follow-up
- Worsening of clinical status within 28 days:
  - admission to hospital or death
  - participants with need for ICU admission or death
- Improvement of clinical status:
  - all initial symptoms resolved (asymptomatic) at day 14, day 28, and up to the longest follow-up
  - time to symptom resolution
- Quality of life, including fatigue and neurological status, assessed with standardized scales (e.g. WHOQOL-100) at up to 7 days, up to 28 days, and longest follow-up available
- Serious adverse events during the trial period, defined as number of participants with any event
- Adverse events (any grade) during the trial period, defined as number of participants with any event
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, and at day 3, 7, and 14

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 trial 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 trial:
  - 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)
- All-cause mortality at day 28, day 60, time-to-event, and up to the longest follow-up
- Worsening of clinical status within 28 days:
  - admission to hospital or death
  - participants with need for ICU admission or death
- Quality of life, including fatigue and neurological status, assessed with standardized scales (e.g. WHOQOL-100) at up to 14 days; up to 28 days, and longest follow-up available
- Adverse events (any grade) during the trial period, defined as number of participants with any event

Timing of outcome measurement

We collected information on outcomes from all time points reported in the publications. If only a few trials contributed data to an outcome, we pooled different time points, provided the trials had produced valid data and pooling was clinically reasonable.

In case of time-to-event analysis, e.g. for time to death, we included the outcome measure based on the longest follow-up time and measured from randomization.

We reported time points of outcome measurement in the footnotes of the forest plots. We included serious adverse events and adverse events occurring during the trial period, including adverse events during active treatment and long-term adverse events as well. 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 7 days), medium-term outcomes (up to 14 days), and longer-term outcomes (28 days or more).

Secondary outcomes

This review update has no secondary outcomes. We treated all outcomes as a primary outcome set which informed the summary of findings tables.

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Search methods for identification of studies

Electronic searches

Our Information Specialist (MIM) conducted systematic searches of the following sources from inception to 16 December 2021 (date of last search for all databases) with no restrictions on the language of publication.

- Cochrane COVID-19 Study Register (CCSR) (www.covid-19.cochrane.org), 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):
  - Science Citation Index Expanded; and
  - Emerging Sources Citation Index.
- WHO Global literature on coronavirus disease database (search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov)
- HTA database (database.inahta.org)

For detailed search strategies, see Appendix 1.

We did not conduct separate searches of the databases required by MECIR standards (Higgins 2021), since these databases are regularly searched in the production of the CCSR.

Since the date of last search (16 December 2021) up to and including February 2022, we used the CCSR to monitor newly published results of RCTs on ivermectin on a weekly basis. In February 2022 we closed the trial pool for this review update. From April onwards we changed our screening to a monthly monitoring schedule, which two review authors will screen. In April, we identified one trial including > 1000 participants. We included this single trial due to its large size and considered this a justifiable compromise between being as up to date as possible in the dynamic of this pandemic and reasons of practicability.

Searching other resources

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

We searched for grey literature using the International HTA database (see previous section). In addition, we screened the sections regarding ivermectin on the COVID-NMA Working Group for eligible trials.

Data collection and analysis

Selection of studies

Inclusion criteria

We performed trial selection in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2020). Two out of three review authors (MP, SR, SW) 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 trials irrespective of whether measured outcome data were reported in a 'usable' way. We collated multiple reports of the same trial, so that the trial, rather than the report, was the unit of interest in the review.

We documented the trial selection process in a PRISMA flow diagram with the total number of trials included, excluded, awaiting classification, and ongoing (Moher 2009). We listed the reasons for exclusion and awaiting classification in the Characteristics of excluded studies and Characteristics of studies awaiting classification tables.

Research integrity screening

During this pandemic, several trials investigating ivermectin for COVID-19 turned out to be problematic and were either retracted or concerns were expressed due to misconduct or lack of research integrity (BBC NEWS; Elgazzar 2020; Retraction Watch Database (ivermectin); Samaha 2021). A ‘problematic study’ is defined by Cochrane as "Any published or unpublished study where there are serious questions about the trustworthiness of the data or findings, regardless of whether the study has been formally retracted; scientific misconduct will not be the only reason that a study might be problematic; problems may result from poor research practices or honest errors" (Cochrane policy - managing problematic studies). To respond to these facts and developments, we changed the inclusion criteria for this review update to identify and handle problematic trials, and considered research integrity of the individual trial as an important eligibility criteria. Current standard tools for systematic reviews do not systematically consider issues of research integrity. However, there are useful tools available, such as the REAPPRAISED checklist for evaluation of publication integrity (Grey 2020), or the data extraction sheet from Cochrane Pregnancy and Childbirth that addresses scientific integrity and trustworthiness (Data extraction template). Additionally, there is available implementation guidance on the Cochrane policy of managing potentially problematic studies (Implementation guidance - problematic studies). We used the Cochrane implementation guidance, modified the existing tools and developed a specific tool for the current review. This tool along with detailed methodological instructions and critical and important signalling questions to key aspects (domains), is available in Appendix 2 and described elsewhere (Weibel 2022). Briefly, trials were only eligible for the current review update if they met critical aspects assuring research integrity, such as retraction notices, prospective trial registration, ethics approval, plausible study authorship, sufficient reporting of methods regarding relevant eligibility criteria (e.g. randomization), and plausibility of study results. Two review authors independently re-evaluated all trials included in the original review version and assessed all new and eligible trials for research integrity. We excluded

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trials if they were retracted or if they were not prospectively registered in a national or international trials' registry according to the WHO guidelines for clinical trial registration (WHO 2018). We held all potentially eligible trials with disparities between the reporting of methods and results in 'awaiting classification' until the trial authors can clarify certain questions upon request. We documented the process and transparently reported all decisions.

Data extraction and management

Five review authors in teams of two (MP, SR, SS, RH, SW), independently extracted data using a standardized data extraction form, including details of the trial, 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.

We extracted the following information, if reported.

- General information: author, title, source, country, language, type of publication, publication date.
- trial characteristics: setting and dates, inclusion/exclusion criteria, number of trial arms, comparability of groups, treatment cross-overs, length of follow-up, funding.
- Participant characteristics: number of participants randomized/ received intervention/analysed, COVID-19 diagnostics, severity of disease, age, gender, comorbidities (e.g. diabetes, immunosuppression), concurrent interventions, time since symptom onset, vaccination status.
- Intervention: dose, frequency, start of treatment since symptom onset, duration and route of administration.
- Control intervention: type of control, frequency, duration and route of administration.
- Outcomes: as specified under Types of outcome measures.

Assessment of risk of bias in included studies

We assessed risk of bias in the included trials using the Cochrane RoB 2 tool (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 trials that we specified as outcomes for the current review and that contributed to the review's summary of findings tables.

Five review authors in teams of two (MP, SR, SS, RH, SW), independently assessed the risk of bias of all results. We resolved any disagreements through discussion with an additional 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.
- 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;
- 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.

Measures of treatment effect

For dichotomous outcomes, we recorded the number of events and the number of analysed 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, standard deviation (SD), and the number of analysed participants in the intervention and control groups. If the SD 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 trials 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 interquartile range (IQR) is approximately 1.35 SDs (Higgins 2020d). We used the MD with 95% CI as effect measure.

If available for future review updates, we plan to extract and report hazard ratios (HRs) for time-to-event outcomes (e.g. time to death). If HRs are not available, we will make every effort to estimate the HR as accurately as possible from available data using the methods proposed by Parmar 1998 and Tierney 2007. If sufficient trials had provided HRs, we planned to use HRs rather than RRs or MDs in a meta-analysis, as they provide more information.

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

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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 randomized participant.

In trials with multiple intervention groups, we combined groups if reasonable (e.g. trial 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 participants. There was no need to split shared groups for the current review.

Dealing with missing data

We have taken into account a number of potential sources of missing data in a systematic review or meta-analysis, which can affect the number of trials, 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. Missing trials 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 trial 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 trial 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 trials within each pairwise comparison were homogeneous enough, with respect to trial 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 trials.

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 trials (200 participants or more), since the interval would be imprecise when a summary estimate was based on only a few small trials. We used the open-source statistical software R package meta to calculate 95% PIs (Meta). We declared statistical heterogeneity if $P < 0.1$ for the Chi^2 statistic, or I^2 statistic ≥ 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 trials 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.

When there are 10 or more relevant trials 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 trials. 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. We will consider $P < 0.1$ 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

In the previous review version, we excluded high risk of bias trials from the primary analysis, with the aim to eliminate biased data and untrustworthy trials. However, to be transparent, we presented all trials in a secondary analysis. With the introduction of our new research integrity assessment, differentiation between primary and secondary analyses based on RoB ratings became dispensable. All included trials were eligible for the main analyses which informed the summary of findings tables and concerns regarding risk of bias were met with respective sensitivity analysis (see Sensitivity analysis).

We analysed 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 (no trials available for the current review version).

We created the comparisons:

- ivermectin plus standard of care versus standard of care plus/minus placebo; and
- Ivermectin versus active pharmacological intervention with proven efficacy (no trials available for the current review version).

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

If clinical and methodological characteristics of individual trials 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 trials. 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 trials. For continuous outcomes, we used the inverse-variance method.

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We planned to present descriptive statistics only if we deemed meta-analysis inappropriate for a certain outcome because of heterogeneity or because of serious trial limitations leading to considerably high risk of bias (e.g competing risk of death not taken into account in outcome measurement). This was not the case for the current review version.

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

Subgroup analysis and investigation of heterogeneity

We reported details of the intervention and severity of the condition at baseline for each trial in the footnotes of the forest plot. We investigated heterogeneity by visual inspection 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 trials had been available (at least 10 trials per outcome); the current review had insufficient trials. In review updates, we will perform subgroup analyses if statistical heterogeneity is present ($P < 0.1$ for the Chi^2 test of heterogeneity, $I^2 \geq 50\%$, 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);
  - severity of condition at baseline (moderate (WHO scale 4 to 5) versus severe disease (WHO scale 6 to 9)); inpatients only.
- Ivermectin used for prevention:
  - dose of ivermectin (low versus high);
  - mode of exposure (e.g. work place, nursing home) and burden of exposure (e.g. living in a high-risk area, high-risk medical contact) in prevention trials;
  - 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:

- trials with overall high risk of bias or some concerns;
- non-peer-reviewed trials (including preprint articles);
- trials 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;
- trials that started ivermectin treatment late (more than 5 days after symptom onset based on reported mean or median value of the trial) and trials without information on time point of treatment;
- participants with a history of SARS-CoV-2 infection/vaccination.

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).

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 and RoB sensitivity analysis to inform the risk of bias judgement underlying the assessment of the certainty of evidence.

We had planned to create 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 trials with active comparators. The summary of findings tables included the following outcomes.

For use of ivermectin investigating treatment of COVID-19 in an inpatient setting:

- all-cause mortality; all-cause mortality at hospital discharge preferred; if not reported, we will include all-cause mortality at day 60, followed by day 28, or time-to-event estimate;
- worsening of clinical status at day 28: participants with new need for invasive mechanical ventilation or death;
- improvement of clinical status at day 28: participants discharged alive;
- quality of life at longest follow-up available;
- serious adverse events during the trial period;
- any adverse events during the trial period;
- viral clearance at day 7.

For use of ivermectin investigating treatment of COVID-19 in an outpatient setting:

- all-cause mortality; all-cause mortality at longest follow-up and > 60 days preferred; if not reported, we will include all-cause mortality at day 60, followed by day 28, or time-to-event estimate;
- worsening of clinical status within 28 days: admission to hospital or death;
- symptom resolution;
  - all initial symptoms resolved (asymptomatic) at day 14
  - duration to symptom resolution
- quality of life at longest follow-up available;
- serious adverse events during the trial period;
- any adverse events during the trial period;
- viral clearance at day 7.

For use of ivermectin investigating prevention of SARS-CoV-2 infection (no trials were available for the current review version, therefore we did not create a summary of findings table):

- 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;
- worsening of clinical status within 28 days - admission to hospital or death;

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- all-cause mortality; all-cause mortality at longest follow-up and > 60 days preferred; if not reported, we will include all-cause mortality at day 60, followed by day 28, or time-to-event estimate;
- quality of life at longest follow-up available;
- any adverse events during the trial period.

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) provided us with a weekly monitoring of published RCTs up to and including February 2022. From April onwards we will change this list to a monthly monitoring schedule, 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 for 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 due to global controversies around the intervention, we will consider republishing an updated review even though our conclusions remain unchanged. We will review the scope and methods of the review 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

We conducted the literature search again completely without date restriction; this resulted in 567 records. We identified a further two records from a hand search of reference lists. Since the date of last search (16 December 2021) up to February 2022, we used the CCSR to monitor newly-published results of RCTs on ivermectin on a weekly basis. In addition, we found one trial that had provided data via personal communication had been published as a journal article during conduction of the review update (I-TECH 2022). Thus, we evaluated 570 records overall. The 22 records we had identified by hand search in the previous review, appeared in searched databases by the time of this updated search, and could be deduplicated. After removing duplicates, 382 records remained. During title and abstract screening, we judged 200 records as irrelevant as they did not meet the prespecified inclusion criteria. We proceeded to full-text screening with 182 records, of which 39 records were newly identified in the updated search and 143 records that had already been screened in the previous review version had to be reassessed for eligibility. The re-evaluation was necessary because the research integrity assessment was introduced as a new eligibility criteria for trials, and additionally, previously ongoing trials had to be reassessed if new information had become available in the meantime. Decisions from the original review version that were changed due to assessment of the trials' research integrity can be found in Table 1. We considered published full texts in journals or on preprint servers or, if these were unavailable, entries in trial registers. We excluded 55 trials (84 records) with reasons after full-text assessment. We identified 31 ongoing trials (37 records) and 28 trials (30 records) awaiting assessment. In February 2022 we set the deadline for inclusion of newly-published trial results for this review update. Hence, after initially closing the trial pool for this review update, we identified one trial with more than 1000 participants, previously classified as ongoing, that published its results in March 2022. We included this trial in the review without an additional systematic search, resulting in 11 trials (32 records) that met our eligibility criteria and enabled us to perform qualitative syntheses and meta-analyses (quantitative syntheses). The search process is shown in Figure 1.

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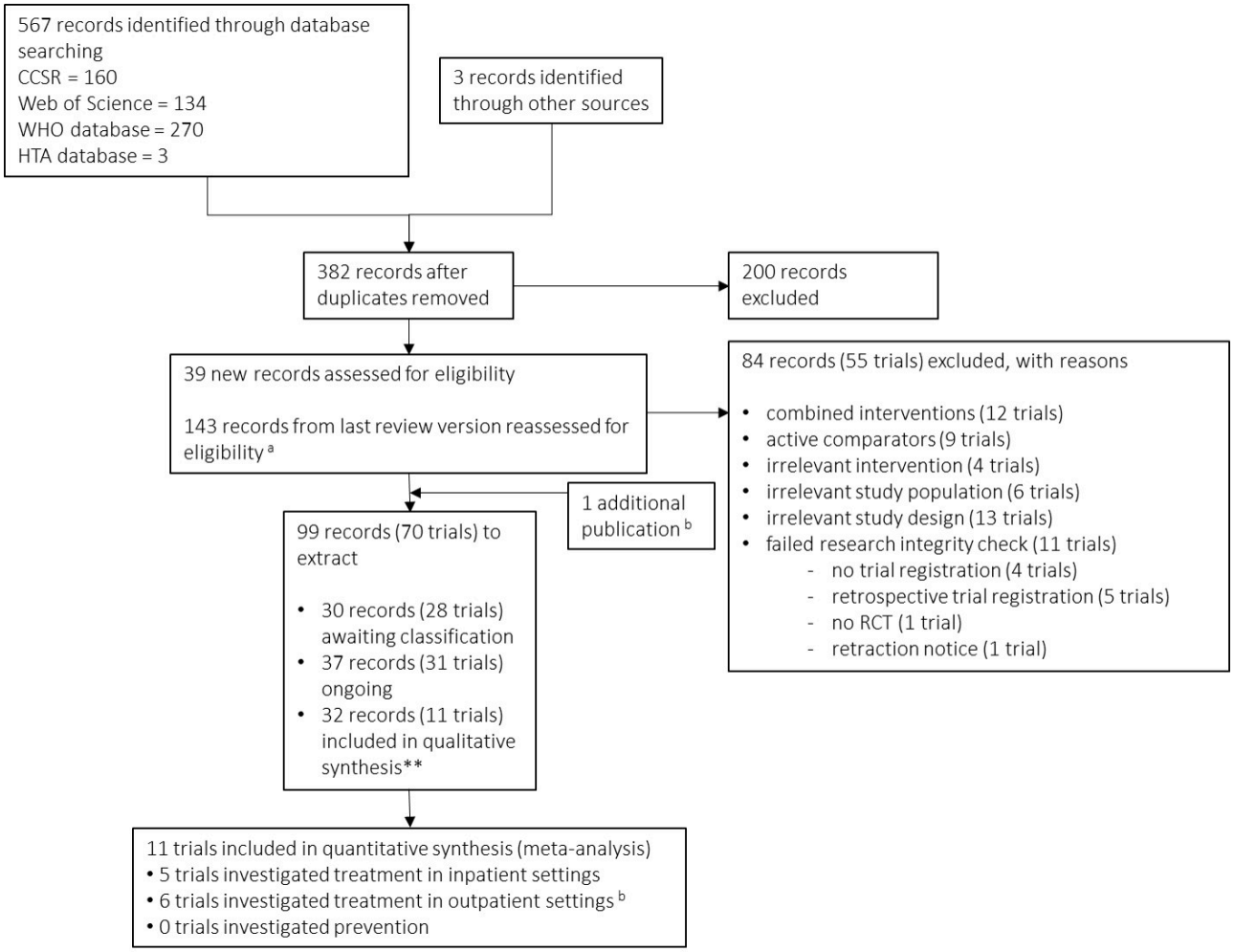
Figure 1. [a]For research integrity we had to reassess the study pool from the original review (new eligibility criteria) (Figure 1; Supplementary File_Ivermectin_Research Integrity); for details on changed decision see Table 1. [b]After initially closing the study pool for this review update in February 2022, we identified one trial with > 1000 participants, previously classified as ongoing, that published its results in March 2022 (TOGETHER 2022). We included the trial in the review without an additional systematic search. We show it here as added after the initial screening process; we performed research integrity assessement before inclusion.



Eligibility screening for research integrity

We evaluated all eligible trials for issues with research integrity:

- 14 included trials from the previous review (Ahmed 2020; Chachar 2020; Kishoria 2020; Okumuş 2021; Podder 2020; Shah Bukhari 2021; Shouman 2021; Chaccour 2021; Gonzalez 2021; Kirti 2021; Krolewiecki 2021; López-Medina 2021; Mohan 2021; Pott-Junior 2021);
- three trials with results awaiting classification from the previous review (Faisal 2020; Samaha 2021; NCT04407507);
- seven trials with results identified by the updated search (Bounfrate 2021; I-TECH 2022; Vallejos 2021; Abd-Elsalam 2021; Biber 2021; Aref 2021; NCT04673214);
- one trial, previously classified as ongoing, including > 1000 participants identified after closing the trial pool for this update (TOGETHER 2022).

The research integrity assessment is described in Appendix 2 and decisions concerning this review's trial pool are transparently reported and publicly available (Supplementary File_Ivermectin_Research Integrity).

One trial awaiting classification in the previous review version was retracted in the meantime (Samaha 2021); we excluded the trial in this review update. We excluded three included trials (Ahmed 2020; Kishoria 2020; Podder 2020), and one trial awaiting classification (Faisal 2020) from the previous review as they were not registered in a national or international trials registry. Before making the final decision on this, we contacted the trial authors to make sure we had not overlooked any registration. Three included trials from the previous review (Chachar 2020; Okumuş 2021; Shah Bukhari 2021), and two trials with newly-identified full-text publications (Abd-Elsalam 2021; Biber 2021) were retrospectively registered; i.e. the date of first enrolment of participants was before the date of first protocol submission to the trials register. We used the date of submission instead of the date first posted to exclude a possible

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delay in the registration process at this point in the pandemic. We excluded these retrospectively registered trials also. One included trial from the previous review turned out to be a non-randomized trial (Shouman 2021). The authors described the method used for randomization via personal communication, which we then assessed as non-randomized alternate allocation; we excluded this trial from this review update.

We held all potentially eligible trials with disparities in the reporting of the methods and results in 'awaiting classification' until the trial authors respond to our information requests. One trial awaiting classification in the previous review version (NCT04407507), and one trial with newly-identified published results (NCT04673214), have not been published as full texts yet, and relevant information assuring research integrity is missing from the trials' registry record. Aref 2021 described their randomization method insufficiently in the journal publication, therefore the actual trial design remained unclear. We requested clarification regarding information on randomization methods and trial results: NCT04602507 investigators responded that they would share any data/information once the trial is published; NCT04673214 investigators could not clarify all outstanding issues in time; and Aref 2021 did not respond at all. We will re-evaluate trials awaiting classification in the next review update.

Study designs and publication status

See Characteristics of included studies table.

We included 11 trials describing 3409 adults randomized to trial arms relevant for the review question (Bounfrate 2021; Chaccour 2021; Gonzalez 2021; I-TECH 2022; Kirti 2021; Krolewiecki 2021; López-Medina 2021; Mohan 2021; Pott-Junior 2021; TOGETHER 2022; Vallejos 2021). Three trials had an open-label design (I-TECH 2022; Krolewiecki 2021; Pott-Junior 2021), and the other eight trials were double-blinded and placebo-controlled (Bounfrate 2021; Chaccour 2021; Gonzalez 2021; Kirti 2021; López-Medina 2021; Mohan 2021; TOGETHER 2022; Vallejos 2021). Four trials were multicentre trials in Argentina (Krolewiecki 2021), Italy (Bounfrate 2021), Brazil (TOGETHER 2022), and Malaysia (I-TECH 2022). The remaining seven trials were single-centre trials in Argentina (Vallejos 2021), Brazil (Pott-Junior 2021), Colombia (López-Medina 2021), India (Mohan 2021; Kirti 2021), Mexico (Gonzalez 2021), and Spain (Chaccour 2021).

Of 11 included trials, seven comprised two trial arms (Chaccour 2021; I-TECH 2022; Kirti 2021; Krolewiecki 2021; López-Medina 2021; TOGETHER 2022; Vallejos 2021), and three trials comprised three trial arms, of which two trials investigated ivermectin at two different dosages (Bounfrate 2021; Mohan 2021), that were pooled for this review, and one included an active comparator not eligible for this review (Gonzalez 2021). One trial comprised four trial arms (Pott-Junior 2021), with three different ivermectin dosages pooled for this review.

The largest trial was TOGETHER 2022 with 1358 randomized participants. Chaccour 2021 had the smallest sample size of 24 randomized participants.

Of the included trials, 10 were available as peer-reviewed journal articles (Bounfrate 2021; Chaccour 2021; I-TECH 2022; Kirti 2021; Krolewiecki 2021; López-Medina 2021; Mohan 2021; Pott-Junior 2021; TOGETHER 2022; Vallejos 2021), of which three trials, included as preprint articles in the previous review have since been published as journal articles (Kirti 2021; Krolewiecki 2021; Mohan 2021). We further included one trial that has not yet been peer-reviewed, and is published on a preprint sever (Gonzalez 2021). In November 2021 trial investigators of I-TECH 2022 directly contacted us and provided unpublished trial details with outcome data without a request from us; we have included the data in this review. Additionally, I-TECH 2022 was officially published as a peer-reviewed journal article in February 2022.

Three trials were funded by pharmaceutical companies producing ivermectin, including Laboratorio Elea Phoenix SA (Krolewiecki 2021), Windlas Biotech Ltd (Mohan 2021), and Sun Pharma Ltd (Kirti 2021). One trial was funded by Insud Pharma (Bounfrate 2021), which provided ivermectin and placebo for the trial. From the company's website it appears that Insud Pharma distributes ivermectin commercially via a subcontractor. Four trials were funded by departmental resources only (Chaccour 2021; Gonzalez 2021; López-Medina 2021; Pott-Junior 2021). Three trials were funded by their respective Ministries of Health, Italy (Bounfrate 2021), Malaysia (I-TECH 2022), and Argentina (Vallejos 2021), and one trial by grants from non-profit organizations (TOGETHER 2022).

Participants

All 11 trials investigated ivermectin for treatment of COVID-19 and included participants with SARS-CoV-2 infection confirmed by RT-PCR or antigen testing. This review update did not include any trials investigating ivermectin for the prevention of SARS-CoV-2-infection. Of the 11 trials, five were performed in an inpatient setting (Gonzalez 2021; Kirti 2021; Krolewiecki 2021; Mohan 2021; Pott-Junior 2021), and six in an outpatient setting (Bounfrate 2021; Chaccour 2021; I-TECH 2022; López-Medina 2021; TOGETHER 2022; Vallejos 2021). I-TECH 2022 included patients hospitalized for the purpose of isolation and close monitoring due to public health policy at the time of trial. Based on that, we classified the setting as outpatient.

Participants included in Chaccour 2021 and TOGETHER 2022 had mild COVID-19 according to a patient state of 2 to 3 on the WHO scale. In I-TECH 2022 severity of the condition according to the WHO scale was described as 2 to 4, but we transferred this to an outpatient population with mild disease, i.e. WHO 2 to 3, based on the trialists statement described above. Participants in López-Medina 2021 had mostly mild COVID-19, defined as WHO 2 to 3, but < 1% of participants were hospitalized with or without supplemental oxygen. Bounfrate 2021 and Vallejos 2021 included mild and asymptomatic COVID-19 patients, defined as WHO 1 to 3. Four of the five inpatient trials included participants with moderate COVID-19 with or without supplemental oxygen according to WHO 4 and 5 (Kirti 2021; Krolewiecki 2021; Mohan 2021; Pott-Junior 2021). In Gonzalez 2021, all participants received supplemental oxygen (WHO 5).

The overall mean age in the trials was 45 years. Chaccour 2021 included the youngest participants with a median age of 28 years. I-TECH 2022 included the oldest participants with a mean age of 63 years. The mean proportion of women in all included trials was 44%. The lowest proportions of men were in López-Medina 2021 and TOGETHER 2022 with 42% men, while Kirti 2021 included the highest proportion with 72% men.

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The trials partially reported comorbidities and relevant risk factors for severe COVID-19, such as obesity, diabetes, respiratory diseases, hypertension, and immunosuppression (see Characteristics of included studies table). I-TECH 2022 only included patients aged 50 years and above with at least one prespecified comorbidity. TOGETHER 2022 defined age (> 50 years) or at least one prespecified comoridity as inclusion criteria. Two trials excluded existing comorbidities and specified them in the inclusion and exclusion criteria (Chaccour 2021; Krolewiecki 2021). One trial reported no data on risk factors in their publications or trial reports (Pott-Junior 2021).

Eight trials were conducted before the global vaccination campaigns. Of the two trials including vaccinated participants, Bounfrate 2021 reported an overall vaccination rate of about 3% and I-TECH 2022 included over 50% of participants with two doses of vaccine and about 30% of unvaccinated participants. The authors of TOGETHER 2022 stated that vaccinated, as well as unvaccinated participants, were eligible for the trial, but did not provide further details on the vaccination status of included participants.

Interventions and comparators

All trials administered ivermectin orally. The daily dosages varied between fixed doses of 12 mg to 24 mg or weight-adjusted doses of 100 µg/kg to 400 µg/kg, two trials used higher doses with 600 µg/kg (Bounfrate 2021; Krolewiecki 2021) and 1200 µg/kg (Bounfrate 2021). Two trials used low doses (200 µg/kg orally, single dose) in at least one trial arm (Mohan 2021; Pott-Junior 2021). All other trials applied higher doses either in one single dose or multiple doses for up to 5 days. Participants received single-dose ivermectin in two trials (Chaccour 2021; Mohan 2021), two doses in two trials (Kirti 2021; Vallejos 2021), three doses in one trial (TOGETHER 2022), and five doses in five trials (Bounfrate 2021; Gonzalez 2021; I-TECH 2022; Krolewiecki 2021; López-Medina 2021). In one trial, 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). In addition to ivermectin all trials administered some form of standard of care that was also equal between intervention and control group.

Most trials started treatment at a mean of 5 days after symptom onset. Kirti 2021 and Pott-Junior 2021 had the longest time since symptom onset with a mean of 6.9 (SD 6.6) days and a median of 8 (IQR 7 to 10) days. Gonzalez 2021 did not report on time since symptom onset.

We found no trials comparing ivermectin to an active comparator with proven efficacy. Eight trials administered placebo tablets as the control intervention in addition to standard of care (Bounfrate 2021; Chaccour 2021; Gonzalez 2021; Kirti 2021; López-Medina 2021; Mohan 2021; TOGETHER 2022; Vallejos 2021). The remaining three trials administered standard of care alone (I-TECH 2022; Krolewiecki 2021; Pott-Junior 2021). Standard of care varied between trials, but was the same in all trial arms of the individual trials. Five trials did not provide details of standard of care (Bounfrate 2021; Chaccour 2021; I-TECH 2022; Krolewiecki 2021; Vallejos 2021). Two trials used a combination of interventions including hydroxychloroquine, favipiravir, and azithromycin (Kirti 2021; Mohan 2021). Five trials administered corticosteroids such as dexamethasone (Gonzalez 2021; Kirti 2021; López-Medina 2021; Mohan 2021; Pott-Junior 2021). López-Medina 2021 and TOGETHER 2022 utilized antipyretic drugs for symptomatic treatment.

Outcome measures

All trials reported at least one outcome eligible for this review update, therefore, all trials contributed data to one or more meta-analyses.

The most investigated primary outcomes, as defined by the trial, were either (time to) viral clearance or a reduction in the viral load which was reported in six trials (Bounfrate 2021; Chaccour 2021; Kirti 2021; Krolewiecki 2021; Mohan 2021; Pott-Junior 2021). López-Medina 2021 defined 'resolution of symptoms' as the primary outcome, while the primary outcome in Vallejos 2021, TOGETHER 2022 and I-TECH 2022 was defined as 'progression of the disease' (measured by hospitalization or need for supplemental oxygen, respectively). The primary outcomes in Gonzalez 2021 were duration of hospitalization until discharge due to clinical improvement and duration of hospitalization. Two trials defined safety outcomes as additional primary outcomes (Bounfrate 2021; Gonzalez 2021).

For the inpatient setting, no new trials contributed data to the primary outcomes of this review update compared to the previous review version. However, meta-analyses changed due to the adjusted primary outcome set. For each outcome, data were available from three trials at the most. We were able to pool data for mortality (measured at 28 days in Gonzalez 2021 and Kirti 2021 and 30 days in Krolewiecki 2021) with clinical reason. Data usable to assess the outcomes, clinical worsening ('participants with new need for invasive mechanical ventilation or death') and clinical improvement ('participants discharged alive') at day 28 were reported for eligible time points by two trials (Gonzalez 2021; Krolewiecki 2021-reporting for 30 days) and one trial (Gonzalez 2021), respectively. Any adverse events during the trial period were reported by Krolewiecki 2021 at 30 days, by Mohan 2021 at 14 days, and by Pott-Junior 2021 at 28 days. Two of those also measured serious adverse events, Krolewiecki 2021 at 30 days and Mohan 2021 at 14 days. The trials used slightly varying, though equally relevant definitions, for both outcomes. As for the time point, we decided it was clinically reasonable to pool the available data as 'during the trial period', because the intervention was not administered in any of the trials for more than 5 days.

Viral clearance was reported by three trials: Kirti 2021 reported this outcome for day 6, Pott-Junior 2021 for day 7, and Mohan 2021 for day 5. We judged these time points as eligible and clinically reasonable for pooling the review's outcome of viral clearance at day 7. Mohan 2021 also reported eligible data for day 3, however we judged the trial's data for day 7 as unusable because no result was available for many participants.

For the outpatient setting, several primary outcomes (as defined by the new outcome set of this review) were reported by all included trials. Five trials reported mortality at 28 or 30 days (Bounfrate 2021; Chaccour 2021; I-TECH 2022; TOGETHER 2022; Vallejos 2021); López-Medina 2021 reported this outcome at 21 days, however as those time points lie closely together, especially in respect to the patient setting, we considered pooling the data clinically reasonable. Serious adverse events and any adverse events during the trial period were reported by Bounfrate 2021 at 30 days, by Chaccour 2021 and I-TECH 2022 at 28 days, by López-

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Medina 2021 at 21 days, and by Vallejos 2021 until the participants were declared SARS-CoV-2 negative, which was at a median of 12 days. The trials used slightly varying, though equally relevant definitions, for both outcomes. As for the time point, we decided it was clinically reasonable to pool the available data as 'during the trial period', because the intervention was not administered in any of the trials for more than 5 days.

Viral clearance was reported by four trials (Bounfrate 2021; Chaccour 2021; TOGETHER 2022; Vallejos 2021) for several time points as defined (3, 7 and 14 days) and we used these trials for meta-analyses. However, for the time point of 7 days (included in the summary of findings tables), only Chaccour 2021 and TOGETHER 2022 contributed outcome data. Outcome data usable for measuring clinical worsening within 28 days ('admission to hospital or death' and 'participants with need for ICU admission or death') were reported by the newly-included trials for 28 and 30 days (Bounfrate 2021; Vallejos 2021 and I-TECH 2022, respectively). Symptom resolution was reported by Bounfrate 2021 at day 14 and 30, as well as by López-Medina 2021 for day 15 and 21. We were able to pool both trials for the review's primary outcomes' symptom resolution at day 14 and 28, respectively, with clinical reason. López-Medina 2021 and TOGETHER 2022 additionally reported duration to symptom resolution.

TOGETHER 2022 measured health-related quality of life in outpatients at 28 days on a standardized scale, the PROMIS Global-10 scale, separated in a physical and mental component. No trial measured quality of life in the inpatient setting and no trial followed up participants for more than 30 days in either setting.

Due to the new eligibility criteria for research integrity, which revealed Shouman 2021 as a non-RCT, no trials in this update investigated prevention of SARS-CoV-2 infection.

Excluded studies

See Characteristics of excluded studies table.

We excluded 55 trials that did not match our inclusion criteria. Twelve trials 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). Nine trials investigated active comparators without proven efficacy (Babalola 2021; CTRI/2020/08/027282; CTRI/2020/08/027394; CTRI/2020/10/028335; CTRI/2021/03/031665; Elgazzar 2020; Galan 2021; NCT04435587; Seet 2021). One of these trials was retracted by Research Square on 14 July 2021 due to an expression of concern (Elgazzar 2020; The Guardian 2021a). Four trials focused on an intervention other than ivermectin (NCT04345419; NCT04374279; NCT04382846; NCT04723459). Six trials analysed an ineligible trial population including RT-PCR negative participants (IRCT20180922041089N4; NCT04530474; NCT04703608; NCT04951362; Niaee 2021; Shahbaznejad 2021). Five trials were registered retrospectively (Abd-Elsalam 2021; Biber 2021; Chachar 2020; Okumuş 2021; Shah Bukhari 2021), and four trials were not registered at all (Ahmed 2020; Faisal 2020; Kishoria 2020; Podder 2020). Of those nine trials, six belonged to the 11 trials overall that we judged as eligible in the previous review, but that we have now excluded because they failed the research integrity check. Fourteen trials were not RCTs (Behera 2020; Cadegiani 2020; Camprubi 2020; Carvallo 2020; Chahla 2021b; Gorial 2020; Lima-Morales 2021; Morgenstern 2020; Mustaq 2021; NCT04373824; NCT04937569; Ozer 2021; Rajter 2021; Shouman 2021). We included Shouman 2021 in the previous review, but have excluded it from this review update as the research integrity check revealed it to be a non-RCT.

Studies awaiting classification

See Characteristics of studies awaiting classification table.

Twenty-eight trials are awaiting classification until publication of results, a protocol update or clarification of details by the trial authors (2020-001971-33/ES; 2020-002091-12/BG; 2020-005015-40/SK; Aref 2021; CTRI/2020/04/024948; CTRI/2020/06/025960; Hosseini 2021; IRCT20111224008507N4; IRCT20180612040068N1; IRCT20190602043787N3; IRCT20190624043993N2; IRCT20200329046892N3; IRCT20200404046937N4; IRCT20200408046987N3; IRCT20200422047168N2; IRCT20210213050344N1; ISRCTN90437126; NCT04351347; NCT04374019; NCT04407130; NCT04407507; NCT04602507; NCT04673214; NCT04746365; NCT04891250; NCT04894721; NCT05076253; PACTR202102588777597).

Of those, three trials were generally eligible for inclusion but did not pass the research integrity check (Aref 2021; NCT04407507; NCT04673214), as relevant information to assure trustworthiness was missing. Contact with the trialists either yielded no or only partial responses that could not fully clarify the issue at the time of completing this review update.

We identified 13 completed and potentially-eligible RCTs from trial register entries, but no results were available or published (2020-002091-12/BG; Hosseini 2021; IRCT20111224008507N4; IRCT20180612040068N1; IRCT20190602043787N3; IRCT20190624043993N2; IRCT20200329046892N3; IRCT20200404046937N4; IRCT20200422047168N2; IRCT20210213050344N1; NCT04407130; NCT04894721; NCT05076253). Of those, seven investigated ivermectin as treatment for inpatients (2020-002091-12/BG; IRCT20180612040068N1; IRCT20190602043787N3; IRCT20200329046892N3; IRCT20200404046937N4; IRCT20200422047168N2; NCT04407130), three investigated the treatment for outpatients (IRCT20111224008507N4; IRCT20210213050344N1; NCT05076253), and one investigated both settings (Hosseini 2021). Only one trial investigated ivermectin as prevention of SARS-CoV-2 infection in close contacts (NCT04894721), and for one trial the setting was unclear (IRCT20190624043993N2). Eight trials compared ivermectin plus standard of care to standard of care plus placebo, five compared ivermectin plus standard of care to standard of care alone. Enrolment numbers ranged from 50 to 1000 participants. Of those 13 completed trials without results, four had a planned completion date of 2020, with the latest updates to the trial register entries between May 2020 and February 2021 (2020-002091-12/BG; IRCT20190602043787N3; IRCT20200422047168N2; NCT04407130) and nine had a planned completion date of 2021, with the latest trial register entries between July 2020 and December 2021 (Hosseini 2021; IRCT20180612040068N1; IRCT20190602043787N3; IRCT20190624043993N2; IRCT20200329046892N3;

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IRCT20200404046937N4; IRCT20210213050344N1; NCT04894721; NCT05076253).
For almost 70% (9/13) of completed trials, the planned completion date was more than 6 months ago, without having published any results, either in the trial registry or as full text (2020-002091-12/BG; Hosseini 2021; IRCT20180612040068N1; IRCT20190602043787N3; IRCT20190624043993N2; IRCT20200329046892N3; IRCT20200422047168N2; IRCT20210213050344N1; NCT04407130).

Three trials have been terminated without publication of interim results so far (2020-005015-40/SK; NCT04602507; PACTR202102588777597). Of those, one trial took place in an inpatient setting (NCT04602507), one in an inpatient as well as prevention setting (PACTR202102588777597), and one in an outpatient setting (2020-005015-40/SK). One trial compared ivermectin plus standard of care to standard of care plus placebo (2020-005015-40/SK) and two compared ivermectin plus standard of care to standard of care alone (NCT04602507; PACTR202102588777597).

Nine trials were not sufficiently explicit in their protocol to allow us to make a final decision on eligibility. First, none of the following seven trials 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; NCT04746365; NCT04891250). Additionally, for one of those trials, it was unclear if a RT-PCR-confirmed SARS-CoV-2 infection was required for inclusion (NCT04351347). Similarly, two trials 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 a total of 31 trials as ongoing. Twenty-six trials investigate ivermectin for treatment of COVID-19 (2021-002024-21/CZ; 2021-000166-15/HU; ACTRN12620000982910; Ashraf 2021; CTRI/2020/05/025068; CTRI/2020/05/025224; Garcia 2021; IRCT20111224008507N5; IRCT20190417043295N2; ISRCTN86534580; NCT04425707; NCT04445311; NCT04510194; NCT04510233; NCT04703205; NCT04712279; NCT04729140; NCT04834115; NCT04836299; NCT04885530; NCT04886362; NCT04944082; NCT05040724; NCT05041907; NCT05155527; SLCTR/2021/020), four trials for prevention of a SARS-CoV-2 infection (ACTRN12621001535864; NCT04527211; NCT05060666; PACTR202102848675636), and one trial investigates both hypotheses (2020-001994-66/ES).

Nine inpatient trials investigate ivermectin plus standard of care versus standard of care plus/minus placebo for treatment of COVID-19 (2021-002024-21/CZ; CTRI/2020/05/025068; CTRI/2020/05/025224; IRCT20111224008507N5; IRCT20190417043295N2; NCT04425707; NCT04836299; NCT04944082; SLCTR/2021/020), with five of those using a placebo in the comparator group (2021-002024-21/CZ; IRCT20111224008507N5; IRCT20190417043295N2; NCT04836299; SLCTR/2021/020). Trial sizes are small, with enrolment numbers mainly below 100. Only two trials plan to enrol more than 200 participants (IRCT20111224008507N5; SLCTR/2021/020). NCT04425707 is still recruiting, although the planned completion date is more than 6 months ago. Two other trials have not started recruitment yet, although their completion date lies in the past (NCT04836299; NCT04944082). Four trials do not indicate a planned completion date in their registry entry (2021-002024-21/CZ; CTRI/2020/05/025068; CTRI/2020/05/025224; SLCTR/2021/020). For two trials, the planned completion date lies in the future (IRCT20111224008507N5; IRCT20190417043295N2).

Three trials, all including less than 200 participants, were unclear whether they plan to investigate ivermectin for COVID-19 treatment in an in- or outpatient setting; they are either still recruiting (Ashraf 2021; NCT04445311), or not yet recruiting (NCT04510233), although the completion date they initially stated in their registry entry was more than 6 months ago.

There are 14 outpatient trials investigating ivermectin plus standard of care versus standard of care plus/minus placebo for treatment of COVID-19 (2021-000166-15/HU; ACTRN12620000982910; Garcia 2021; ISRCTN86534580; NCT04510194; NCT04703205; NCT04712279; ; NCT04729140; NCT04834115; NCT04885530; NCT04886362; NCT05040724; NCT05041907; NCT05155527), with only two of those not using a placebo in the comparator group (ISRCTN86534580; NCT05041907). Trial sizes vary, but enrolment numbers of all trials are above 100. Only three trials plan to enrol less than 200 participants (2021-000166-15/HU; Garcia 2021; NCT04729140), five trials plan to enrol more than 500 participants (ISRCTN86534580; NCT04510194; NCT04885530; NCT04886362; NCT05041907). Eight outpatient trials are still recruiting (Garcia 2021; ISRCTN86534580; NCT04510194; NCT04703205; NCT04729140; NCT04834115; NCT04885530; NCT05041907), five are not yet recruiting (ACTRN12620000982910; NCT04712279; NCT04886362; NCT05040724; NCT05155527), and one trial does not report its recruitment status (2021-000166-15/HU). Two trials are still recruiting, although the planned completion date is more than 6 months ago (Garcia 2021; NCT04834115), and one trial with a planned completion date of more than 6 months ago has not yet started recruitment (NCT04712279). Two trials do not indicate a planned completion date in their registry entry (2021-000166-15/HU; ACTRN12620000982910). One trial had planned to be completed in December 2021, but has not yet started recruitment (NCT04886362). Eight trials are planned to be completed in the course of 2022 (ISRCTN86534580; NCT04703205; NCT04729140; NCT05040724; NCT05155527; NCT04510194) or 2023 (NCT04885530; NCT05041907).

Trials to prevent SARS-CoV-2 infection compare ivermectin with placebo; in general these trials have not yet started recruiting (ACTRN12621001535864; NCT04527211; NCT05060666; PACTR202102848675636). Two of those trials should have already been completed (NCT04527211; PACTR202102848675636), with the former trial indicating a completion date of more than 6 months ago (NCT04527211). The trial investigating both treatment and prevention was planned to be completed more than 6 months ago, and has no information on recruitment status (2020-001994-66/ES).

In summary, 15 of the ongoing trials have passed their completion dates, i.e. up to mid-2021, or the trial register did not contain any information on a planned completion date; about 50% (8/15)

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should have been completed more than 6 months ago, but none have published results, either in a trial registry or as full text.

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

Risk of bias in included studies

We assessed methodological quality and risk of bias for 11 RCTs contributing results to our primary outcomes using the RoB 2 tool (Bounfrate 2021; Chaccour 2021; Gonzalez 2021; I-TECH 2022; Kirti 2021; Krolewiecki 2021; López-Medina 2021; Mohan 2021; Pott-Junior 2021; TOGETHER 2022; Vallejos 2021). In total, the 11 trials contributed 44 trial results to 19 outcomes (7 outcomes for hospitalized COVID-19 individuals; 12 outcomes for outpatients), that we assessed using RoB 2. The RoB 2 judgements for all trial results per outcome and for all domains are available in an interactive risk of bias table (Supplementary File_Ivermectin_Risk of Bias) and are briefly summarized below. The complete set of data is available in the Supplementary File_Ivermectin_Risk of Bias.

Overall risk of bias by outcome

Of 44 trial results, we assessed 22 (50%) at overall low risk of bias, 17 (38.6%) with some concerns, and 5 (11.4%) at overall high risk of bias.

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

Ivermectin for treating COVID-19 in inpatient settings with moderate to severe disease

We have at least some level of concern regarding risk of bias across trials for all outcomes included in the summary of findings tables. For the outcomes 'all-cause mortality at day 28', 'improvement of clinical status at day 28: participants discharged alive' and 'serious adverse events during the trial period', we assessed all trials contributing estimable data to the meta-analyses as having some concern for bias due to concerns across various domains.

For the outcome 'worsening of clinical status at day 28: participants with new need for invasive mechanical ventilation or death', 91.6% of weight in the meta-analysis came from one trial (Gonzalez 2021); we were concerned with insufficient information about allocation concealment and blinding of healthcare providers, and concerned that the protocol failed to define the time point of this outcome measurement.

Key concerns across trials and per outcome were identified for the following outcomes: ‘any adverse events during the trial period’ due to lack of blinding of participants and outcome assessors for a patient-reported outcome in two trials, 63.9% weight in the meta-analysis (Krolewiecki 2021; Pott-Junior 2021), and 'viral clearance at day 7' due to an inappropriate per-protocol analysis and missing outcome data in two trials, 54.7% weight in the meta-analysis (Kirti 2021; Pott-Junior 2021).

Ivermectin for treating COVID-19 in outpatient settings with asymptomatic or mild disease

We have no concerns regarding risk of bias across trials for the outcomes ‘worsening of clinical status within 28 days: admission to hospital or death’, 'quality of life (physical component) at up to 28 days', and 'quality of life (mental component) at up to 28 days'; three low risk of bias trials contributed data to these results (Bounfrate 2021; TOGETHER 2022; Vallejos 2021).

We identified some concerns across trials and per outcome for the outcomes 'symptom resolution: all initial symptoms resolved (asymptomatic) at day 14' and 'serious adverse events during the trial period', with 68.3% and 100% of weight in the meta-analyses coming from trials with some level of concern due to lack of information on definition and measurement of the outcome (Bounfrate 2021; Chaccour 2021), not prospectively registering the outcome (Bounfrate 2021; Chaccour 2021), lack of blinding of outcome assessors (I-TECH 2022), or inappropriate analysis (López-Medina 2021). We had concerns for the outcome 'all-cause mortality at day 28' due to inappropriate per-protocol analysis in one trial with 2.3% weight in the meta-analysis (López-Medina 2021). We assessed the outcome 'viral clearance at day 7' as having some concerns regarding risk of bias due to insufficient explanation for missing outcome data in one trial with 98.5% weight in the meta-analysis (TOGETHER 2022).

We identified key concerns for the outcome ‘any adverse events during the trial period’; the high risk of bias in this outcome measurement was caused by lack of blinding of the outcome assessors in one trial, contributing 13.8% weight to the meta-analysis.

Effects of interventions

See: **Summary of findings 1** Summary of findings table 1; **Summary of findings 2** Summary of findings table 2

We included 11 trials in the qualitative synthesis as well as in the meta-analyses (quantitative synthesis) of this review (Bounfrate 2021; Chaccour 2021; Gonzalez 2021; I-TECH 2022; Kirti 2021; Krolewiecki 2021; López-Medina 2021; Mohan 2021; Pott-Junior 2021; TOGETHER 2022; Vallejos 2021). All included trials compared ivermectin plus standard of care to standard of care plus/minus placebo.

Five trials investigated ivermectin for treating COVID-19 in an inpatient setting and contributed data to meta-analyses (Gonzalez 2021; Kirti 2021; Krolewiecki 2021; Mohan 2021; Pott-Junior 2021). All trials investigated participants with moderate COVID-19, no trial investigated severe disease. Therefore, planned subgroup analyses for severity at baseline were not possible. No trial followed up participants for more than 1 month. The main findings are summarized in Summary of findings 1.

Six trials investigated ivermectin for treating COVID-19 in an outpatient setting and contributed data to meta-analyses (Bounfrate 2021; Chaccour 2021; I-TECH 2022; López-Medina 2021; TOGETHER 2022; Vallejos 2021). All trials investigated participants with asymptomatic to mild COVID-19. No trial followed up participants for more than 1 month. The main findings are summarized in Summary of findings 2.

We planned to investigate heterogeneity for the characteristics: dose, age and severity of the condition, within the different settings by subgroup analysis, if at least 10 trials per outcome had been available; due to insufficient trials, we were unable to perform this.

We used sensitivity analyses to test the robustness of meta-analyses by excluding trials with overall high or some risk of

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bias, non-peer-reviewed trials, and trials that started ivermectin treatment late (more than 5 days after symptom onset): only one trial was not peer-reviewed (Gonzalez 2021 for inpatients); and we excluded three trials in the sensitivity analyses because they started treatment later than 5 days after symptom onset (Gonzalez 2021 days not reported; Kirti 2021 with mean 6.9 ± 6.6 days; Pott-Junior 2021 with median 8 (IQR 7 to 10) days), all other trials started treatment at a mean of 5 days after symptom onset. We did not perform sensitivity analyses regarding vaccination status, since most of the trials recruited non-vaccinated participants before vaccines became available. I-TECH 2022 and Bounfrate 2021 included vaccinated participants, however the proportion was either insignificant (I-TECH 2022 with 2% vaccination), or outcome data were not reported for the vaccinated subgroup (Bounfrate 2021). According to the trial protocol of TOGETHER 2022, vaccinated participants were eligible for inclusion, however there is no information whether any vaccinated people were included in the trial. History of SARS-CoV-2 infection was not investigated in the included trials.

In this update, no eligible trial investigated ivermectin for preventing SARS-CoV-2 infection.

Ivermectin for treating COVID-19 in inpatient settings with moderate to severe disease

All-cause mortality at day 28

Three trials comparing ivermectin plus standard of care to standard of care plus/minus placebo reported data on mortality at day 28 for 230 participants with moderate disease (Gonzalez 2021; Kirti 2021; Krolewiecki 2021). In the meta-analysis, five participants died in the ivermectin group and nine participants in the comparator group (Analysis 1.1). We are uncertain whether ivermectin plus standard of care reduces or increases all-cause mortality at 28 days compared to standard of care plus/minus placebo (risk ratio (RR) 0.60, 95% confidence interval (CI) 0.14 to 2.51; 3 trials, 230 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, very few events, and wide CI. Two trials had some concerns regarding risk of bias (Gonzalez 2021; Kirti 2021). The sensitivity analysis including only one trial with low risk of bias was not estimable due to zero events (1 trial, 45 participants). This equals the sensitivity analysis including only one trial starting treatment at a mean of 5 days after symptom onset (Krolewiecki 2021). Again, we had to exclude Gonzalez 2021 and Kirti 2021 because they did not report time since symptom onset or started treatment late, respectively. One trial was published as a preprint article (Gonzalez 2021). The sensitivity analysis including only trials published in a journal (Kirti 2021; Krolewiecki 2021), estimated the intervention effect with even more imprecision at RR 0.15 (95% CI 0.01 to 2.80; 2 trials, 157 participants).

Mohan 2021 reported mortality for inpatients at 14 days, which was too short and not eligible for meta-analysis. The data were not comparable with trials reporting our predefined time point of 28 days.

Worsening of clinical status

Participants with new need for invasive mechanical ventilation or death at day 28

Two trials comparing ivermectin plus standard of care to standard of care plus/minus placebo reported data on clinical worsening, assessed by new need for invasive mechanical ventilation or death at day 28 for 118 participants with moderate disease (Gonzalez 2021; Krolewiecki 2021). Seven participants in the ivermectin group and eight participants in the comparator group showed clinical worsening (Analysis 1.2). We are uncertain whether ivermectin plus standard of care reduces or increases clinical worsening, assessed by participants with new need for invasive mechanical ventilation or death compared to standard of care plus/minus placebo at day 28 (RR 0.82, 95% CI 0.33 to 2.04; 2 trials, 118 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, very few events, and wide CI. One trial had some concerns regarding risk of bias, was published as a preprint article, and did not report time since symptom onset (Gonzalez 2021). The sensitivity analysis including only the trial with low risk of bias, being published in a journal and started treatment early (Krolewiecki 2021), estimated the intervention effect with even more imprecision at RR 1.55 (95% CI 0.07 to 35.89; 1 trial, 45 participants).

One trial in an inpatient setting reported worsening of clinical status at 14 days (Mohan 2021), and one trial reported participants with new need for invasive mechanical ventilation at day 28 (Kirti 2021), but without the competing endpoint of death. Those trials were clinically not comparable with trials reporting our predefined outcome and were therefore not eligible for meta-analysis.

Participants with need for ICU admission or death

No trial reported data for participants with need for ICU admission or death at day 28. Two trials reported ICU admission at day 28 without the endpoint of death. Those trials did not take into account the competing risk of death in outcome measurement and were therefore not eligible for meta-analysis (Kirti 2021; Pott-Junior 2021).

Improvement of clinical status

Participants discharged alive

One trial comparing ivermectin plus standard of care to standard of care plus placebo in 73 participants with moderate disease reported participants discharged alive at day 28 (Gonzalez 2021). In both groups, 27 participants were discharged alive at 28 days (Analysis 1.3). Ivermectin plus standard of care may have little or no effect on clinical improvement, assessed by the number of participants discharged alive at day 28 compared to standard of care plus placebo (RR 1.03, 95% CI 0.78 to 1.35; 1 trial, 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 and a wide CI. Gonzalez 2021 had some concerns regarding risk of bias, was published as a preprint article, and did not state when they started treatment.

Mohan 2021 reported this outcome for inpatients at 14 days which was too short, and Kirti 2021 reported the outcome but without the time point of assessment. Those trials were clinically not

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comparable with trials reporting our predefined outcome and were therefore not eligible for meta-analysis.

Quality of life at longest follow-up available

No trial reported data for quality of life at any time point.

Serious adverse events during the trial period

Two trials comparing ivermectin plus standard of care to standard of care plus/minus placebo reported serious adverse events during the trial period in 197 participants with moderate disease (Krolewiecki 2021; Mohan 2021). Only one participant showed any serious adverse events in the ivermectin group (Analysis 1.4). We are uncertain whether ivermectin plus standard of care increases or reduces serious adverse events during the trial period compared to standard of care plus/minus placebo (RR 1.55, 95% CI 0.07 to 35.89; 2 trials, 197 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, very few events, and wide CI. Sensitivity analysis was not necessary since both trials had some concerns regarding risk of bias, were published as journal articles, and started treatment no longer than an average of 5 days after symptom onset.

Adverse events (any grade) during the trial period

Three trials comparing ivermectin plus standard of care to standard of care plus/minus placebo reported any adverse events during the trial period in 228 participants with moderate disease (Krolewiecki 2021; Mohan 2021; Pott-Junior 2021). Thirty-four participants in the ivermectin group and 13 participants in the comparator group experienced adverse events (Analysis 1.5). Ivermectin plus standard of care may have little or no effect on any adverse events during the trial period compared to standard of care plus/minus placebo (RR 1.04, 95% CI 0.61 to 1.79; 3 trials, 228 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 and a wide CI. We did not judge any trial at low risk of bias, and sensitivity analysis excluding two trials with high risk of bias regarding this outcome (Krolewiecki 2021; Pott-Junior 2021), did not change the conclusion (RR 1.21, 95% CI 0.50 to 2.97; 1 trial, 152 participants). The same accounts for excluding the trial that started treatment late after symptom onset (Pott-Junior 2021), which resulted in an estimated effect of the intervention at RR 1.26 (95% CI 0.69 to 2.31; 2 trials, 197 participants). All trials were published as journal articles.

Viral clearance at day 3

One trial comparing ivermectin plus standard of care to standard of care plus placebo reported viral clearance at day 3 in 125 participants with moderate disease (Mohan 2021). Ten participants in the ivermectin group and 7 participants in the placebo group reached viral clearance at day 7 (Analysis 1.6). Due to a very wide CI and few participants, the effect of ivermectin plus standard of care compared to standard of care plus placebo for viral clearance at day 3 remained unclear (RR 0.80, 95% CI 0.33 to 1.96; 1 trial, 125 participants). The trial had low risk of bias, was published in a journal, and started treatment early.

Viral clearance at day 7

Three trials comparing ivermectin plus standard of care to standard of care plus/minus placebo reported viral clearance at day 7 in 231 participants with moderate disease (Kirti 2021; Mohan 2021; Pott-Junior 2021). Sixty-three participants in the ivermectin group and 34 participants in the comparator group reached viral clearance at day 7 (Analysis 1.7). Ivermectin plus standard of care may have little or no effect on viral clearance at 7 days compared to standard of care plus/minus placebo (RR 1.12, 95% CI 0.80 to 1.58; 3 trials, 231 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 and a wide CI. Excluding two trials with high risk of bias regarding this outcome (Kirti 2021; Pott-Junior 2021) did not change the conclusion (RR 1.33, 95% CI 0.80 to 2.20; 1 trial, 125 participants). This sensitivity analysis is the same as for analysing the only trial that started treatment early (Mohan 2021). All trials were published as journal articles.

Viral clearance at day 14

No trial reported data for viral clearance at day 14.

Ivermectin for treating COVID-19 in outpatient settings with asymptomatic or mild disease

All-cause mortality at day 28

Six trials comparing ivermectin plus standard of care to standard of care plus/minus placebo reported data on mortality at day 28 for 2860 participants with mild disease (Bounfrate 2021; Chaccour 2021; I-TECH 2022; López-Medina 2021; TOGETHER 2022; Vallejos 2021). Sixty-six deaths occurred overall, 28 in the ivermectin group and 38 in the comparator group (Analysis 2.1). Ivermectin plus standard of care probably has little or no effect compared to standard of care plus/minus placebo on all-cause mortality at day 28 (RR 0.77, 95% CI 0.47 to 1.25; 6 trials, 2860 participants; moderate-certainty evidence). Heterogeneity was low ($I^2 = 0$) and the 95% prediction interval (PI) (0.26 to 2.25) revealed a similar clinical interpretation of the effect estimate compared to the 95% CI. We downgraded the certainty of evidence one level for serious imprecision due a wide CI. Sensitivity analysis, excluding one trial with some concerns regarding risk of bias (López-Medina 2021), did not change the conclusion (RR 0.75, 95% CI 0.38 to 1.46; 5 trials, 2462 participants). All trials started treatment no longer than an average of 5 days after symptom onset.

Worsening of clinical status

Admission to hospital or death within 28 days

Two trials comparing ivermectin plus standard of care to standard of care plus placebo reported data on clinical worsening, assessed by admission to hospital or death within 28 days for 590 participants with mild disease (Bounfrate 2021; Vallejos 2021). Eighteen participants in the ivermectin group and 21 participants in the comparator group showed clinical worsening (Analysis 2.2). Ivermectin plus standard of care may have little or no effect compared to standard of care plus placebo on clinical worsening, assessed by admission to hospital or death within 28 days (RR 1.09, 95% CI 0.20 to 6.02; 2 trials, 590 participants; low-certainty evidence). We downgraded the certainty of evidence one level for serious inconsistency, due to moderate heterogeneity between trials ($I^2 = 44\%$) and one level for serious imprecision due to few events and a wide CI. Both trials had low risk of bias, were peer-reviewed, and started treatment early.

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Participants with need for ICU admission or death within 28 days

One trial comparing ivermectin plus standard of care to standard of care alone reported data on clinical worsening, assessed by need for ICU admission or death within 28 days for 490 participants with mild disease (I-TECH 2022). Eight participants in the ivermectin group and 13 participants in the comparator group showed clinical worsening (Analysis 2.3). Due to a very wide CI and few events, the effect of ivermectin plus standard of care compared to standard of care alone for ICU admission or death within 28 days remained unclear (RR 0.64, 95% CI 0.27 to 1.51; 1 trial, 490 participants). The trial had low risk of bias, started treatment early, and was peer-reviewed.

Improvement of clinical status

All initial symptoms resolved (asymptomatic) at day 14

Two trials comparing ivermectin plus standard of care to standard of care plus placebo reported data on symptom resolution at 14 days in 478 participants with mild disease (Bounfrate 2021; López-Medina 2021). In the ivermectin group 143 participants and in the comparator group 133 participants were asymptomatic at day 14 (Analysis 2.4). Ivermectin plus standard of care may have little or no effect compared to standard of care plus placebo on clinical improvement, assessed by the number of participants with all initial symptoms resolved up to 14 days (RR 0.90, 95% CI 0.60 to 1.36; 2 trials, 478 participants; low-certainty evidence). We downgraded one level for serious risk of bias and one level for serious inconsistency, due to substantial heterogeneity between trials (I^2 = 57%). Sensitivity analysis excluding the trial with some concerns regarding risk of bias widened the CI, but did not change the conclusion (RR 0.67, 95% CI 0.38 to 1.16; 1 trial, 80 participants). Both trials started treatment early and were peer-reviewed.

I-TECH 2022 reported this outcome for outpatients at day 5 which was too short, clinically not comparable with trials reporting our predefined outcome, and was therefore not eligible for meta-analysis.

All initial symptoms resolved (asymptomatic) at day 28

Two trials comparing ivermectin plus standard of care to standard of care plus placebo reported data on symptom resolution at 28 days in 478 participants with mild disease (Bounfrate 2021; López-Medina 2021). In the ivermectin group 204 participants and in the comparator group 177 participants were asymptomatic at day 28 (Analysis 2.5). Ivermectin plus standard of care showed no effect compared to standard of care plus placebo for improvement of clinical status, assessed by the number of participants with all initial symptoms resolved up to 28 days (RR 1.03, 95% CI 0.94 to 1.13; 2 trials, 478 participants). Sensitivity analysis excluding the trial with some concerns regarding risk of bias widened the CI, but did not change the conclusion (RR 0.97, 95% CI 0.75 to 1.25; 1 trial, 80 participants). Both trials started treatment early and were peer-reviewed.

Time to symptom resolution

Two trials comparing ivermectin plus standard of care to standard of care plus placebo reported data on time of symptom resolution (López-Medina 2021; TOGETHER 2022). In both trials, data were reported as median with interquartile range (IQR) in 398 and 1358 participants with mild disease, respectively. In 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; TOGETHER 2022 reported 14 days (IQR 11 to 14 days) for both groups. Neither trial was eligible for meta-analysis due to asymmetric distribution of the data. Bounfrate 2021 narratively reported median time to symptom resolution but without IQRs.

Quality of life at longest follow-up available

One trial comparing ivermectin plus standard of care to standard of care plus placebo reported quality of life at up to 28 days in 1458 participants with mild disease (TOGETHER 2022). In the trial, health-related quality of life was measured on a standardized scale using the PROMIS Global-10 scale, separated into a physical and mental component. Normalized scores from 16.2 and 21.2 points to 67.7 and 67.6 points, indicate lowest to the highest physical and mental quality of life, respectively.

The trial reported data as median with IQR, and we transformed the data into mean with standard deviation (SD). For the physical component, the mean score in participants in the ivermectin group was 49.6 points with a SD of 7.8 points and 49.6 points with a SD of 10.4 points in the comparator group (Analysis 2.6). Ivermectin plus standard of care has little or no effect on quality of life at up to 28 days compared to standard of care plus placebo (mean difference (MD) 0.00, 95% CI -0.98 to 0.98; 1 trial, 1358 participants; high-certainty evidence).

For the mental component, the mean score in participants in the ivermectin group was 52.5 points with a SD of 11.2 points and 52.5 points with a SD of 9 points in the comparator group (Analysis 2.7). Ivermectin plus standard of care has little or no effect on quality of life at up to 28 days compared to standard of care plus placebo (MD 0.00, 95% CI -1.08 to 1.08; 1 trial, 1358 participants; high-certainty evidence).

TOGETHER 2022 had low risk of bias for both outcomes, was published as a journal article, and started treatment no longer than an average of 5 days after symptom onset.

Serious adverse events during the trial period

Five trials comparing ivermectin plus standard of care to standard of care plus/minus placebo reported data on serious adverse events during the trial period for 1502 participants with mild disease (Bounfrate 2021; Chaccour 2021; I-TECH 2022; López-Medina 2021; Vallejos 2021). With 13 participants experiencing serious adverse events, there were very few events overall (Analysis 2.8). Ivermectin plus standard of care may have little or no effect on serious adverse events during the trial period compared to standard of care plus/minus placebo (RR 2.27, 95% CI 0.62 to 8.31; 5 trials, 1502 participants; low-certainty evidence). Heterogeneity was low (I^2 = 0) and the 95% PI was not presented because it was not reliable as two out of five trials were not estimable due to zero events in both trial arms. We downgraded the certainty of evidence one level for serious risk of bias and one level for serious imprecision due to very few events and a wide CI. Sensitivity analysis only including trials with low risk of bias (Vallejos 2021), revealed a non-estimable effect of the intervention due to zero events (1 trial, 501 participants). All trials started treatment no longer than an average of 5 days after symptom onset.

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Adverse events (any grade) during the trial period

Five trials comparing ivermectin plus standard of care to standard of care plus/minus placebo reported data for any adverse events during the trial period for 1502 participants with mild disease (Bounfrate 2021; Chaccour 2021; I-TECH 2022; López-Medina 2021; Vallejos 2021). In the ivermectin group 280 participants and in the comparator group 237 participants experienced adverse events during the trial period (Analysis 2.9). Ivermectin plus standard of care may have little or no effect on any adverse events during the trial period compared to standard of care plus/minus placebo (RR 1.24, 95% CI 0.87 to 1.76; 5 trials, 1502 participants; low-certainty evidence). We downgraded the certainty of evidence one level for serious risk of bias. We did not downgrade two levels for risk of bias because exclusion of one unblinded trial with high risk of bias revealed an effect estimate of RR 1.07 (0.84 to 1.36), indicating no difference between ivermectin and placebo. We downgraded the certainty of evidence another level for serious inconsistency due to substantial heterogeneity between trials (I^2 = 80%, 95% PI 0.38 to 4.02). Sensitivity analysis only including trials with low risk of bias (Chaccour 2021; Vallejos 2021), estimated the effect of the intervention at RR 0.94 (95% CI 0.65 to 1.37; 2 trials, 525 participants) which did not change the conclusion. All trials started treatment no longer than an average of 5 days after symptom onset.

TOGETHER 2022 reported this outcome as adverse events separated into grade 1 to 4 for outpatients at 28 day which was not eligible for meta-analysis of adverse events of any grade, since one patient could experience several outcomes of different grades and would therefore potentially be counted multiple times.

Viral clearance at day 3

Two trials comparing ivermectin plus standard of care to standard of care plus placebo reported data on viral clearance at day 3 in 819 participants with mild disease (Vallejos 2021; TOGETHER 2022). In the ivermectin group 124 participants and in the comparator group 137 participants reached viral clearance at day 3 (Analysis 2.10). Ivermectin plus standard of care showed no effect compared to standard of care plus placebo for viral clearance at day 3 (RR 0.93, 95% CI 0.78 to 1.12; 2 trials, 819 participants). Sensitivity analysis excluding one trial with some concerns regarding risk of bias (TOGETHER 2022), did not change the conclusion (RR 0.95, 95% CI 0.78 to 1.14; 1 trial, 501 participants). Both trials started treatment early and were peer-reviewed.

Viral clearance at day 7

Two trials comparing ivermectin plus standard of care to standard of care plus placebo reported viral clearance at day 7 in 331 participants with mild disease (Chaccour 2021; TOGETHER 2022). Thirty-seven participants in the ivermectin group and 42 participants in the placebo group reached viral clearance at day 7 (Analysis 2.11). Ivermectin plus standard of care may have little or no effect on viral clearance at day 7 compared to placebo (RR 1.01, 95% CI 0.69 to 1.48; 2 trials, 331 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 a wide CI. One trial had some concerns regarding risk of bias (TOGETHER 2022). The sensitivity analysis, including only one trial with low risk of bias estimated the intervention effect with more imprecision at RR 3.00 (95% CI 0.13 to 67.06; 1 trial, 24 participants), supporting the decision on the certainty of the evidence. Both trials were published as a journal article and started treatment early.

Viral clearance at day 14

Two trials comparing ivermectin plus standard of care to standard of care plus placebo reported data on viral clearance at day 14 for 588 participants with mild disease (Bounfrate 2021; Vallejos 2021). In the ivermectin group 243 participants and in the comparator group 237 participants reached viral clearance at day 14 (Analysis 2.12). Ivermectin plus standard of care showed no effect compared to standard of care plus placebo for viral clearance at day 14 (RR 0.96, 95% CI 0.90 to 1.03; 2 trials, 588 participants). Both trials had low risk of bias, were peer-reviewed, and started treatment early.

Ivermectin for preventing SARS-CoV-2 infection

No eligible trials investigated ivermectin plus standard of care with standard of care plus/minus placebo for prevention of SARS-CoV-2 infection.

DISCUSSION

Summary of main results

For this review update, we reappraised eligible trials for research integrity. We excluded 7 of the 14 trials included in the previous review version; six were not prospectively registered and one turned out to be non-randomized. Four trials of the updated search passed the research integrity assessment and were eligible for this review. Finally, this review included 11 trials with 3409 participants investigating ivermectin plus standard of care compared to standard of care plus/minus placebo. Investigating treatment of COVID-19, five trials were conducted in inpatient settings with moderate COVID-19 (WHO 4 to 5) only and six trials in outpatient settings with mild COVID-19 (WHO 1 to 3). No trial investigated ivermectin for the prevention of SARS-CoV-2 infection. The included trials contributed 44 trial results to the review, about one-half of which we assessed as having some concerns or high risk of bias. The main findings of this review are summarized in Summary of findings 1 (treatment; inpatients) and Summary of findings 2 (treatment; outpatients). The number of trials per outcome increased compared to the previous review version, especially in the outpatient setting. For the inpatient setting though, there were still no more than three trials per outcome providing useful data for our updated outcome set.

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 (3 trials) nor outpatients (6 trials). The certainty of evidence for this finding was very low and moderate, respectively. Since the last review, the certainty of evidence increased for mortality in outpatients from very low to moderate.

For all other outcomes relevant for inpatients with moderate disease, such as risk of clinical worsening, being discharged alive, adverse or serious adverse events, and viral clearance, ivermectin showed no evidence of an effect, neither for improving nor worsening the respective outcome. The certainty of evidence for those findings varied from very low to low. Compared to the previous review version, certainty of evidence for any adverse events and viral clearance at day 7 in the inpatient setting increased from very low to low in this update.

For the outpatient setting, the relevant outcome of admission to hospital or death as well as quality of life, that were not reported

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by any trial in the previous review version, could be evaluated in this update. Overall, for all the outcomes relevant for outpatients with mild disease, such as risk of needing hospitalization, resolving symptoms, adverse or serious adverse events and viral clearance, ivermectin showed no evidence of an effect neither for improving nor worsening the respective outcome. The certainty of evidence for all of those findings was low. With high certainty, we found that ivermectin showed no effect on quality of life for the outpatient setting.

No trial investigated ivermectin for the prevention of SARS-CoV-2 infection. Hence, no evidence could be found for postexposure prophylaxis in this matter.

Overall completeness and applicability of evidence

First, with the new outcome set in this update, we mainly addressed the issue of competing outcome risk. We combined outcomes that represent clinical worsening with the outcome of death which would allow evidence on ivermectin to become more unambiguous and patient-relevant.

Four newly-included trials for the outpatient setting increased certainty of evidence on ivermectin for this purpose compared to the previous review version. Overall, the included trials investigated participants with COVID-19 at WHO 1 to 3 and WHO 4 to 5. Therefore, findings of this review are transferable to patients with COVID-19 at mild to moderate stages. In this update, no trials investigated ivermectin for severe COVID-19 (WHO 6 to 9). Considering the proposed mode of action, no effect of the drug would be expected if given at such a late stage of the disease. Hence, we do not consider this to be an evidence gap that needs to be closed. Moreover, with few exceptions, most included trials reported treatment initiation within a mean of 5 days after symptom onset, which is in line with the propagated hypothesis of ivermectin's inhibitory effect on virus replication in early stages of the disease.

In contrast to the hype around ivermectin's potential to prevent a SARS-CoV-2 infection after high-risk contact, no RCT investigating this purpose has been published since the previous review version. Most trials were conducted before any form of vaccination was available, leading to 93% of participants across trials knowingly not being vaccinated. Therefore, we could not assess the influence of vaccination status in this review update. Equally, we could not identify any evidence on the effect of ivermectin on the newly-emerging Omicron variant.

Overall, most trials reported a mean age far below 60 years (overall mean age was 45 years with a mean range from 28 to 63 years). Additionally, in the inpatient setting, trials included people with few or no comorbidities. Considering age and pre-existing conditions as the most important risk factors for developing severe COVID-19 and complications from the disease, the current evidence for inpatients is not applicable to patients who are at most risk of suffering COVID-19 with serious consequences such as death or need for mechanical ventilation. In the outpatient setting, applicability of the evidence improved compared to the previous review version, since three of six trials included large proportions of participants with comorbidites, such as obesity and hypertension.

COVID-19 vaccinations provide the most reliable and safest protection against the SARS-CoV-2 virus and progression to severe disease, however due to global inequity, not every region of the world has unlimited access to vaccinations. Therefore, it is to be expected that countries with low and middle healthcare expenditure, focus research efforts on repurposing of drugs. Accordingly, six trials were conducted in Latin America, three in Asia, and only two in Europe. In some of these countries, uncontrolled ivermectin use is making it difficult to test the effectiveness of the antiparasite drug against SARS-CoV-2 (Rodríguez-Mega 2020).

All trials administered ivermectin per mouth, but the doses and durations of administration varied. We set 200 µg/kg/day orally as the low dose based on the dosing recommendation for strongyloidiasis (WHO 2019). Five of the 11 trials used low doses in at least one trial arm. All other trials utilized higher doses, either in a single dose or over 2 to 5 days. Due to the small number of trials 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.

Overall, although we were able to increase the certainty of evidence in this review update, 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. During the literature search, we found two major ongoing trials soon to be completed (ISRCTN86534580; NCT04510194), which might contribute evidence for patient treatment, especially in the outpatient setting.

We found no trials that compared ivermectin to an active comparator with confirmed efficacy. Three of the 11 trials had an open-label design and used standard of care alone as comparators. All other trials were placebo-controlled trials. Standard of care must be the same between the individual trials' arms. There are several trials 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 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.

Finally, we found 31 ongoing trials, of which around 50% (15/31) should have been completed by mid-2021 or else no planned completion date was stated. Twenty-eight trials are awaiting classification of which 13, that we judged as potentially eligible, have already been completed without publication of results. When conducting the previous review version, we expected many of these trials to be published by the end of 2021. By contrast, we discovered that 70% of the completed trials (9/13) and about 50% (8/15) of ongoing trials should have been completed more than 6 months ago, but their results have not been published in trial registries, preprint servers or journals. After this amount of time, it seems unlikely that trial data will become available from those trials,

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for whatever reasons. Given those numbers, we think it will be necessary to consider publication bias in the next review update.

Certainty of the evidence

The certainty of evidence for prioritized outcomes presented in the summary of findings tables ranged from very low to high (Summary of findings 1; Summary of findings 2). Compared to the previous review version, the certainty of evidence increased one level for any adverse events and viral clearance at day 7 for inpatients and two levels for all-cause mortality in outpatients. New outcomes for the review update were serious adverse events (in both settings), new need for invasive mechanical ventilation or death (inpatients), as well as quality of life, and admission to hospital or death (outpatients).

For the summary of findings tables and assessment of the certainty of evidence according to Schünemann 2020, we used the results from analysis of our primary outcome sets. We assessed one-half of the trial results at overall low and one-ninth at overall high risk of bias. This is a considerable improvement compared to the previous review version, in which one-third of trial results were at overall high risk of bias. In the current update, after assessing trials for research integrity, we eliminated most of the trial results we had assessed at high risk of bias in the previous review version.

On the one hand, this update has resulted in four newly-included outpatient trials, contributing 2452 new participants to the review. On the other hand, the introduction of our research integrity assessment tool served to improve quality and trustworthiness of the included trial pool. Through this tool, we excluded six of the 14 trials included in the previous review version, because they were not prospectively registered. Five out of six trials reported relevant outcomes (Ahmed 2020; Kishoria 2020; Okumuş 2021; Podder 2020; Shah Bukhari 2021); we rated four of these five trials at high risk of bias for all outcomes (Kishoria 2020; Okumuş 2021; Podder 2020; Shah Bukhari 2021). Only one trial contributed data to three outcomes in the respective summary of findings table (Ahmed 2020). In the previous review version, we excluded high risk of bias trials from the primary analysis, with the aim to remove biased data and untrustworthy trials. However, to be transparent, all trials were presented in a secondary analysis. After all, the result of the research integrity assessment – inclusion of prospectively registered RCTs only - was comparable to the exclusion of high risk of bias trials from the primary analysis. Nevertheless, in this review update we downgraded the certainty of evidence one level due to serious risk of bias for all inpatient outcomes and four of nine outpatient outcomes because we assessed at least one of the results as having 'some concerns' of bias. Details of the risk of bias assessments per outcome are reported in Risk of bias in included studies.

Another limitation for the certainty of evidence was the low number of participants, events, or both leading to wide CIs and uncertainty of the estimated effects. We downgraded all outcomes included in the summary of findings tables for inpatients one or two levels for imprecision. In the outpatient setting, the number of analysed participants increased for all outcomes in this update. This improved the quality of the evidence, especially for mortality compared to the previous review update. For the newly-available outcome of 'quality of life', results were precise, so we could grade certainty of the evidence as high. However, due to few events resulting in wide CIs, we had to downgrade one level for imprecision for several outpatient outcomes.

Heterogeneity was no reason to downgrade the certainty of evidence for treatment of inpatients. This is mainly due to the small number of trials per meta-analysis. In the outpatient setting, we downgraded certainty of evidence one level for serious inconsistency in three outcomes with moderate to substantial heterogeneity. Those were 'admission to hospital or death within 28 days' ($I^2 = 44\%$), 'all initial symptoms resolved at day 14' ($I^2 = 57\%$), and 'any adverse events during the trial period' ($I^2 = 80\%$).

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 still difficult to reliably assess the risk of publication bias. In this update, we still did not downgrade for publication bias for any outcome. However, as explained above this will probably change in future updates of this review.

Potential biases in the review process

This review aimed to provide a complete and updated evidence profile for ivermectin with regard to efficacy and safety for postexposure prophylaxis of SARS-CoV-2 infection and treatment of COVID-19 based on current Cochrane standards (Higgins 2020a).

The review team was part of the German research project 'CEOsys' (COVID-19 Evidence-Ecosystem) until 31 December 2021. 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 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 screened reference lists of included trials and compared our search results with those from the living network meta-analysis (e.g. COVID-NMA Working Group). Considering it a justifiable compromise between being as up to date as possible in the dynamic of this pandemic and reasons of practicability, we set February 2022 the deadline for inclusion of newly published trial results for this review update. Hence, after initially closing the trial pool for this review update, we identified one trial with more than 1000 participants, previously classified as ongoing, that published its results in March 2022. Therefore, we are confident that we have identified all relevant trials, and we continue to monitor ongoing trials, as well as full publication of preprints closely, following the publication of this review update.

Members of the CEOsys group established and performed a Cochrane Living Systematic Reviews Series on different interventions for treatment of COVID-19 (Ansems 2021; Kreuzberger 2021; Mikolajewska 2021; Popp 2021c; Stroehlein 2021; Wagner 2021). In accordance with this review series, we updated our review's outcomes to overcome competing risks. We added outcomes for inpatients and outpatients that aim to simultaneously capture all participants of the population with clinical worsening and all participants with clinical improvement. This was possible by using composite outcomes, e.g. combining 'new need for invasive mechanical ventilation' and 'death' as clinical worsening for inpatients, and combining 'admission

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to hospital' and 'death' for outpatients. Clinical improvement for inpatients was represented by the 'number of participants discharged alive within the same time period' used for clinical worsening, and for outpatients as 'complete resolution of initial symptoms'.

We sent data requests to trial authors if parts of the new outcome set were reflected in the respective trial outcomes. Equally, we contacted trial authors if their publication included unclear or inconclusive information or in case of missing information, especially for assessing research integrity. Unfortunately, not all attempts at gathering data were successful; details of communication with authors are provided in the Characteristics of included studies table.

Almost all the trials that were only available as preprints in the previous review version, were published as peer-reviewed journal publications in the meantime. Compared to five preprints in the previous review, we included only one non-peer-reviewed article in this update (Gonzalez 2021). We are aware that preprint 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. We were unable to judge the eligibility of three trials with published results due to inconsistencies in trial descriptions (Aref 2021; NCT04407507; NCT04673214). We contacted the corresponding authors to clarify questions, but we did not receive a satisfying response at the time of review publication. We classified another 13 completed trials as 'awaiting classification' because they are eligible, but have not yet published results appropriately. Additionally, 31 potentially eligible trials are still ongoing. In the face of this immense amount of potential upcoming data, it could be considered that conclusions of a future update may differ from those of the present review. However, it should be kept in mind that a number of trials never actually publish results, as described in Overall completeness and applicability of evidence.

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 trials.

Agreements and disagreements with other studies or reviews

When we conducted the previous review version, there were numerous reviews circulating that investigated the efficacy of ivermectin for treatment of COVID-19 and prophylaxis of SARS-CoV-2 infection with inconsistent results in meta-analyses and conclusions, in many cases conflicting with our findings. Conflicts were mainly due to inclusion of trials investigating active comparators with unproven efficacy (e.g. hydroxychloroquine), pooling of trials with active and inactive comparators, different definitions of outcomes or outcomes assessment times, and different interpretations of the certainty of evidence. In the meantime, some of the reviews that had received major attention and that we discussed in the previous review version, have been retracted or concerns regarding their methodology have been expressed.

In our previous review version, we highlighted the withdrawal of the large Elgazzar 2020 trial, which apparently showed signs of fraudulence and was therefore withdrawn over ethical concerns by Research Square on 14 July 2021 (Elgazzar 2020; The Guardian 2021a). The authors have yet to clarify those issues.

In August 2021, the authors of an often-cited meta-analysis on ivermectin (Hill 2021a), retracted their article due to it being based on the withdrawn trial (Elgazzar 2020). The authors have not yet published an updated meta-analysis (Hill 2021b).

In the discussion concerning ivermectin, two groups are especially worth mentioning, the Front Line COVID-19 Critical Care Alliance (FLCCC) and the British Ivermectin Recommendation Development (BIRD) group. Several of the founders and supporters are members of both groups. As described in our previous review version, both groups and individual group associates had 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 2021a; 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. Main findings of the reviews, disagreements to our findings, and facts that have become public since, are briefly summarized in the following paragraphs.

A meta-analysis from FLCCC members was published by Bryant 2021a in the *American Journal of Therapeutics* (same journal as Kory 2021), and updated with exclusion of Elgazzar 2020 in August 2021 (Bryant 2021b). This review estimated a beneficial effect of ivermectin on mortality (risk ratio (RR) 0.41, 95% confidence interval (CI) 0.23 to 0.74). However, this review included several trials that were not eligible for our review due to ineligible trial design, ineligible comparator, or not having passed the research integrity assessment of RCTs for this review update. We have already discussed such aspects in a published editorial (Popp 2021d).

The Kory 2021 review published in April 2021 in *The American Journal of Therapeutics*, identified seven RCTs on the efficacy of ivermectin in outpatients with mild COVID-19 and six RCTs in hospitalized people with COVID-19. Kory 2021 concluded there was a mortality benefit based on the inclusion of six of the 13 trials (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 2021 were not eligible for the reasons described above, and Cadegiani 2020 was not a RCT. In an update in September 2021 (Marik 2021), the authors state that the review data were revised, excluding the meanwhile retracted trial of Elgazzar 2020. Taking a closer look at the revision, however, Rothrock 2021 discovered that the authors, without explanation, deleted a second trial while adding two others, one of which included participants with negative PCR results at baseline. Further, it came to our attention that the manuscript of the review by Kory 2021, had been provisionally accepted and posted as preprint by *Frontiers in Pharmacology* in January 2021, but was ultimately rejected and is now listed on the Retraction Watch Database (ivermectin) due to 'bias issues or lack of balance' and 'conflict of interest' (The Scientist 2021). Last but not least, results of an observational trial that had long been retracted (Patel 2020), influences the review's conclusion on mortality benefits. The cited publication was withdrawn from the *SSRN* preprint server in May 2020 due to concerns being expressed by one of the co-authors themselves, regarding trustworthiness of

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the now-discredited company that provided the patient database (Retraction Watch Database (ivermectin); The Scientist 2021).

The website ivmmeta.com provides several meta-analyses of pooled effects, including up to 76 trials. 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 23% improvement when used as late treatment to 62% improvement when used as early treatment. 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.

The most recent systematic review on ivermectin for COVID-19 by Izcovich 2021 including 29 RCTs, came to the conclusion that 'ivermectin may not improve clinically important outcomes in patients with COVID-19 and its effects as a prophylactic intervention in exposed individuals are uncertain'. Despite their conclusion being similar to ours, this review contains major discrepancies regarding the trial pool. Izcovich 2021 included trials that used combination treatments with active substances and active comparators without proven efficacy, or included participants with negative PCR results (Babalola 2021; Chahla 2021a; Galan 2021; Hashim 2020; Mahmud 2021; Niaee 2021; Seet 2021; Shahbaznejad 2021). Moreover, the review included several trials that were either not actually RCTs (Chowdhury 2021; Shouman 2021), or that were officially retracted (Elgazzar 2020; Samaha 2021). Further, in our review update we strengthened the focus on research integrity and trustworthiness in response to the apparent poor research practices associated with COVID-19. As such, we excluded or left assessment pending until clarification from trial authors for a further nine trials included in Izcovich 2021 (Abd-Elsalam 2021; Ahmed 2020; Biber 2021; Chachar 2020; Faisal 2020; Kishoria 2020; Okumuş 2021; Podder 2020; Shah Bukhari 2021).

Research malpractice in the field of ivermectin research for treatment and prevention of COVID-19, has led us to develop a tool to help identify potentially-problematic RCTs within systematic reviews. We believe the new tool will serve as a platform for urgent developments in research integrity in evidence synthesis. We plan to publish a methods paper on this subject in the next few months, with the aim of disseminating the research integrity assessment tool among systematic reviewers.

National and international guidelines regarding the use of ivermectin for the treatment or prevention of COVID-19 have been developed over the past 18 months. Recommendations from the WHO, updated 14 January 2022 (WHO 2021b); European Medicines Agency (EMA), updated 22 March 2021 (EMA 2021); Infectious Diseases Society of America, updated 18 January 2022 (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. In the meantime, Peru's ministry of health has also withdrawn their previous recommendation for using ivermectin against COVID-19 (The Guardian 2021b). The EMA additionally advises against the use of ivermectin for prophylaxis outside RCTs (EMA 2021). The US National Institutes of Health (NIH) guidance, updated on 19 January 2022, describes 'insufficient data' to permit a recommendation for or against the use of ivermectin for the treatment of COVID-19 (NIH 2021), and the FDA recently published a consumer update warning people of the inefficacy and danger of toxicity when self-medicating with ivermectin (FDA 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

For the outpatient setting, there is currently moderate- to high-certainty evidence that ivermectin has no beneficial effect on risk of death and quality of life for people with COVID-19. The same accounts with low-certainty evidence for all other outpatient outcomes and clinical improvement, viral clearance, and adverse events in the inpatient setting. Based on the current very low-certainty evidence, we are still uncertain whether ivermectin prevents death or worsening of clinical status or increases serious adverse events in inpatients. No evidence is available on ivermectin to prevent a SARS-CoV-2 infection in people after having high-risk exposure. Overall, the reliable evidence available does not support the use of ivermectin for treatment or prevention of COVID-19 outside well-designed randomized controlled trials (RCTs). With respect to the number of identified trials 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. Based on our review, we define the following gaps in the evidence.

- High-quality RCTs: double-blind, placebo-controlled, randomized trials with sufficient power and conducted in accordance with 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 (WHO) Clinical Progression Scale (Marshall 2020).
- Dose-finding trials.
- Although widely discussed, there is a complete gap in the evidence investigating ivermectin for preventing a SARS-CoV-2 infection after high-risk exposure.

If researchers plan future trials on ivermectin, we would suggest considering an approach of starting treatment only very early after symptom onset, within 5 days from symptom onset at the latest. Any potential antiviral and anti-inflammatory effect could have a greater influence on the disease at that early stage of viral replication. For the same reason, we do not define the missing data on severe disease, which are considered as long-term infections, as an evidence gap.

Regarding the large amount of trials that have been or should have been completed in the past, we appeal to trialists to indicate

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recruitment status of trials in their respective registry entry and share data transparently as soon as possible, e.g. via preprint servers, in order to make all findings on ivermectin available for the public and prevent publication bias. Currently, there is still an urgent need for good-quality evidence, based on RCTs with appropriate randomization procedures, comparability of trial arms, and preferably a double-blind design. However, the potential amount of data already, and soon to be available from completed and ongoing RCTs, may close the evidence gap without more new trials being launched. We are currently trying to contact investigators of those trials, encouraging them to make their data publicly available.

In accordance with the living approach of this review, we will continually update our search and include eligible trials.

Problematic trials may distort evidence synthesis. For this review update, we developed a tool to help us identify trials that are potentially problematic regarding aspects of research integrity. We believe that this tool, which consists of six domains to assess research integrity of RCTs included in systematic reviews, is a new transparent option to consider the concept of research integrity in evidence synthesis and will serve as a platform for urgent developments in this direction.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bounfrate 2021

Study characteristics	
Methods	• Trial design: triple-blind RCT with 3 parallel arms, the 2 intervention arms were pooled for this review • Type of publication: pre-proof journal publication • Setting: outpatient • Recruitment dates: July 2020 to May 2021 • Country: Italy • Language: English • Number of centres: 4 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04438850 • Date of registration: 19 June 2020
Participants	• Number of participants (randomized/analysed): 93/89 • Age (median): overall 47 years • Males, n: overall 54 (58%) • Severity of condition according to study definition: mild disease, defined as not requiring hospitalization or oxygen supplementation • Severity of condition according to WHO scale: 1 to 3 • Time from symptom onset to enrolment (median): overall 4 (IQR 3 to 5.5) days • Comorbidities: any pre-existing condition, obesity, diabetes, cardiovascular disease, respiratory disease • Virus detection performed at baseline (test-positive at baseline): RT-PCR (100%) • Vaccination status: overall 91 (98%) participants without any vaccination • 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

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Bounfrate 2021 *(Continued)*

	• Exclusion criteria: pregnant or lactating women (pregnancy test not required, if doubt person is excluded); people with known central nervous system disease; 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: ivermectin 0.6 mg/kg and 1.2 mg/kg (pooled), once daily for 5 days
	  ○ Route of administration: oral
	• Treatment details of control group
	  ○ Placebo
	• Concomitant therapy: NA
	• Duration of follow-up: 30 days
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  ○ Number of serious adverse drug reaction within 14 days
	  ○ Viral load at 7 days
	• Relevant review outcomes reported
	  ○ Symptom resolution at 14 and 30 days
	  ○ Hospitalization rate within 30 days
	  ○ Mortality rate at 30 days (outcome provided by study author via personal communication)
	  ○ Proportion of participants with virological clearance at 14 days (detailed data provided by study author via personal communication)
	  ○ Serious adverse events within 30 days (outcome provided by study author via personal communication)
	  ○ Any adverse events within 30 days (number of participants with any adverse event provided by study author via personal communication)
	• Additional study outcomes reported
	  ○ Trend over time of quantitative viral load at 7, 14 and 30 days measured by quantitative, digital droplet PCR
	  ○ Time to clinical resolution (for symptomatic participants) within 14 and 30 days
	  ○ Proportion of participants with virological clearance at day 30
	  ○ COVID-19 Severity Score at 14 and 30 days

Notes	• Date of pre-proof publication: 22 December 2021 • Sponsor/funding: Italian Ministry of Health and Insud Pharma • Correspondence with the author team: author request sent (review relevant outcome data, number of analysed participants); response received from author • Information on ethics votum: ethics committee approval number reported by a nationally-recognized ethics committee, as defined in the country's clinical trial regulations

Chaccour 2021

Study characteristics	
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

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Chaccour 2021 *(Continued)*

	• Study purpose (treatment, prevention): treatment • Trial registration number: NCT04390022 • Date of registration: 15 May 2020
Participants	• Number of participants (randomized/analysed): 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 • Time from symptom onset to enrolment (median): intervention 1 (IQR 1 to 2) day, control 2 (IQR 1.5 to 2) days • Comorbidities: existing comorbidity was specified as exclusion criterion. • Virus detection performed at baseline (test-positive at baseline): RT-PCR (100%) • Vaccination status: NR, study period before vaccination was available • 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; comorbidities 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 at 7 days
	• 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: ethics committee approval by a nationally-recognized ethics committee, as defined in the country's clinical trial regulations: approval number not reported, but approval letter provided by study author via personal communication

Gonzalez 2021

Study characteristics

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Gonzalez 2021 *(Continued)*

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/analysed): 108/106 (relevant arms: NR/73s • 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 • Time from symptom onset to enrolment: NR • Comorbidities: any pre-existing condition, diabetes, hypertension, respiratory disease • Virus detection performed at baseline (test-positive at baseline): RT-PCR (100%) • Vaccination status: NR, study period before vaccination was available • 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 to 18 mg (weight-adjusted), once daily for 5 days
	  ○ Route of administration: oral
	• Treatment details of control group
	  ○ Placebo
	• 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
	  ○ Improvement of clinical status – patients discharged without respiratory deterioration or death at 28 days (outcome provided by study author via personal communication)
	  ○ Worsening of clinical status – need for invasive mechanical ventilation or death at 28 days (outcome provided by study author via personal communication)
	• Additional study outcomes reported
	  ○ None

Notes	• Date of publication: 23 February 2021 • Sponsor/funding: departmental resources

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Gonzalez 2021 *(Continued)*

- 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, review relevant outcome data); response received from author
- Information on ethics votum: ethics committee approval number reported by a nationally-recognized ethics committee, as defined in the country's clinical trial regulations

I-TECH 2022

Study characteristics	
Methods	• Trial design: open-label RCT with 2 parallel arms • Type of publication: journal publication • Setting: outpatient • Recruitment dates: May to October 2021 • Country: Malaysia • Language: English • Number of centres: 21 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04920942 • Date of registration: 10 June 2021
Participants	• Number of participants (randomized/analysed): 500/490 • Age (mean): overall 63 years • Males, n: overall 264 (58%) • Severity of condition according to study definition: the study author stated, that the majority of participants were ambulatory and well during admission, hospitalization mostly for isolation and close monitoring only in case of high risk of disease progression (based on public health policy at the time of study). • Severity of condition according to WHO scale: 2 to 4, but accounting for an outpatient population (WHO 2 to 3) based on the study author's statement. • Time from symptom onset to enrolment (mean): overall 5 (SD 1.3) days • Comorbidities: at least one pre-existing condition, obesity, diabetes, hypertension, respiratory disease • Virus detection performed at baseline (test-positive at baseline): RT-PCR or RAT (100%) • Vaccination status: overall 159 (32%) participants without any vaccination • Inclusion criteria: ≥ 1 comorbidity; aged ≥ 50 years; confirmed SARS-CoV-2 by RT-PCR or antigen detection; beginning of symptoms in the past 7 days; mild to moderate disease; informed consent • Exclusion criteria: asymptomatic SARS-CoV-2 infection; need for supplemental oxygen or pulse oximetry oxygen saturation (SpO_2) level < 95% at rest; severe hepatic impairment (ALT level > 10 times of upper normal limit); acute medical or surgical emergency; concomitant viral infection; pregnancy or breastfeeding; warfarin therapy; history of taking ivermectin or any antiviral drugs with reported activity against COVID-19 (favipiravir, hydroxychloroquine, lopinavir, and remdesivir) in the past 7 days before enrolment.

Interventions	• Details of intervention
	  ○ Type and dose: ivermectin 0.4 mg/kg (rounded to the nearest 6 mg or 12 mg whole tablets), 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 (only symptomatic therapy) administered in both study arms
	• Duration of follow-up: 28 days

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I-TECH 2022 *(Continued)*

	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  ○ Proportion of patients with progression to severe COVID-19 disease, defined as hypoxic stage requiring supplemental oxygen to maintain SpO2 ≥ 95%
	• Relevant review outcomes reported
	  ○ All-cause mortality at 28 days
	  ○ Clinical worsening - ICU admission or death at 28 days
	  ○ Adverse events at 28 days (outcome provided by study author via personal communication upon request)
	  ○ Serious adverse events at 28 days (outcome provided by study author via personal communication upon request)
	• Additional study outcomes reported
	  ○ Time of progression to severe disease
	  ○ Length of hospital stay after study enrolment
	  ○ Clinical worsening - rate of mechanical ventilation at 28 days
	  ○ Symptom resolution at 5 days

Notes	• Date of publication: 18 February 2022 • Sponsor/funding: Ministry of Health Malaysia • Correspondence with the author team: initially author provided unpublished study data without request, in the meantime results are already published as journal article; author request sent regarding further review relevant outcome data as indicated above; response received from author • Information on ethics votum: ethics committee approval number reported by a nationally-recognized ethics committee, as defined in the country's clinical trial regulations

Kirti 2021

Study characteristics	
Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of publication: journal publication • 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/analysed): 115/112 • Age (mean): overall 53 (SD 14.7) years • Males, n: overall 81 (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 • Time from symptom onset to enrolment (mean): overall 6.9 (SD 6.6) days • Comorbidities: diabetes, hypertension, respiratory disease • Vaccination status: NR, study period before vaccination was available • Virus detection performed at baseline (test-positive at baseline): RT-PCR or RAT (100%) • Inclusion criteria: RT-PCR positive or RAT positive; mild-to-moderate COVID-19; aged > 18 years

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Kirti 2021 *(Continued)*

	• 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
	• 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
	• Relevant review outcomes reported
	  ○ RT-PCR negativity at 6 days
	  ○ Mortality at 28 days (details on time point provided by study author via personal communication)
	• Additional study outcomes reported
	  ○ Discharged at 10 days
	  ○ Worsening of clinical status – need for invasive mechanical ventilation/need for ICU admission at 28 days (outcome combined with mortality not provided by study author upon request via personal communication)
	  ○ ICU admission within 28 days (outcome combined with mortality not provided by study author upon request via personal communication)
	  ○ Symptom resolution at 6 days

Notes	• Date of publication: 15 July 2021 • Sponsor/funding: Sun Pharma Pvt Ldt and AIIMS, Patna administration • Correspondence with the author team: author request sent (ethics approval number, publication status, review relevant outcome data); only partial response received from author • Information on ethics votum: ethics committee approval by a nationally-recognized ethics committee, as defined in the country's clinical trial regulations: approval number not reported, but provided by study author via personal communication

Krolewiecki 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: 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/analysed): 45/45 • Age (mean): overall 41 (SD 12.48) years

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Krolewiecki 2021 *(Continued)*

	• 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 • Time from symptom onset to enrolment (mean): overall mean 3.55 days • Comorbidities: obesity, diabetes, hypertension, respiratory disease • Virus detection performed at baseline (test-positive at baseline): RT-PCR (100%) • Vaccination status: NR, study period before vaccination was available • 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 comorbidities affecting the patient's prognosis, rendering them at high risk; documented acceptance to participate by means of execution of 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
	  ○ Worsening of clinical status – need for invasive mechanical ventilation or death at 30 days
	  ○ Mortality at 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: 1 July 2021 • Sponsor/funding: Laboratorio Elea Phoenix S.A. (provided intervention drug) • Correspondence with the author team: author request sent (publication status before journal publication was available); author responded • Information on ethics votum: ethics committee approval by a nationally-recognized ethics committee, as defined in the country's clinical trial regulations: approval number not reported, but provided by study author via personal communication

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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 • Date of registration: 28 May 2020
Participants	• Number of participants (randomized/analysed): 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) • Time from symptom onset to enrolment (median): overall 5 (IQR 4 to 6) days • Comorbidities: any pre-existing condition, obesity, diabetes, hypertension, respiratory disease • Virus detection performed at baseline (test-positive at baseline): RT-PCR or RAT (100%) • Vaccination status: NR, study period before vaccination was available • Inclusion criteria: aged ≥ 18 years; confirmed SARS-CoV-2 by RT-PCR or antigen detection in a Colombian National Institute of Health-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
	  ○ 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

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López-Medina 2021 *(Continued)*

- Relevant review outcomes reported
  - Mortality at 21 days
  - Symptom resolution at 15 days and 21 days
  - Duration to symptom resolution, reported as median
  - Adverse events within 21 days
  - Serious adverse events within 21 days
- Additional study outcomes reported
  - Deterioration of ≥ 2 points in an ordinal 8-point scale
  - Overall number of participants hospitalized with or without supplemental oxygen, which could not be judged as either worsening or improvement due to overlap with status at baseline; (outcome as needed combined with mortality not provided by study author upon request via personal communication)
  - 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 15 and 21 days
    - Worsening of clinical status – need for non-invasive mechanical ventilation or high flow at 15 and 21 days

Notes	• Date of publication: 4 March 2021 • Sponsor/funding: Centro de Estudios en Infectología Pediátrica • Correspondence with the author team: author request sent (review relevant outcome data); no response received from author • Information on ethics votum: ethics committee approval number reported by a nationally-recognized ethics committee, as defined in the country's clinical trial regulations

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: journal publication • 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/analysed): 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 • Time from symptom onset to enrolment (median): overall 5 (IQR 3 to 7) days • Comorbidities: diabetes, hypertension

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Mohan 2021 *(Continued)*

	• Virus detection performed at baseline (test-positive at baseline): RT-PCR (relevant population 100% test-positive) • Vaccination status: NR, study period before vaccination was available • 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 RAT • 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 ms) on ECG; any other severe comorbidity as per investigator's assessment; enrolment in a concomitant clinical trial

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
	• 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 5 days (detailed data provided by study author via personal communication)
	  ○ 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
	  ○ Viral clearance (RT-PCR) at 7 days (not reported for complete intention-to-treat population)

Notes	• Date of publication: 24 August 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, clarification of viral clearance outcome); only partial response received from author • Information on ethics votum: ethics committee approval number reported by a nationally-recognized ethics committee, as defined in the country's clinical trial regulations

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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 • 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/analysed): 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 • Time from symptom onset to enrolment (median): 8 (IQR 7 to 10) days • Comorbidities: NR • Virus detection performed at baseline (test-positive at baseline): RT-PCR (100%) • Vaccination status: NR, study period before vaccination was available • 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

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Pott-Junior 2021 *(Continued)*

- 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
  - ICU admission within 28 days (outcome combined with mortality not provided by study author upon request via personal communication)

Notes

- Date of publication: 9 March 2021
- Sponsor/funding: Federal University of Sao Carlos, Brazil
- Correspondence with the author team: author request sent (details of intervention, especially deviations between protocol and publication; review relevant outcome data); no response received from the author
- Information on ethics votum: ethics committee approval number reported by a nationally-recognized ethics committee, as defined in the country's clinical trial regulations

TOGETHER 2022

Study characteristics

Methods

- Trial design: double-blind randomized platform trial with adaptive intervention arms, only 2 arms relevant; other arms investigate e.g. fluvoxamine and metformin
- Type of record: journal publication
- Sample size: 1358
- Setting: outpatient
- Country: Brazil
- Language: English
- Number of centres: 12
- Study purpose (treatment, prevention): treatment
- Trial registration number: NCT04727424
- Date of registration: 27 January 2021

Participants

- Number of participants (randomized/analysed): 1358/1358
- Age (mean): overall 49 (SD 13.3) years
- Males, n: overall 576 (42%)
- Severity of condition according to study definition: outpatients with non-severe symptoms
- Severity of condition according to WHO scale: 2 to 3
- Time from symptom onset to enrolment (mean): overall 3.8 (SD 1.9) days
- Comorbidities: obesity, diabetes, hypertension, respiratory disease
- Virus detection performed at baseline (test-positive at baseline): RAT (100%)
- Vaccination status: patients with vaccination against SARS-CoV-2 were eligible for inclusion, but no numbers were reported
- Inclusion criteria: patients ≥ 18 years with the ability to provide free and informed consent; patients presenting to an outpatient care setting with an acute clinical condition compatible with COVID-19 and symptoms beginning within 7 days from the randomization date; patients with at least ONE of the following criteria:
  - age ≥ 50 years (does not need any other risk criteria)
  - diabetes mellitus requiring oral medication or insulin
  - systemic arterial hypertension requiring at least 1 oral medication for treatment
  - known cardiovascular diseases (heart failure, congenital heart disease, valve disease, coronary artery disease, cardiomyopathies being treated, clinically manifested heart disease and with clinical repercussion)
  - symptomatic lung disease and/or being treated (emphysema, fibrosing diseases)

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TOGETHER 2022 *(Continued)*

- symptomatic asthma patients requiring chronic use of agents to control symptoms
- obesity, defined as BMI > 30 kg/m^2 (weight and height information provided by the patient)
- transplant patients
- patient with stage IV chronic kidney disease or on dialysis
- immunosuppressed patients/using corticosteroid therapy (equivalent to a maximum of 10 mg prednisone/day) and/or immunosuppressive therapy
- patients with a history of cancer in the last 5 years or undergoing current cancer treatment
- patients with documented fever at screening (> 38 °C)
- patients with at least one of the following symptoms: cough, dyspnoea, pleuritic chest pain AND/OR myalgias with limited daily activities (to a maximum of 25% of enrolment)
- patients with a positive rapid test for SARS-CoV-2 antigen performed at the time of screening or patients with positive SARS-CoV-2 diagnostic test within 7 days of symptom onset
- willingness to use the proposed investigational treatment and follow the research procedures
- female patients of childbearing potential and male patients with partners of childbearing potential must agree to use adequate methods of contraception during the study and through 90 days after the last dose of study medication.

- Exclusion criteria: patients with acute respiratory condition compatible with COVID-19 treated in the primary care and with hospitalization need; patients with acute respiratory condition due to other causes; severe terminal illness irrespective of type or aetiology; acute flu showing at least ONE of the criteria:
  - respiratory rate > 28/min
  - SaO_2 < 90% or < 93% on nasal oxygen therapy at 10 L/min;
  - PaO_2/FIO_2 < 300 mmHg
  - use of certain medications in the last 14 days: monoamine oxide inhibitors: (phenelzine, tranylcypromine, selegiline, isocarboxazid, moclobemide), alpha-1 antagonists, sotalol, clonidine, phosphodiesterase 5 inhibitors, methyldopa, prazosin, terazosin, doxazosin, serotonin reception inhibitors
  - use of antiretroviral agents
  - pregnant or breastfeeding patients
  - surgical procedure or use of contrast planned to occur during treatment or up to 5 days after the last dose of the study medication
  - inability of the patient or representative to give informed consent or adhere to the procedures proposed in the protocol
  - known hypersensitivity and/or intolerance to investigational product, or taking medications contraindicated by investigational product
  - inability to follow protocol-related procedures

Interventions	• Details of intervention for relevant arms
	  ○ Type and dose: ivermectin 0.4 mg/kg, once daily for 3 days
	  ○ Route of administration: oral
	• Treatment details of control group
	  ○ Placebo
	• Concomitant therapy: standard of care (only symptomatic therapy if necessary) administered in both study arms

Outcomes	• Primary study outcome
	  ○ Composite of hospitalization due to the progression of COVID-19 or an emergency department visit of > 6 hours that was due to clinical worsening of COVID-19
	• Relevant review outcomes planned
	  ○ All-cause mortality at 28 days
	  ○ Time to clinical recovery, reported as median
	  ○ Viral clearance at 3 and 7 days
	  ○ Quality of life at 28 days (measured with a standardized scale: PROMIS, physical and mental component)

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TOGETHER 2022 *(Continued)*

- Additional study outcomes
  - Adverse events, separated into grade 1-5
  - Time to hospitalization
  - Mean survival time
  - Hospitalization for any cause
  - Time to death
  - Number of days with mechanical ventilation

Notes	• Date of publication: 30 March 2022 • Sponsor/funding: FastGrants and the Rainwater Charitable Foundation • Correspondence with the author team: author request sent (review relevant outcome data, details on outcome measurement of viral clearance, vaccination status); no response received from author yet • Information on ethics votum: ethics committee approval number reported by a nationally-recognized ethics committee, as defined in the country's clinical trial regulations

Vallejos 2021

Study characteristics	
Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of publication: journal publication • Setting: outpatient • Recruitment dates: August 2020-Febuary 2021 • Country: Argentina • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04529525 • Date of registration: 27 August 2020
Participants	• Number of participants (randomized/analysed): 501/501 • Age (mean): overall 42 years • Males, n: overall 246 (53%) • Severity of condition according to study definition: mild disease, defined as not requiring home oxygen or hospitalization • Severity of condition according to WHO scale: 1 to 3 • Time from symptom onset to study enrolment (median): overall 4 (IQR 3 to 6) days • Comorbidities: any pre-existing condition, obesity, diabetes, hypertension, respiratory disease • Virus detection performed at baseline (test-positive at baseline): RT-PCR (100%) • Vaccination status: NR, study period before vaccination was available • Inclusion criteria: age > 18 years, 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; weight at inclusion > 48 kg • Exclusion criteria: current home oxygen use, requiring hospitalization for COVID-19 at the time of diagnosis; history of hospitalization for COVID-19; pregnant or breastfeeding women; known allergy to ivermectin or the components of ivermectin or placebo tablets; presence of malabsorptive syndrome; presence of any other concomitant acute infectious disease; known history of severe liver disease; recent or expected need for dialysis; concomitant use of hydroxychloroquine or antiviral drugs due to a pathology other than COVID-19 at the time of admission; use of ivermectin up to 7 days before randomization; participation in a research study that involved the administration of a drug within the last 30 days

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Vallejos 2021 *(Continued)*

Interventions	• Details of intervention
	  ○ Type and dose: ivermectin 12 mg to 24 mg (weight-adjusted), once daily for 2 days
	  ○ Route of administration: oral
	• Treatment details of control group:
	  ○ Placebo
	• Concomitant therapy
	  ○ NA
	• Duration of follow-up: 30 days
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  ○ Percentage of hospitalization at 30 days
	• Relevant review outcomes planned
	  ○ Percentage of hospitalization at 30 days or death (outcome provided by study author via personal communication)
	  ○ Negative swab at 3 and 12 days after entering the study
	  ○ Number of participants with non-serious adverse events at 30 days
	  ○ All-cause mortality at 30 days
	  ○ Serious adverse events at 30 days
	• Additional study outcomes
	  ○ Time to hospitalization
	  ○ Time to invasive mechanical ventilation support
	  ○ Percentage of use of invasive mechanical ventilation support at 30 days
	  ○ Percentage of dialysis in each arm at 30 days

Notes	• Date of publication: 2 July 2021 • Sponsor/funding: Ministry of Health of the Province of Corrientes, Argentina • Correspondence with the author team: author request sent (trial protocol, details on compliance rate, review relevant outcome data); response received from the author • Information on ethics votum: ethics committee approval number reported by a nationally-recognized ethics committee, as defined in the country's clinical trial regulations

ALT: alanine transaminase; AST: aspartate aminotransferase; BMI: body mass index; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; CT: computer tomography; ECG: electrocardiograph; ICU: intensive care unit; IgG: immunoglobulin G; IQR: interquartile range; LDH: lactose dehydrogenase; PaO_2/FiO_2: partial pressure of oxygen/fraction of inspired oxygen; PCR: polymerase chain reaction; n: number; NA: not available; NR: not reported; NSAID: non-steroidal anti-inflammatory drug; PCR: polymerase chain reaction; RAT: rapid antigen test; RCT: randomized controlled trial; RT-PCR: reverse transcription polymerase chain reaction; rRT-PCR: real-time reverse transcription polymerase chain reaction; SaO_2:oxygen saturation as measured by blood analysis; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SD: standard deviation; SpO_2: oxygen saturation as measured by pulse oximeter; WHO: World Health Organization.

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

Study	Reason for exclusion
Abd-Elsalam 2021	**Retrospective trial registration**
Ahmed 2020	**No trial registration**
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	**Irrelevant study design:** case-control study

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Study	Reason for exclusion
Biber 2021	**Retrospective trial registration**
Cadegiani 2020	**Irrelevant study design:** historical control group, i.e. not RCT
Camprubi 2020	**Irrelevant study design:** retrospective study
Carvallo 2020	**Irrelevant study design:** prospective cohort study; additionally ivermectin was administered in combination with other active drugs with unknown influence on COVID-19
Chachar 2020	**Retrospective trial registration**
Chahla 2021a	**Combined intervention:** ivermectin administered in combination with another active substance (iota-carrageenan) with unknown influence on prevention of COVID-19, which we did not consider eligible to determine ivermectin's true effect.
Chahla 2021b	**Irrelevant study design:** cluster-randomized 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.
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.
CTRI/2021/03/031665	**Active comparator:** ivermectin compared to a control (vitamin C) with unknown influence on COVID-19, which we did not consider eligible to determine ivermectin's true effect.
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. **Irrelevant 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**
Faisal 2020	**No trial registration**; further author request sent (unclear study design, the term "cross-sectional study" is used, which indicates that it is not a RCT); no clarifying response received from the author
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	**Irrelevant study design:** historical control group, i.e. not RCT

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Study	Reason for exclusion
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	**Irrelevant 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.
Kishoria 2020	**No trial registration**
Lima-Morales 2021	**Irrelevant 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	**Irrelevant study design:** retrospective study
Mustaq 2021	**Irrelevant study design:** quasi-experimental study
NCT04345419	**Irrelevant 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.
NCT04373824	**Irrelevant study design:** non-randomized study
NCT04374279	**Irrelevant intervention:** registry entry changed investigated intervention from ivermectin to only bicalutamide.
NCT04382846	**Irrelevant intervention:** registry entry changed investigated intervention from ivermectin to only nitazoxanide.
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.

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Study	Reason for exclusion
NCT04530474	**Irrelevant population:** study plans to include participants with diagnosis of COVID-19 only based on suspected 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	**Irrelevant 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	**Irrelevant 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.
NCT04937569	**Irrelevant study design:** prospective cohort study
NCT04951362	**Irrelevant population:** participants investigated are in a post-infection state. No examination on effect on acute COVID-19.
Niaee 2021	**Irrelevant 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. Furhter expressions of concerns regarding the study's design were published.
Okumuş 2021	**Retrospective trial registration**
Ozer 2021	**Irrelevant study design:** observational study
Podder 2020	**No trial registration**
Rajter 2021	**Irrelevant study design:** retrospective study.
Samaha 2021	**Retraction notice**
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	**Irrelevant population:** study included 76.8% participants with unknown or negative SARS-CoV-2 status, which we did not consider appropriate to include in evidence regarding treatment of COVID-19.
Shah Bukhari 2021	**Retrospective trial registration**
Shouman 2021	**Irrelevant 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); response received from the author revealed that the study was not a RCT
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.

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COVID-19: coronavirus disease 2019; CT: computer tomography; PCR: polymerase chain reaction; RCT: randomized controlled trial.

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

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 with SARS-Co2 infection: cough or expectoration or fever > 38 °C with or without radiological infiltrate in chest X-ray; with SARS-CoV-2 PCR or radiological, clinical and analytical findings of COVID-19
	  ■ Initial symptom onset between 3 and 8 days
	  ■ basal oxygen saturation ≥ 93% breathing ambient air
	  ■ signed informed consent
	• Exclusion criteria
	  ○ People with pneumonia due to SARS-CoV-2 that require 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 ms
	  ○ 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 mg/kg to 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.

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

- Relevant review outcomes planned
  - To assess the clinical cure rate after 2 weeks of treatment
  - To evaluate the microbiological cure rate 72 h after treatment
  - To analyze adverse events to treatment
- 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
- Planned completion date more than 6 months ago: unclear
- 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 gastrointestinal disorders, extensive bowel resection or bowel obstruction
  - Previous (in the past 3 months) or concurrent use of any other investigational product
  - Use of prohibited medications during 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 day 7
	• Relevant review outcomes planned
	  ○ Rate of participant's conversion to negative SARS-CoV-2 (qualitative) test on day 7
	  ○ Rate of subjects conversion converted to a negative SARS-CoV-2 (qualitative) test on day 4
	  ○ Rate of subjects conversion converted to a negative SARS-CoV-2 (qualitative) test on day 14
	  ○ Number of patients who have needed ICU treatment

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

	• 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
	  ○ Time to achieving clinical improvement within 28 days
	  ○ Time to achieving clinical recovery until Day 28
	  ○ Time to hospital discharge
	  ○ Number of patients who have needed high-flow oxygen therapy
	  ○ Inflammatory and full blood count markers

Notes	• Reason for awaiting classification: study completed, but results not published yet • Recruitment status: completed • Prospective completion date: October 2020, study completed • Planned completion date more than 6 months ago: yes • 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

2020-005015-40/SK

Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 832 • Setting: outpatient • Country: Slovakia • Language: English • Number of centres: NR • Study purpose (treatment, prevention): prevention • Trial registration number: 2020-005015-40 • Date of registration: 25 March 2021

Participants	• Inclusion criteria
	  ○ Male or female adult > 50 years of age
	  ○ SARS-CoV-2 infection diagnosed either through a rapid antigen-based test or an RNA based RT-PCR diagnostic test performed in nasopharyngeal sample
	  ○ Onset of COVID-19 symptoms < 120 hours prior to screening
	  ○ Written informed consent
	  ○ Not pregnant and use contraception

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2020-005015-40/SK *(Continued)*

	• Exclusion criteria ○ Intake of ivermectin within 30 days before screening ○ Routine intake of antivirals, including antiretroviral treatment ○ Allergy, hypersensitivity or contraindication to ivermectin, metabolites or excipients ○ Subjects with symptoms of disease severity ○ Subjects requiring hospitalization for any reason ○ Epidemiological risk or suspicion of being infected by Loa loa or other filariases ○ Previous enrolment in this trial or participation in any other drug investigational trial within the past 30 days ○ Weight < 50 kg ○ Pregnancy or lactation ○ Inability to take oral medications ○ Acute/chronic disease or deficiency ○ Active cardiac disease or a history of cardiac dysfunction ○ Concomitant use of barbiturates, sodium oxybate, valproic acid or warfarin ○ Laboratory abnormalities relevant for the trial, including but not limited to: neutropenia < 500/mm^3, thrombocytopenia < 100,000/mm^3 ○ Any other significant disease, disorder or finding which, in the opinion of the investigator, may significantly increase the risk to the subject because of participation in the study, affect the ability of the subject to participate in the study or impair interpretation of the study data ○ Employees of the investigator or clinical trial site, with direct involvement in the proposed trial or other studies under the direction of that investigator or clinical trial site, as well as family members of the employees or the principal investigator ○ Persons committed to an institution by virtue of an order issued either by the judicial or other authorities
Interventions	• Details of intervention ○ Type and dose: ivermectin 9 mg to 18 mg, no details on frequency scheme ○ Route of administration: oral • Treatment details of control group ○ Placebo • Concomitant therapy: NR
Outcomes	• Primary study outcome ○ Percentage of subjects requiring SARS-CoV-2 hospitalization during 28 days after first investigational product administration • Relevant review outcomes planned ○ Percentage of subjects requiring SARS-CoV-2 hospitalization during 28 days after first investigational product administration ○ any adverse event related to Ivermectin treatment • Additional study outcomes ○ change in subjects' clinical status on Day 28
Notes	• Reason for awaiting classification: study terminated, interim results might be published • Recruitment status: terminated due to low recruitment • Prospective completion date: June 2021, study terminated • Planned completion date more than 6 months ago: yes • Date last update posted: NR • Sponsor/funding: Chemo Research SL

Aref 2021

Methods	• Trial design: open-label RCT with parallel arms

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Aref 2021 *(Continued)*

	• Type of publication: journal publication • Setting: outpatient • Recruitment dates: February to March 2021 • Country: Egypt • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04716569 • Date of registration: 20 January 2021
Participants	• Number of participants (randomized/analysed): NR/114; unclear if participants were actually randomized • Age (mean): overall 45 (SD 18.9) years • Males, n: overall 82 (71.9%) • Severity of condition according to study definition: outpatients with mild symptoms • Severity of condition according to WHO scale: 1 to 3 • Time from symptom onset to enrolment: NR • Comorbidities: any pre-existing condition, diabetes, cardiovascular disease, respiratory disease • Virus detection performed at baseline (test-positive at baseline): NR, but RT-PCR positivity defined as inclusion criterion • Inclusion criteria: RT-PCR confirmed SARS-CoV-2 infection with mild symptoms • Exclusion criteria: severe disease COVID-19; receiving systemic ivermectin; chronic ENT disorders, systemic use of nasal sprys, steroids; allergy to ivermectin

Interventions	• Details of intervention
	  ○ Type and dose: ivermectin, twice daily, no information on dosing scheme
	  ○ Route of administration: intranasal spray
	• Treatment details of control group
	  ○ Standard of care
	• Concomitant therapy: standard of care (according to the Egyptian protocol of treatment) administered in both study arms
	• Duration of follow-up: NR
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  ○ Progression of COVID-19 clinical picture within 14 days
	• Relevant review outcomes planned
	  ○ None
	• Additional study outcomes
	  ○ Side effects for ivermectin
	  ○ Negative PCR swabs, time point unclear
	  ○ Duration to PCR negative conversion
	  ○ Improvement of abnormal routine laboratory parameters 7 days after treatment

Notes	• Reason for awaiting classification: study did not pass reseach integrity, because relevant information on trial design and to assure trustworthiness are missing. Trialist was contacted for clarification. No response received. • Date of results first published: 15 June 2021 • Sponsor/funding: South Valley University

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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/min to 30/min or SpO_2 90% to 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
	  ○ Unco-operative patients (in the opinion of the investigator, if it is difficult to ensure patient co-operation 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 day 6
	• Relevant review outcomes planned
	  ○ Adverse effects noted within 14 days
	  ○ Proportion of participants having virological cure at day 6
	• 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 • Planned completion date more than 6 months ago: unclear • Date last update posted: 30 April 2020 • Sponsor/funding: Lady Hardinge Medical College

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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 judgement 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
	  ○ Safety of ivermectin within 15 days
	• Additional study outcomes
	  ○ Duration of hospitalization
	  ○ 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 • Planned completion date more than 6 months ago: unclear • Date last update posted: 17 June 2020 • Sponsor/funding: Symbiosis Medical College for Women, Lavale

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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 until discharge date
	  ○ Need for ICU until discharge date
	  ○ Need for mechanical ventilation until discharge date
	• Relevant review outcomes planned
	  ○ Need for ICU until discharge date
	  ○ Need for mechanical ventilation until discharge date
	  ○ incidence of serious adverse reactions before intervention and daily during the study

Notes	• Reason for awaiting classification: study completed, but results not published yet • Recruitment status: completed • Prospective completion date: February 2021, study completed • Planned completion date more than 6 months ago: yes • Date last update posted: 17 November 2020 • Sponsor/funding: Bandare-abbas University of Medical Sciences

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IRCT20111224008507N4	
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 SARS-CoV-2 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 defined as reduction in persistent cough (more than 1 hour of excessive coughing, or 3 periods of coughing in 24 hours that disrupts daily life and ability to work) and tachypnea and O_2 saturation > 94%, time point unclear
	  ○ Negative RT-PCR result at 6 days
	• Relevant review outcomes planned
	  ○ Negative RT-PCR result at 6 days
	  ○ Mortality, time point unclear
	  ○ Drug adverse effects, time point unclear
	  ○ Need to be hospitalized, time point unclear
	  ○ The main complaint's recovery time, time point unclear

Notes	• Reason for awaiting classification: study completed, but results not published yet • Recruitment status: completed • Prospective completion date: August 2021, study completed • Planned completion date more than 6 months ago: yes • Date last update posted: 6 March 2021 • Sponsor/funding: Mazandaran University of Medical Sciences

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IRCT20180612040068N1

Methods	• Trial design: triple-blind RCT with 3 parallel arms; only 2 arms relevant; the other arm investigate metronidazol • Type of record: trial register entry • Sample size: 135 • Setting: inpatient • Country: Iran • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: IRCT20180612040068N1 • Date of registration: 19 April 2021

Participants	• Inclusion criteria
	  ○ Hospitalized patient with positive SARS-CoV-2 test
	  ○ > 18 years old
	  ○ Willing to participate in the study
	• Exclusion criteria
	  ○ Allergic history to metronidazole or ivermectin or hypersensitivity reaction to them during trial
	  ○ Pregnant patients
	  ○ COPD patients suspected of ILD
	  ○ Long history of diabetes
	  ○ Cirrhotic patients
	  ○ Epileptic patients
	  ○ Patients with severe renal failure and GFR < 20 mL/min
	  ○ Participating in another RCT

Interventions	• Details of intervention
	  ○ Type and dose: ivermectin, once daily (weight-adjusted)
	  ○ 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 all study arms

Outcomes	• Primary study outcome
	  ○ Length of time to recover from shortness of breath
	  ○ Length of time to not require oxygen
	  ○ Reduction of CRP
	  ○ Normalization of lymphopenia, measured by specialists
	  ○ Length of hospital stay
	  ○ Likelihood of admission to ICU
	  ○ Likelihood of mortality
	• Relevant review outcomes planned
	  ○ Likelihood of admission to ICU
	  ○ Likelihood of mortality
	• Additional study outcomes
	  ○ None

Notes	• Reason for awaiting classification: study completed, but results not published yet • Recruitment status: completed • Prospective completion date: April 2021, study completed • Planned completion date more than 6 months ago: yes • Date last update posted: 19 April 2021

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IRCT20180612040068N1 *(Continued)*

- Sponsor/funding: Shiraz 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
	  ○ 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
	• Relevant review outcomes planned
	  ○ None
	• Additional study outcomes
	  ○ Need for mechanical ventilation, time point unclear

Notes	• Reason for awaiting classification: study completed, no results published yet • Recruitment status: completed • Prospective completion date: December 2020, study completed • Planned completion date more than 6 months ago: yes • Date last update posted: 20 July 2020 • Sponsor/funding: Mashhad University of Medical Sciences

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IRCT20190624043993N2

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 onset of symptoms
	• 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

Notes	• Reason for awaiting classification: study completed, but results not published yet • Recruitment status: completed • Prospective completion date: February 2021, study completed • Planned completion date more than 6 months ago: yes • Date last update posted: 12 July 2020 • Sponsor/funding: Kermanshah University of Medical Sciences

IRCT20200329046892N3

Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 60 • Setting: inpatient • Country: Iran

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IRCT20200329046892N3 *(Continued)*

	• Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: IRCT20200329046892N3 • Date of registration: 29 March 2021

Participants	• Inclusion criteria
	  ○ All COVID-19 patients admitted to the coronavirus ward of Razi Hospital in Rasht for period of April to July 2021
	  ○ ≥ 18 years old
	  ○ Patients admitted with fever (oral temperature greater than 37.2 °C), dry cough, severe tiredness or dyspnea
	  ○ positive PCR or lung involvement on chest X-ray/CT scan
	• Exclusion criteria
	  ○ Lack of informed consent
	  ○ Lack of patient co-operation
	  ○ Pulmonary embolism or intravascular thrombosis
	  ○ Any major drug interaction between routine patient's drugs with any of the study drugs
	  ○ Pregnancy and lactation
	  ○ Simultaneous presence in other research study

Interventions	• Details of intervention
	  ○ Type and dose: ivermectin, 12 mg once/day for 2 days + standard care for 10 days
	  ○ Route of administration: oral
	• Treatment details of control group
	  ○ placebo once/day for 2 days + standard care for 10 days
	• Concomitant therapy: standard of care (no details provided) administered in both study arms

Outcomes	• Primary study outcome
	  ○ Time required to improve clinical symptoms within 10 days of treatment start
	• Relevant review outcomes planned
	  ○ Mortality
	• Additional study outcomes
	  ○ Body temperature
	  ○ Heart rate
	  ○ Blood pressure
	  ○ Respiration rate
	  ○ Duration of hospitalization
	  ○ SpO_2
	  ○ Creatine phosphokinase, before intervention, day 5 and 10
	  ○ CRP, before intervention, day 5 and 10
	  ○ ESR, before intervention, day 5 and 10

Notes	• Reason for awaiting classification: study completed, but results not published yet • Recruitment status: completed • Prospective completion date: July 2021, study completed • Planned completion date more than 6 months ago: yes • Date last update posted: 29 March 2021 • Sponsor/funding: Rasht University of Medical Sciences

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IRCT20200404046937N4

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 • 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
	  ○ None
	• Additional study outcomes
	  ○ Fever, respiratory rate, dyspnoea, cough
	  ○ Blood cell count, CRP, first day of the study and the end of the study
	  ○ CT scan, first day of the study and the end of the study

Notes	• Reason for awaiting classification: study completed, but results not published yet • Recruitment status: completed • Prospective completion date: September 2021, study completed • Planned completion date more than 6 months ago: no • Date last update posted: 11 June 2021 • Sponsor/funding: Ahvaz University of Medical Sciences

IRCT20200408046987N3

Methods	• Trial design: double-blind RCT with 4 parallel arms; 2 arms investigate prevention, 2 arms investigate treatment

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IRCT20200408046987N3 *(Continued)*

	• 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)
	  ○ Giving consent for participating in study
	• Exclusion criteria
	  ○ Pregnant or breastfeeding women
	  ○ People with 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 at day 0, 3, 7, 14, 21, 28
	  ○ Duration of illness at day 0, 3, 7, 14, 21, 28
	  ○ Severity of disease at day 0, 3, 7, 14, 21, 28
	• Relevant review outcomes planned
	  ○ Drug adverse effects during the study at day 0, 3, 7, 14, 21, 28
	  ○ 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, IgM and IgG
	  ○ Drug adverse effects during the study at day 0, 3, 7, 14, 21, 28

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, but results not published yet • Recruitment status: completed • Prospective completion date: December 2020, study completed • Planned completion date more than 6 months ago: yes • Date last update posted: 6 December 2020 • Sponsor/funding: Akam Tejarat Fartak Farasoo Company

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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)
	  ○ Quite obvious pneumonia virus in CT scans of lungs
	  ○ 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 mg/kg to 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
	• Additional study outcomes
	  ○ Treatment period within 7 days
	  ○ Duration of infection within 7 days
	  ○ Duration of admission time within 7 days
	  ○ Duration of ICU admission time within 7 days
	  ○ Discharge situation: alive or dead within 7 days
	  ○ Fever, blood SpO_2 percentage, respiratory rate, heart rate 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: July 2020, study completed • Planned completion date more than 6 months ago: yes • Date last update posted: 30 May 2020 • Sponsor/funding: Ahvaz University of Medical Sciences

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IRCT20210213050344N1

Methods	• Trial design: double-blind RCT with 3 parallel arms • Type of record: trial register entry • Sample size: 375 • Setting: outpatient • Country: Iran • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: IRCT20210213050344N1 • Date of registration: 6 April 2021

Participants	• Inclusion criteria
	  ○ Only mild symptoms and clinical manifestations of COVID-19 disease
	  ○ 18 - 80 years old
	  ○ Positive RT-PCR test result
	  ○ People with underlying disease (to evaluate the effectiveness of the drug on people with underlying disease)
	  ○ Individuals who have completed and signed the written consent to participate in the project
	  ○ Blood oxygen level ≥ 93%
	• Exclusion criteria
	  ○ Patients with severe clinical signs and symptoms of COVID-19
	  ○ Patients with HIV
	  ○ Patients with severe disease; liver, kidney, lung, and with COPD
	  ○ Pregnant or breastfeeding mothers
	  ○ Participation in another RCT
	  ○ Dissatisfaction with participating in the study

Interventions	• Details of intervention
	  ○ Type and dose:
	  ■ ivermectin, 12 mg on the first day (arm 1)
	  ■ ivermectin, 12 mg on the first and second day (arm 2)
	  ○ Route of administration: oral
	• Treatment details of control group
	  ○ Placebo on the first day (arm 3)
	• Concomitant therapy: NR

Outcomes	• Primary study outcome
	  ○ Clinical manifestations on days 0, 1, 3, 7, 14, 21 and 28
	  ○ Blood oxygen levels on days 0, 1, 3, 7, 14, 21 and 28
	  ○ Need for hospitalization on days 0, 1, 3, 7, 14, 21 and 28
	  ○ Admission to ICU or intubation on days 0, 1, 3, 7, 14, 21 and 28
	  ○ Deaths on days 0, 1, 3, 7, 14, 21 and 28
	• Relevant review outcomes planned
	  ○ Need for hospitalization on day 28
	  ○ Admission to ICU or intubation on day 28
	  ○ Deaths on day 28
	• Additional study outcomes
	  ○ None

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

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IRCT20210213050344N1 *(Continued)*

- Prospective completion date: May 2021, study completed
- Planned completion date more than 6 months ago: yes
- Date last update posted: 6 April 2021
- Sponsor/funding: Shiraz 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
	  ○ COVID-19 case diagnosis (conversion from being asymptomatic pretreatment to symptomatic post-treatment for COVID-19) by using a questionnaire for screening clinical symptoms of COVID-19, at baseline, and during the follow-up at day 7, 14, 30 and 90
	• Relevant review outcomes planned
	  ○ 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
	  ○ Rate of adverse events within 7 days after treatment
	  ○ Hospitalization rate at 30 days
	  ○ Rate of adverse events using active case detection with questionnaire and adverse events grades (mild, moderate and severe) using Common Terminology Criteria for Adverse Events (CTCAE) v5.0 at days 2 and 7 after treatment

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ISRCTN90437126 *(Continued)*

	• Additional study outcomes
	  ○ 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
	  ○ Hospitalization rate at 7, 14 and 90 days
	  ○ Deaths at 90 days

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: August 2022, postponed from June 2022 • Planned completion date more than 6 months ago: no • Date last update posted: 30 December 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

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: December 2030 • Planned completion date more than 6 months ago: no • Date last update posted: 10 March 2021

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NCT04351347 *(Continued)*

- 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 kg/m^2, living in a nursing home or long-term facility, underlying serious heart condition as determined by the treating physician, immunocompromized 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 ms for men and QTc ≥ 480 ms 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

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

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NCT04374019 *(Continued)*

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 14 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 2022, postponed from May 2021 • Planned completion date more than 6 months ago: no • Date last update posted: 30 June 2021 • 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

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

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NCT04407130 *(Continued)*

	• 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 (ALT > 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
	• 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
	  ○ Duration of hospitalization within 14 days

Notes	• Reason for awaiting classification: study completed, but results not published yet • Recruitment status: completed • Prospective completion date: November 2020, study completed • Planned completion date more than 6 months ago: yes • 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 • 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

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NCT04407507 *(Continued)*

Participants	• Number of participants (randomized/analysed): 66/56; 66 participants analysed 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 • Time from symptom onset to enrolment: NR • Comorbidities: 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 defined by RT-PCR; asymptomatic or mild symptoms treated as outpatients; signed informed consent • Exclusion criteria: severe COVID-19; positive to proof of infection by some other virus such as influenza H1N1, SARS syndrome, etc.; recurrent urinary tract infections; ALT or AST > 5 times ULN; 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
	  ○ Type and dose: ivermectin 12 mg, once daily for 3 days
	  ○ Route of administration: oral
	• Treatment details of control group
	  ○ Placebo
	• 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
	  ○ None
	• Additional study outcomes reported
	  ○ SARS-CoV-2 viral load at 5 and 14 days
	  ○ Presence and frequency of symptoms associated with COVID-19 within 14 days

Notes	• Reason for awaiting classification: study did not pass reseach integrity, because relevant information to assure trustworthiness are missing. Trialist was contacted for clarification. Response received from the trialist stating that the full article is under revision for a journal publication; before publication the author did not want to share details or data. • Date of results first posted: 21 May 2021 • Sponsor/funding: Investigacion Biomedica para el Desarrollo de Farmacos SA de CV

NCT04602507

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

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NCT04602507 *(Continued)*

	• 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 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
	• Concomitant therapy: standard of care (no details provided) administered in both study arms

Outcomes	• Primary study outcome
	  ○ Admission to the intensive care unit within 21 days
	• Relevant review outcomes planned
	  ○ Admission to the intensive care unit within 21 days
	  ○ Mortality at 21 days
	  ○ Adverse effects of ivermectin within 21 days
	• Additional study outcomes
	  ○ Hospital length of stay at 21 days
	  ○ ICU length of stay at 21 days
	  ○ Length of stay in ventilator time within 21 days

Notes	• Reason for awaiting classification: terminated, interm results might be published • Recruitment status: terminated due to lack of severe COVID-19 cases in the place of study • Prospective completion date: December 2021, study terminated • Planned completion date more than 6 months ago: no • Date last update posted: 4 January 2022 • Sponsor/funding: CES University

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NCT04673214

Methods	• Trial design: RCT with 2 parallel arms, unclear blinding method • Type of publication: trial registry entry with posted results • Setting: outpatient • Recruitment dates: December 2020 to February 2021 • Country: Mexico • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04673214 • Date of registration: 17 December 2020
Participants	• Number of participants (randomized/analysed): 114/111; unclear if participants were actually randomized • Age (mean): NR • Males, n: overall 53 (47.7%) • Severity of condition according to study definition: patients in a mild COVID-19 phase • Severity of condition according to WHO scale: presumably 1 to 3 • Time from symptom onset to enrolment: NR • Comorbidities: NR • Virus detection performed at baseline (test-positive at baseline): NR, but RT-PCR positivity defined as inclusion criterion • Inclusion criteria: eligible for family medicine unit No.20 and family medicine unit No.13 belonging to the Northern District of the Mexican Institute for Social Security; 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; 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 Northern District of the Mexican Institute for Social Security have 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
	• Concomitant therapy
	  ○ Standard of care including azithromycin, ribaroxaban and paracetamol administered in both study arms
	• Duration of follow-up: 14 days
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  ○ Average days with COVID-19 symptoms by type of therapy at 14 days
	  ○ Statistical differences between clinical evolution vs therapeutic failure by type of treatment were evaluated at 14 days
	• Relevant review outcomes reported
	  ○ None

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NCT04673214 *(Continued)*

	• Additional study outcomes reported
	  ○ Number of participants who were alive and had COVID-19 symptoms by type of therapy during a 14-day follow-up
	  ○ Average days of COVID-19 symptoms under treatment of early intervention due to outcome in family medicine unit 13 and 20 of the Mexican Institute for Social Security at 14 days

Notes	• Reason for awaiting classification: study did not pass reseach integrity check, because relevant information to assure trustworthiness is missing. Trialist was contacted for clarification. Only a partial response was received which could not fully clarify the issue up until now. • Date of results first posted: August 2021 • Sponsor/funding: Gilberto Cruz Arteaga, Coordinación de Investigación en Salud, Mexico

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 • 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, 3 times 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

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NCT04746365 *(Continued)*

	• Relevant review outcomes planned
	  ○ 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: study completed, but results not published yet • Recruitment status: completed • Prospective completion date: February 2021, study completed • Planned completion date more than 6 months ago: yes • Date last update posted: 9 February 2021 • Sponsor/funding: Elaraby Hospital

NCT04891250

Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 800 • Setting: NR • Country: Zambia • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment (unclear prevention substudy) • 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

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NCT04891250 *(Continued)*

	• Additional study outcomes
	  ○ Patient cure rate at 14–28 days
	  ○ Participant infection rate at 90 days

Notes	• Reason for awaiting classification: unclear description regarding intervention details, standard of care, design of prevention substudy • Recruitment status: not yet recruiting • Prospective completion date: June 2022 • Planned completion date more than 6 months ago: no • Date last update posted: 1 September 2021 • Sponsor/funding: Centre for Infectious Disease Research in Zambia, Ministry of Health and University of Zambia

NCT04894721

Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 750 • Setting: outpatient • 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

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NCT04894721 *(Continued)*

	• 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

Notes	• Reason for awaiting classification: study completed, but results not published yet • Recruitment status: completed • Prospective completion date: October 2021, study completed • Planned completion date more than 6 months ago: no • Date last update posted: 7 December 2021 • Sponsor/funding: Ministry of Public Health, Argentina

NCT05076253

Methods	• Trial design: triple-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 72 • Setting: inpatient • Country: Thailand • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT05076253 • Date of registration: 13 October 2021

Participants	• Inclusion criteria
	  ○ Adult men and women age 18-80 years
	  ○ Non-pregnant or breast-feeding women
	  ○ Had mild to moderate symptoms as defined by the WHO severity score for COVID-19
	• Exclusion criteria
	  ○ Were allergic to ivermectin
	  ○ Have the potential for a drug-drug interaction with ivermectin such as tamoxifen or warfarin
	  ○ Previously treated with ivermectin in the last 7 days
	  ○ Had received any herbal medicine
	  ○ Had severe chronic illness (severe congestive heart failure, chronic kidney disease stage 4-5, chronic liver disease, terminal cancer diseases)
	  ○ Had concurrent bacterial infection or unwilling to participate in the trial
	  ○ Patients with severe symptoms, likely due to cytokine release syndrome
	  ○ Uncontrolled comorbidities and immunocompromized states

Interventions	• Details of intervention
	  ○ Type and dose: ivermectin 12 mg, once daily for 5 days
	  ○ Route of administration: oral
	• Treatment details of control group
	  ○ Placebo
	• Concomitant therapy: standard of care including favipiravir or andrographolide, corticosteroids, cetrizine and paracetamol administered in both study arms

Outcomes	• Primary study outcome ○ Viral clearance of SARS- CoV-2 intervention in 7 days and 14 days

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NCT05076253 *(Continued)*

	• Relevant review outcomes planned
	  ○ Viral clearance of SARS- CoV-2 intervention in 7 days and 14 days
	  ○ Mortality rate in 28 days
	• Additional study outcomes
	  ○ Duration of hospitalization
	  ○ Frequency of clinical worsening in 28 days
	  ○ Need for mechanical ventilation in 28 days
	  ○ Mortality rate in 28 days

Notes	• Reason for awaiting classification: study completed, but results not published yet • Recruitment status: completed • Prospective completion date: December 2021, study completed • Planned completion date more than 6 months ago: no • Date last update posted: 15 December 2021 • Sponsor/funding: Bangkok Metropolitan Administration Medical College and Vajira Hospital

PACTR202102588777597

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 randomization
	  ○ Substudy prevention
	  ■ Household contacts of adults with laboratory-positive COVID-19

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PACTR202102588777597 *(Continued)*

	• 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
	  ○ Mortality at 7 days
	• Relevant review outcomes planned
	  ○ SARS-CoV-2 clearance at 4 and 6 days
	• Additional study outcomes
	  ○ 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

Notes	• Reason for awaiting classification: terminated, interim results might be published • Recruitment status: terminated • Prospective completion date: March 2022, study terminated • Planned completion date more than 6 months ago: no • Date last update posted: 12 February 2021 • Sponsor/funding: Lagos State Ministry of Health

ALT: alanine aminotransferase; AST: aspartate aminotransferase; COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; CT: computer tomography; ESR: erythrocyte sedimentation rate; GFR: glomeruler filtration rate; GGT: gamma glutamyl transferase; ICU: intensive care unit; IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; NR: not reported; PaO_2: partial pressure of oxygen in arterial blood; PCR: polymerase chain reaction; PO_2:partial pressure of oxygen; RCT: randomized controlled trial; RT-PCR: reverse transcription polymerase chain reaction; rRT-PCR: real-time reverse transcription polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SpO_2: oxygen saturation by pulse oximetry; ULN: upper limit of normal; WHO: World Health Organization.

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

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2020-001994-66/ES *(Continued)*

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
	  ■ Agree 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
	  ■ Agree 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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2020-001994-66/ES *(Continued)*

- 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/min/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/min/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
	  ○ Substudy treatment: compare viral clearance in people with SARS-CoV-2 treated with ivermectin and placebo, time point unclear

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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	6 May 2020
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: December 2020 • Planned completion date more than 6 months ago: yes • Date last update posted: NR • Sponsor/funding: Fundació Assistencial Mútua Terrassa

2021-000166-15/HU

Study name	A randomized, double-blind, placebo-controlled study to assess the safety and efficacy of ivermectin in asymptomatic and mild severity COVID-19 patients
Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 140 • Setting: outpatient • Country: Hungary • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: 2021-000166-15/HU • Date of registration: 25 January 2021

Participants	• Inclusion criteria
	  ○ Both gender, 18-75 years old
	  ○ Ambulatory patients with confirmed SARS-CoV-2 infection by RAT or PCR, regardless whether they show symptoms or are asymptomatic
	  ○ Asymptomatic or mild COVID-19 cases: no dyspnoe and no tachypnoe (respiratory rate < 22/min), no need for oxygen-supplementation; no radiological findings of pneumonia (note: no medical imaging will be conducted within the scope of the study. If previous medical imaging report is available, its result however be utilized)
	  ○ BMI: ≤ 20 kg/m^2 to ≤ 28 kg/m^2
	  ○ Subjects who are able to communicate with the Investigator and research staff, who understand the study, are able to comply with all study procedures, and willing to provide written informed consent prior to screening examinations

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2021-000166-15/HU *(Continued)*

	• Exclusion criteria ○ Moderate or severe or critical COVID-19 cases ○ High-risk patient for progression of COVID-19 ○ Concomitant or previous administration of any experimental, non-established COVID-19 therapy, either in off-label indication of a registered medicinal product or as a non-registered drug candidate in a clinical trial setting or compassionate use programme (or equivalents thereof) ○ No previous COVID-19 therapies allowed ○ Concomitant administration of coumarin-derivatives or warfarin ○ Concomitant administration of cytochrom-P450 or membrane drug transporter ○ Any clinically-significant abnormality identified during screening full physical examination, vital signs, laboratory tests and ECG which is deemed by the investigator to be incompatible/inappropriate for study participation ○ Current or recent history of drug or substance abuse, including alcohol ○ Patients who regularly consume more than 4 cups daily of beverage containing caffeine ○ Current strong smoker (> 10 cigarettes a day, or its equivalent) ○ Positive pregnancy test ○ Women who are pregnant or nursing, or who are planning to get pregnant within 3 months after the last dose of study drug ○ History of allergy, intolerance or sensitivity to ivermectin or any component of the study drug formulation ○ Exhibiting any pathology, contraindicated with ivermectin administration ○ Undergone surgery or have donated blood within 12 weeks prior to the start of the study ○ History of bleeding diathesis or other bleeding disorders ○ Investigational drug administration or investigational device application within 1 month preceding study entry, or within 5 terminal half-life of the investigational drug of the previous study, whichever is the longer ○ History of malignancy within 5 years from screening visit, with the exception of resected basal cell carcinoma or squamous cell carcinoma of the skin, or resected cervical intraepithelial neoplasia ○ Particular central nervous system interventions and disorders, which may cause breakdown of the blood-brain-barrier (BBB) and result in transport of ivermectin to brain
Interventions	• Details of intervention ○ Type and dose: ivermectin, no information on dose or frequency scheme ○ Route of administration: oral • Treatment details of control group ○ Placebo • Concomitant therapy: NR
Outcomes	• Primary study outcome ○ Percentage of SARS-CoV-2 virus at day 7 compared to baseline • Relevant review outcomes planned ○ Time to virus clearance, defined as days from randomization (day 1) to negative SARS-CoV-2 RT-PCR test ○ Time to recovery in patients who have developed symptoms ○ Time to resolution from fever, cough burden, dysgeusia-ageusia, anosmia, fatigue ○ Percentage of patients hospitalized due to progression of COVID-19 • Additional study outcomes ○ Time to virus clearance, defined as days from randomization (day 1) to negative SARS-CoV-2 RT-PCR test ○ Time to recovery in patients who have developed symptoms ○ Time to resolution from fever, cough burden, dysgeusia-ageusia, anosmia, fatigue ○ Percentage of patients hospitalized due to progression of COVID-19 ○ Absenteeism, by self-reporting, expressed in days absent from workplace, due to COVID-19

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2021-000166-15/HU *(Continued)*

Starting date	3 March 2021
Contact information	Cortex Pharma Services CRO Jozsef nador ter 5-6 1051 Budapest Hungary info@cortexps.hu
Notes	• Recruitment status: NR • Prospective completion date: NR • Planned completion date more than 6 months ago: unclear • Date last update posted: NR • Sponsor/funding: Meditop Gyógyszeripari Kft

2021-002024-21/CZ

Study name	Randomized placebo controlled clinical trial evaluating the safety and efficacy of ivermectin in hospitalized patients with Covid-19 disease
Methods	• Trial design: double-blinded RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 136 • Setting: inpatient • Country: Czech Republic • Language: English • Number of centres: 1 • Study purpose (treatment, prevention): treatment • Trial registration number: 2021-002024-21/CZ • Date of registration: 28 April 2021

Participants	• Inclusion criteria
	  ○ Age ≥ 18 years
	  ○ Willingness to participate in the clinical trial expressed by signing the informed consent form
	  ○ Patients with confirmed COVID-19 disease requiring hospitalization with at least one of the following symptoms: febrile illness > 38.5 °C; shortness of breath at rest or with minimal exertion; oxygen-free saturation < 93% SpO_2; inability to self-service; general exhaustion and more
	  ○ Laboratory PCR-confirmed positive SARS-CoV-2 (nasopharyngeal swab) or positive RAT not older than 5 days)
	  ○ Clinical trial subjects of childbearing potential must agree to the use of contraception for the duration of clinical trial and 3 months after the end of clinical trial

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2021-002024-21/CZ *(Continued)*

	• Exclusion criteria: ○ Pregnancy, breastfeeding, positive chorionic gonadotropin (hCG) ○ Inadequacy of classification of the subject on the basis of individual assessment of the examining physician ○ Outpatient treatment of patients with COVID-19 disease ○ Hepatic impairment - ALT and/or AST > 3 times ULN detected before IP administration ○ Known hypersensitivity to the components of the preparation ○ Eating and fluid intake disorders and conditions limiting the bioavailability of the drug ○ Participation in another clinical trial ○ BMI > 35 kg/m^2 ○ Inability to swallow drugs ○ Current use of potent CYP3A4 inhibitors: fluconazole, fluoxetine, indinavir, itraconazole, clarithromycin, nifedipine, ritomavir, verapamil, voriconazole ○ Use of ivermectin 1 month before inclusion in study ○ Bone marrow transplantation, history of disorders ○ Neurological disorders such as epilepsy that are treated with GABA agonists or past suicidal ideation or attempts
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: standard of care (no details provided) administered in both study arms
Outcomes	• Primary study outcome ○ Severity, expectations, intensity adverse events and association with IP and placebo ○ Nature of adverse events, duration ○ Improvement by at least one grade at the 8-level Ordinal Scale S1 assessment level, assessed on day 10 after the first IP/placebo administration • Relevant review outcomes planned ○ Mortality (until day 28) • Additional study outcomes ○ Evaluation of the condition of patients at the level of 8-level Ordinal Scale S1 on individual days of clinical trial (until day 28) ○ Time to first improvement by 1 category compared to day 1 on the 8-speed Ordinal Scale S1 (until day 28) ○ Time to first deterioration by 1 category compared to day 1 on the 8-degree Ordinal Scale S1 (until day 28) ○ Duration of oxygen therapy (until day 28) ○ Duration of non-invasive ventilation or high-flow oxygenation (until day 28) ○ Duration of intubation and mechanical ventilation or organ support by vasopressors, dialysis or extracorporeal membrane oxygenation (ECMO) (until day 28) ○ Mortality (until day 28) ○ Length of hospitalization (until day 28) ○ Change of X-ray findings on the lungs during the 10th day ○ Evaluation of concomitant treatment in both arms ○ Evaluation of the change in viral load over time ○ Serum concentration of CRP ○ Number of subjects with increased ALT and/or AST > 3 times ULN
Starting date	9 June 2021
Contact information	Pekarska 53

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	65691 Brno Czechia trials.icrc@fnusa.cz
Notes	• Recruitment status: NR • Prospective completion date: NR • Planned completion date more than 6 months ago: unclear • Date last update posted: NR • Sponsor/funding: Fakultní nemocnice usv. Anny v Brně

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 nucleic acid amplification test/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 ○ 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/min) 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 ICU due to SARS-CoV-2 or death at 7, 21, and 28 days ○ Proportion of participants progressing to death at 7, 14, and 21 days and up to 6 months

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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/min) 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 ICU 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 • Planned completion date more than 6 months ago: unclear • Date last update posted: 27 January 2021 • Sponsor/funding: The Leona M and Harry B Helmsley Charitable Trust (USA)

ACTRN12621001535864

Study name	Ivermectin to prevent coronavirus
Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 40 • Setting: outpatient • Country: USA • Language: English • Number of centres: NR • Study purpose (treatment, prevention): prevention • Trial registration number: ACTRN12621001535864 • Date of registration: 10 November 2021

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ACTRN12621001535864 *(Continued)*

Participants	• Inclusion criteria
	  ○ 1-80 years old
	  ○ In the preceding 72 hours, had close contact with a person infectious with SARS-CoV-2 (COVID-19)
	  ■ AND that contact was in the context of a participant's home or an indoor work environment or a family gathering or a social or a religious function or a ceremony each being of less than 30 people.
	  ■ AND since that contact, tested negative for SARS-CoV-2 on PCR of pharyngeal swab
	  ■ AND are asymptomatic of fever, cough, sore throat, rhinorrhoea, loss of smell, loss of taste, or more difficulty breathing than usual.

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ACTRN12621001535864 *(Continued)*

- Exclusion criteria
  - Residing outside the current geographic recruitment area
  - The close contact with an infectious index case of SARS-CoV-2 occurred in a hospital
  - The index case who has SARS-CoV-2 lives in the same residence as the potential participant
  - Another person who lives in the same residence as the potential participant has returned a positive pharyngeal PCR for SARS-CoV-2 in the last 2 weeks
  - Unable to provide the name, address and phone number of the potential participant's general practitioner/primary care physician OR does not have such a general practitioner/primary care physician
  - Has not attended a doctor at the practice of the above general practitioner/primary care physician for more than 12 months
  - Lives alone
  - Unable to provide the name and phone number of a back-up contact person
  - History of past infection with SARS-CoV-2
  - Use of ivermectin for any purpose in 5 weeks prior to enrolment
  - Known past allergy or severe adverse reaction to Ivermectin
  - Weight < 45kg or > 120kg
  - Pregnant or breast feeding
  - Not willing to refrain from falling pregnant or fathering a child for 6 months after last dose of investigational product
  - Cirrhosis or known decompensated liver disease (Child-Pugh B or C)
  - Current use, or use within the last 3 months, of the drug amiodarone
  - Current use of any of the following drugs: warfarin, verapamil, diltiazem, quinidine, spironolactone, ciclosporin, tacrolimus, cobicistat, indinavir, ritonavir, didanosine (DDI), ketoconazole, itraconazole, fusidic acid, erythromycin, clarithromycin
  - Past sedation or somnolence from products containing codeine
  - History of residency or travel to Loa loa endemic areas
  - Severe asthma
  - Encephalopathy
  - Head injury requiring medical attention in the last 6 months
  - Concussion within the last 6 months
  - Fit, seizure, stroke, transient ischaemic attack or transient global amnesia in the last 6 months
  - History of Epilepsy
  - Dementia of any type
  - Not usually fully independent in activities of daily living and self-care including: washing, toileting, dressing and dental care
  - Inability of participant or person responsible to communicate to the level necessary to provide verbal or written consent
  - Incarcerated by local, state or federal authorities
  - Conditions 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, poorly controlled mental state disorder
  - Unable to advise trial staff of coronavirus vaccination status including date of administration of last vaccine dose. Already enrolled in another coronavirus RCT
  - In Australia, lack of a valid Medicare number
  - Participant declines to be at home when IP is delivered

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

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ACTRN12621001535864 *(Continued)*

Outcomes	• Primary study outcome
	  ○ Proportion of participants who received ivermectin and convert to a positive PCR for SARS-CoV-2
	• Relevant review outcomes planned
	  ○ Proportion of participants who received ivermectin and convert to a positive PCR for SARS-CoV-2
	  ○ Participants who convert to a positive PCR for SARS-CoV-2, the difference (those who received ivermectin versus those who received placebo) in days alive free of SARS-CoV-2 symptoms at day 14 and 28
	  ○ Participants who convert to a positive PCR for SARS-CoV-2, the difference (those who received ivermectin versus those who received placebo) in days alive free of presentation to hospital and/or acute hospital care and/or to outpatient care under hospital supervision at day 28 will be assessed as a composite secondary outcome.
	• Additional study outcomes
	  ○ Participants who convert to a positive PCR for SARS-CoV-2, the difference (those who received ivermectin versus those who received placebo) in days alive free of SARS-CoV-2 symptoms at day 14 and 28
	  ○ Participants who convert to a positive PCR for SARS-CoV-2, the difference (those who received Ivermectin versus those who received placebo) in days alive free of presentation to hospital and/or acute hospital care and/or to outpatient care under hospital supervision at day 28 will be assessed as a composite secondary outcome.
	  ○ Participants who convert to a positive PCR for SARS-CoV-2, the difference (those who received Ivermectin versus those who received placebo) in time from exposure to an index case of SARS-CoV-2 to a positive PCR for SARS-CoV-2.

Starting date	10 January 2022
Contact information	Dr Kylie Wagstaff Monash University Wellington Road Clayton, Vic 3800 Australia kylie.wagstaff@monash.edu
Notes	• Recruitment status: not yet recruiting • Prospective completion date: NR • Planned completion date more than 6 months ago: unclear • Date last update posted: 23 December 2021 • Sponsor/funding: The Leona M and Harry B Helmsley Charitable Trust

Ashraf 2021

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 and published protocol • Sample size: 180 • Setting: NR • Country: Pakistan • Language: English • Number of centres: 2 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04472585

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Ashraf 2021 *(Continued)*

	• 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 ○ BMI 18 kg/m^2 to 28 kg/m^2 • Exclusion criteria ○ Allergy to any drug ○ Comorbidities: any pre-existing cardiac disease, pulmonary disease ○ Arrhythmias ○ Pregnancy ○ RT-PCR performed > 3 days prior to enrolment
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 ○ Severity of symptoms up to 14 days • Relevant review outcomes planned ○ Time needed to turn positive COVID-19 PCR to negative within 14 days ○ Time taken for alleviation of symptoms within 14 days ○ Time needed to make participants clinically well within 14 days • Additional study outcomes ○ Time needed to make participants clinically well within 14 days
Starting date	14 November 2020, postponed from 14 Juli 2020
Contact information	Shoaib Ashraf, PhD Harvard University Boston USA sashraf@mgh.harvard.edu
Notes	• Recruitment status: recruiting • Prospective completion date: October 2021, postponed from September 2020 • Planned completion date more than 6 months ago: no • Date last update posted: 17 February 2021 • Sponsor/funding: Sohaib Ashraf

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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

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
	  ○ Viral load reduction in participants with haematological illnesses admitted with COVID-19 infection at 7 days
	  ○ To study the incidence of serious adverse events and safety of this drug when used in haematological illnesses
	• 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

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

Notes	• Recruitment status: not yet recruiting • Prospective completion date: NR • Planned completion date more than 6 months ago: unclear • 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

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 RD 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
	  ○ Eradication of virus at 1, 3, and 5 days
	  ○ Overall safety of study drug
	• Additional study outcomes
	  ○ Overall safety of study drug
	  ○ Duration of hospitalization
	  ○ Improvement in abnormal laboratory values

Starting date	24 May 2020
Contact information	Dr Ashish Pathak

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

	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 • Planned completion date more than 6 months ago: unclear • Date last update posted: 18 May 2020 • Sponsor/funding: RD 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 • 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
	  ○ Able to give informed consent
	  ○ Not current user 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 of 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

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Garcia 2021 *(Continued)*

	• Concomitant therapy: NA

Outcomes	• Primary study outcome
	  ○ Proportion of participants with a positive SARS-CoV-2 PCR result from a nasopharyngeal swab 7 days after treatment
	• Relevant review outcomes planned
	  ○ Participants progressing to severe disease or death during the trial
	  ○ Proportion of drug-related adverse events at 7 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 ≤ 21 days
	  ○ Frequency of innate immune cells ≤ 7 days
	  ○ Results from cytokine Human Magnetic 30-Plex Panel ≤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 • Prospective completion date: April 2021 • Planned completion date more than 6 months ago: yes • Date last update posted: 18 March 2021 • Sponsor/funding: Universidad Peruana Cayetano Heredia

IRCT20111224008507N5

Study name	Double-blind placebo-controlled clinical trial 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

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IRCT20111224008507N5 *(Continued)*

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
	• Concomitant therapy: standard of care according to national treatment protocol administered in both study arms

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
	  ○ Mortality, time point unclear
	  ○ Drug adverse effects (wheezing, itching, skin rash, oedema, and hypotension)
	  ○ 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: August 2022 • Planned completion date more than 6 months ago: no • Date last update posted: 4 March 2021 • Sponsor/funding: Mazandaran University of Medical Sciences

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IRCT20190417043295N2

Study name	Evaluation of the effect of ivermectin in intubated COVID-19 patients
Methods	• Trial design: double-blind 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: IRCT20190417043295N2 • Date of registration: 20 September 2021

Participants	• Inclusion criteria
	  ○ Intubated patients on ICU
	  ○ COVID-19 PCR test positive
	  ○ No increase in liver enzymes
	  ○ > 18 years old
	• Exclusion criteria
	  ○ History of drug allergy
	  ○ Pregnant Women
	  ○ Patient's refusal to continue participating in the study

Interventions	• Details of intervention
	  ○ Type and dose: Ivermectin, 6 mg twice daily on day 1 and 3 mg twice daily on day 2-5
	  ○ Route of administration: oral
	• Treatment details of control group
	  ○ Placebo
	• Concomitant therapy: standard of care (no details provided) administered in both study arms

Outcomes	• Primary study outcome
	  ○ Mortality rate at 30 days
	• Relevant review outcomes planned
	  ○ Mortality rate at 30 days
	• Additional study outcomes
	  ○ Intubation period
	  ○ Lung Compliance

Starting date	23 September 2021
Contact information	Reza Baghbanian Assistant professor at Ahvaz University of Medical Sciences 24 metery street, east sahely highway, Ahvaz Khouzestan baghbanian.r@ajums.ac.ir shouman66@gmail.com
Notes	• Recruitment status: recruiting • Prospective completion date: January 2022 • Planned completion date more than 6 months ago: no • Date last update posted: 20 September 2021 • Sponsor/funding: Ahvaz University of Medical Sciences

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ISRCTN86534580

Study name	PRINCIPLE: A clinical trial evaluating treatments for suspected and confirmed COVID-19 for recovery at home
Methods	• Trial design: open-label RCT, dynamic platform trial with mulitple arms; only 2 arms relevant • Type of record: trial register entry • Sample size: 8523 • Setting: outpatient • Country: UK • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: ISRCTN86534580 • Date of registration of ivermectin arm: 12 May 2021

Participants	• **Inclusion criteria**
	  ○ Participant willing and able to give informed consent for participation in the study
	  ○ Participant willing to comply with all trial procedures
	  ○ Suspected COVID-19 using the National Health Service syndromic definition, or symptoms consistent with COVID-19 (including, but are not limited to, shortness of breath, general feeling of being unwell, muscle pain, diarrhoea and vomiting) and with a positive test for SARS-CoV-2 infection within the past 14 days
	  ○ Aged ≥ 65 years or over, aged 18-64 and is experiencing shortness of breath as part of COVID-19 illnesses, or aged 18-64 and has underlying health conditions
	• **Exclusion criteria**
	  ○ Patient currently admitted to hospital
	  ○ Almost recovered (generally much improved and symptoms now mild or almost absent)
	  ○ Judgement of the recruiting clinician deems ineligible
	  ○ Previous randomization to an arm of the PRINCIPLE trial
	  ○ Additional intervention-specific exclusion criteria

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
	  ○ No treatment except standard of care
	• Concomitant therapy: standard of care (no details provided) administered in both study arms

Outcomes	• Primary study outcome
	  ○ Reducing time to recovery
	  ○ Reducing the incidence of hospitalization and/or death
	• Relevant review outcomes planned
	  ○ Hospitalization and/or death
	  ○ Time taken to self-reported recovery
	• Additional study outcomes
	  ○ Time taken to self-reported recovery
	  ○ Hospitalization and/or death

Starting date	12 March 2020
Contact information	Prof. Christopher Butler Chief Investigator principle@phc.ox.ac.uk
Notes	• Recruitment status: recruiting

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ISRCTN86534580 *(Continued)*

- Prospective completion date: September 2022; ivermectin arm is temporarily stopped due to delayed ivermectin shipment (information provided by trialist via personal communication)
- Planned completion date more than 6 months ago: no
- Date last update posted: 16 August 2021
- Sponsor/funding: University of Oxford/UK Research and Innovation, National Institute for Health and Care Research (NIHR)

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 • 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, no information on dosing and frequency 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

Outcomes	• Primary study outcome
	  ○ Role of ivermectin in the cure of COVID-19 patients
	• Relevant review outcomes planned
	  ○ Rate of viral clearance in comparison to other treatment protocols
	• Additional study outcomes
	  ○ Rate of viral clearance in comparison to other treatment protocols

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NCT04425707 *(Continued)*

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: September 2020 • Planned completion date more than 6 months ago: yes • Date last update posted: 11 June 2020 • Sponsor/funding: Ministry of Health and Population, Egypt

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: outpatient • 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
	  ○ Refusal to participate
	  ○ Pregnant or lactating
	  ○ Hypersensitivity to ivermectin
	  ○ Receiving any drug that interacts with ivermectin

Interventions	• Details of intervention
	  ○ Type and dose: ivermectin for 3 days, no information 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

Outcomes	• Primary study outcome
	  ○ Time to be symptom free within 21 days
	• Relevant review outcomes planned
	  ○ Time to be symptom free within 21 days
	  ○ Need for hospital admission within 21 days
	  ○ Mortality at 30 days

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NCT04445311 *(Continued)*

	• Additional study outcomes
	  ○ Need for hospital admission within 21 days
	  ○ Need for mechanical ventilation within 21 days
	  ○ Length of stay within 30 days
	  ○ Mortality at 30 days

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: August 2020 • Planned completion date more than 6 months ago: yes • Date last update posted: 24 June 2020 • Sponsor/funding: Zagazig University

NCT04510194

Study name	COVID-OUT: Early outpatient treatment for SARS-CoV-2 infection (COVID-19)
Methods	• Trial design: quadruple-blind RCT with 6 parallel arms, only 2 arms relevant; the other 4 arms investigate metformin and fluvoxamin in various combinations • Sample size: 1160 • Setting: outpatient • Country: USA • Language: English • Number of centres: 7 • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04510194 • Date of registration: 12 August 2020

Participants	• Inclusion criteria
	  ○ Positive laboratory test for active SARS-CoV-2 viral infection based on local laboratory standard (i.e. positive PCR result) within 3 days of randomization
	  ○ No known history of confirmed SARS-CoV-2 infection
	  ○ BMI ≥ 25 kg/m^2 by self-report or ≥ 23 kg/m^2 in patients who self-identify in South Asian or Latinx background
	  ○ Willing and able to comply with study procedures (i.e. swallow pills)
	  ○ Has an address and electronic device for communication
	  ○ GFR > 45 mL/min within 2 weeks for patients > 75 years old, or with history of heart, kidney, or liver failure

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NCT04510194 *(Continued)*

	• Exclusion criteria ○ Hospitalized, for COVID-19 or other reasons ○ Symptom onset greater than 7 days before randomization (symptoms not required for inclusion) ○ Immune compromized state (solid organ transplant, bone marrow transplant, AIDS, on high-dose steroids) ○ Hepatic impairment (Child-Pugh B and C) or other condition that, in the opinion of the investigator, would affect safety ○ Inability to obtain informed consent ○ Enrolment in another blinded RCT for COVID-19 ○ Already received an effective (Food and Drug Administration approved/emergency use authorization) therapy for COVID-19 (currently monoclonal antibody treatment) ○ Alcohol use disorder ○ Other unstable medical condition or combination of home medications that in the view of the PI make it unsafe for the individual to participate ○ History of severe kidney disease ○ Unstable heart failure (stage 3 or 4 heart failure) ○ Allergic reaction to metformin, fluvoxamine, or ivermectin in the past ○ Bipolar disease: individuals who report they have bipolar disorder or are taking medication for bipolar disorder (lithium, valproate, high-dose antipsychotic), unless the investigator concludes that the risk for mania is unlikely ○ Current Loa loa or onchocerciasis infection ○ Typhoid, BCG, or cholera vaccination within 14 days or 3 days after enrolment ○ Co-medication specified in protocol
Interventions	• Details of intervention of relevant arms ○ Type and dose: ivermectin 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 ○ Decreased oxygenation (SpO2 ≤ 93% on home monitoring) within 14 days ○ Emergency department use for COVID-19 symptoms within 14 days • Relevant review outcomes planned ○ None • Additional study outcomes ○ Maximum symptom severity within 14 and 28 days ○ Clinical progression scale within 14 and 28 days ○ Time to meaningful recovery within 14 and 28 days ○ Laboratory outcome subsidy - viral load, CRP, albumin, microbiome at several time points ○ Post-acute sequelae of SARS-CoV-2 infection (PASC) questionnaire at 6 and 12 months
Starting date	1 January 2021, postponed from September 2020
Contact information	University of Minnesota 3 Morrill Hall 100 Church St. SE Minneapolis MN 55455 United States
Notes	• Recruitment status: recruiting • Prospective completion date: January 2022 (date provided by trialist via personal communication)

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NCT04510194 *(Continued)*

- Planned completion date more than 6 months ago: no
- Date last update posted: 18 November 2021
- Sponsor/funding: University of Minnesota

NCT04510233

Study name	Ivermectin nasal spray for COVID-19 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
	• 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: December 2020

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NCT04510233 *(Continued)*

- Planned completion date more than 6 months ago: yes
- 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

Participants	• Inclusion criteria
	  ○ Healthcare workers aged > 18 years of either sex, actively working during study recruitment in health services that do not screen and exclude acutely ill workers
	  ○ Healthcare workers who have not presented with general symptoms such as general discomfort, fever, cough, dyspnoea, or muscle pain in the last week
	  ○ Healthcare workers with negative COVID-19 serological antibody diagnostic tests
	• Exclusion criteria
	  ○ Healthcare workers considered recovered from 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
	  ○ BMI < 18.5 kg/m^2 and > 35 kg/m^2

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
	  ○ Clinical development of COVID-19 disease during the 7-week intervention period
	  ○ Seroconversion at 8 weeks
	  ○ Hospitalization requirement within 8 weeks
	  ○ Safety of the intervention within 8 weeks

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NCT04527211 *(Continued)*

	• Additional study outcomes
	  ○ Seroconversion at 8 weeks
	  ○ Hospitalization requirement within 8 weeks
	  ○ ICU 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: December 2020 • Planned completion date more than 6 months ago: yes • Date last update posted: 26 August 2020 • Sponsor/funding: Javeriana University

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 surgical sterilization such as vasectomy or intrauterine device, taking oral contraceptive, using condoms

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NCT04703205 *(Continued)*

	○ 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 GFR 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 ○ Period until the COVID-19 PCR test (SARS-CoV-2 nucleic acid detection) becomes negative within 14 days • 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: May 2022, postponed from May 2021 • Planned completion date more than 6 months ago: no • Date last update posted: 26 October 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/min) or hypotension (systolic/diastolic blood pressure < 90/60 mmHg)
	  ○ Allergic to the investigational product or similar drugs (or any excipients)
	  ○ QTcF > 450 ms
	  ○ 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 ULN
	  ○ Estimated GFR < 30 mL/min 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
	• Concomitant therapy: standard of care (hydroxychloroquine) administered in both study arms

Outcomes	• Primary study outcome
	  ○ WHO Clinical Progression Scale at 14 days
	• Relevant review outcomes planned
	  ○ WHO Clinical Progression Scale at 14 days
	  ○ WHO COVID-19 Ordinal Scale for Clinical Improvement at 7 days
	  ■ Proportion of hospitalizations at 28 days
	  ○ Time-to-recovery within 28 days
	  ○ Proportion of deaths at 28 days
	  ○ Proportion of hospitalizations

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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
	  ○ Duration of clinical manifestations within 14 days
	  ○ Proportion of participants needing additional drugs or interventions within 28 days
	  ○ Proportion of subjects needing oxygen use
	  ○ Proportion of hospitalizations
	  ○ Duration of mechanical ventilation within 28 days
	  ○ Proportion of vasopressor use at 28 days
	  ○ Proportion of deaths 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 hospitalization
	  ○ Proportion of increased ultrasensitive CRP, ESR, 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: April 2021 • Planned completion date more than 6 months ago: yes • Date last update posted: 15 January 2021 • Sponsor/funding: Corpometria Institute

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

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NCT04729140 *(Continued)*

	• Study purpose (treatment, prevention): treatment • Trial registration number: NCT04729140 • Date of registration: 28 January 2021

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
	  ○ Immunocompromized 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 (BMI ≥ 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-19 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 within 5 weeks

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NCT04729140 *(Continued)*

	• Additional study outcomes
	  ○ Mortality within 5 weeks
	  ○ 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: March 2022, postponed from March 2021 • Planned completion date more than 6 months ago: no • 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 cases within 8 days from onset of symptoms
	  ○ Asymptomatic cases within 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 within 30 days
	• Relevant review outcomes planned
	  ○ Proportion of participants with hospitalization criteria within 30 days
	  ○ 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
	  ○ Proportion of participants with ivermectin adverse events within 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: May 2021 • Planned completion date more than 6 months ago: yes • Date last update posted: 6 April 2021 • 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

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NCT04836299 *(Continued)*

	• Country: Bolivia • Language: English • Number of centres: 1 • 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 within 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
	  ○ Clinical remission within 28 days

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NCT04836299 *(Continued)*

	• Additional study outcomes
	  ○ Hospital stay within 3 months
	  ○ Clinical signs of toxicity or adverse effects within 28 days
	  ○ Need for supplemental oxygen at 28 days
	  ○ Need for mechanical ventilation at 21 days

Starting date	8 May 2021
Contact information	Jorge L Aviles, MPH Universidad Mayor de San Simón Cochabamba Bolivia
Notes	• Recruitment status: not yet recruiting • Prospective completion date: December 2021 • Planned completion date more than 6 months ago: no • 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: 15000 • 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 mg/kg to 0.4 mg/kg, once daily for 3 days
	  ○ Route of administration: oral
	• Treatment details of control group
	  ○ Placebo

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NCT04885530 *(Continued)*

	• 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
	  ○ 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
	• 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
	  ○ Number of deaths as measured by patient 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	8 June 2021
Contact information	Allison DeLong Duke Clinical Research Institute Durham 27701 North Carolina USA allison.hayes@duke.edu
Notes	• Recruitment status: recruiting • Prospective completion date: March 2023 • Planned completion date more than 6 months ago: no • Date last update posted: 23 December 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-blind 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

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NCT04886362 *(Continued)*

Participants	• Inclusion criteria
	  ○ Age ≥ 18 years
	  ○ Positive antigen test or RT-PCR for SARS-CoV-2
	  ○ < 7 days from symptom 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
	• 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
	  ○ Composite outcome, first outcome that occurs in each participant during 28 days
	  ■ Need for hospitalization includes general bed or ICU or
	  ■ Death from any cause
	  ○ 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
	  ○ Number and type of serious and non-serious adverse events within 28 days

Starting date	July 2021
Contact information	Juan Carlos Chacón Jimenez, MD ceivercol@suramericana.com.co

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NCT04886362 *(Continued)*

Notes	• Recruitment status: not yet recruiting • Prospective completion date: December 2021 • Planned completion date more than 6 months ago: no • Date last update posted: 14 May 2021 • Sponsor/funding: Ayudas Diagnosticas Sura SAS

NCT04944082

Study name	Remdesivir-ivermectin combination therapy in severe Covid-19
Methods	• Trial design: open-label RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 60 • Setting: inpatient • Country: Egypt • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: NCT04944082 • Date of registration: 29 June 2021

Participants	• Inclusion criteria
	  ○ Adult, hospitalized severe COVID-19 patients
	  ○ Both genders
	  ○ Given informed consent (COVID-19 infection confirmed by PCR, severe illness is defined as patients with $SpO^2 \leq 94\%$ on room air, including patients on supplemental oxygen)
	• Exclusion criteria
	  ○ Patients under 18 years old
	  ○ Pregnant women
	  ○ Advanced renal diseases (cr. clearance < 30 mL/hr)
	  ○ Raised liver enzymes > 3 times normal
	  ○ Arrhythmia

Interventions	• Details of intervention
	  ○ Type and dose: ivermectin 6 mg, once daily for 4 days
	  ○ Route of administration: oral
	• Treatment details of control group
	  ○ Standard of care alone
	• Concomitant therapy: standard of care (remdesivir) administered in both study arms

Outcomes	• Primary study outcome
	  ○ Improvement in level of oxygenation
	  ○ Need for ventilator support
	  ○ Development of complication by end of 4th day
	  ○ Mortality rate
	• Relevant review outcomes planned
	  ○ Need for ventilator support
	  ○ Mortality rate
	  ○ Development of complication by end of 4th day
	• Additional study outcomes
	  ○ None

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NCT04944082 *(Continued)*

Starting date	1 July 2021
Contact information	Maiada K. Hashem Lecturer Assiut University, Department of Chest Diseases Assiut Egypt
Notes	• Recruitment status: not yet recruiting • Prospective completion date: December 2021 • Planned completion date more than 6 months ago: no • Date last update posted: 29 June 2021 • Sponsor/funding: Assiut University

NCT05040724

Study name	Evaluation of the impact of the administration of single dose of ivermectin in the early phase of COVID-19 (IVERCoV)
Methods	• Trial design: triple-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 200 • Setting: outpatient • Country: France • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: NCT05040724 • Date of registration: 10 September 2021

Participants	• Inclusion criteria
	  ○ Patient ≥ 18 years old
	  ○ Symptomatic COVID-19 for < 96 hours
	  ○ Tested positive for SARS-CoV-2 by RT-PCR on a nasopharyngeal sample within 48 hours of inclusion
	  ○ Following an effective method of contraception for women of childbearing age
	  ○ Affiliated to a social security scheme
	  ○ Informed and written consent from patient
	• Exclusion criteria
	  ○ Patient requiring normal hospitalization or intensive care
	  ○ Oxygen-requiring patient
	  ○ With a history of parasitosis, in particular filariasis
	  ○ With a history of hypereosinophilia
	  ○ Recent travel (less than 3 months) in poor hygienic conditions
	  ○ Taking ivermectin in the last 12 months
	  ○ Contraindications to ivermectin or one of the constituents of the drug (known history of allergies)
	  ○ Pregnant or breastfeeding women
	  ○ Participation in another interventional study relating to COVID-19 concerning a drug during this research
	  ○ Patient without social security coverage

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NCT05040724 *(Continued)*

Interventions	• Details of intervention
	  ○ Type and dose: ivermectin 400 µg/kg, single dose
	  ○ Route of administration: oral
	• Treatment details of control group
	  ○ Placebo
	• Concomitant therapy: standard of care (no details provided) administered in both study arms

Outcomes	• Primary study outcome
	  ○ Negatie RT-PCR test on nasopharyngeal samples of SARS-CoV-2 on day 3
	• Relevant review outcomes planned
	  ○ Negative RT-PCR test on nasopharyngeal samples of SARS-CoV-2 on day 3
	  ○ Number of patients hospitalized/ or requiring oxygen therapy
	  ○ Number of patients admitted to ICU
	  ○ Number of deaths
	• Additional study outcomes
	  ○ Evolution of symptoms within 28 days
	  ○ SARS-CoV-2 viral load negative kinetics after treatment by ivermectin
	  ○ Comparison of the number of RT-PCR amplification cycles
	  ○ Number of patients having recourse to home oxygen therapy
	  ○ Number of patients hospitalized and/or requiring oxygen therapy
	  ○ Number of patients admitted to ICU
	  ○ Number of deaths

Starting date	28 May 2021, postponed from 9 June 2021
Contact information	GHI Le Raincy Montfermeil Montfermeil France
Notes	• Recruitment status: not recruiting • Prospective completion date: June 2022 • Planned completion date more than 6 months ago: no • Date last update posted: 10 September 2021 • Sponsor/funding: Raincy Montfermeil Hospital Group

NCT05041907

Study name	Finding treatments for COVID-19: a trial of antiviral pharmacodynamics in early symptomatic COVID-19 (PLATCOV) (PLATCOV)
Methods	• Trial design: open-label RCT with 5 parallel arms, only 2 arms relevant; the third arm investigates favipavir, the fourth arm arms investigates remdesivir, the fifth arm investigates monoclonal antibodies • Type of record: trial register entry • Sample size: 750 • Setting: outpatient • Country: Thailand • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: NCT05041907

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NCT05041907 *(Continued)*

	• Date of registration: 13 September 2021
Participants	• Inclusion criteria ○ Patient understands the procedures and requirements and is willing and able to give informed consent for full participation in the study ○ Previously healthy adults, male or female, aged 18-50 years at time of consent with early symptomatic COVID-19 ○ SARS-CoV-2 positive by lateral flow antigen test ○ Symptoms of COVID-19 (including fever, or history of fever) < 4 days (96 hours) ○ Oxygen saturation ≥ 96% measured by pulse oximetry at time of screening ○ Able to walk unaided and unimpeded in activities of daily living ○ Agrees and is able to adhere to all study procedures, including availability and contact information for follow-up visits • Exclusion criteria ○ Taking any concomitant medications or drugs ○ Presence of any chronic illness/ condition requiring long-term treatment, or other significant comorbidity ○ Laboratory abnormalities discovered at screening ○ For females: pregnancy, actively trying to become pregnant, or lactation ○ Contraindication to taking, or known hypersensitivity reaction to any of the proposed therapeutics ○ Currently participating in another COVID-19 therapeutic or vaccine trial ○ Evidence of pneumonie (although imaging is not required)
Interventions	• Details of intervention of relevant arms ○ Type and dose: ivermectin 0.6 mg/kg, once daily for 7 days ○ Route of administration: oral • Treatment details of control group ○ No treatment except standard of care • Concomitant therapy: standard of care (supportive care only) administered in both study arms
Outcomes	• Primary study outcome ○ Rate of viral clearance for repurposed drugs within 7 days ○ Rate of viral clearance of positive control (monoclonal antibodies) over time relative to the negative control within 7 days ○ Rate of viral clearance for small novel molecule drugs within 7 days • Relevant review outcomes planned ○ Rates of hospitalization by treatment arm within 28 days ○ Viral cleareance • Additional study outcomes ○ Viral kinetic levels in early COVID-19 disease within 7 days ○ Number of antiviral treatment arms that show a positive signal (> 90% probability of > 5% acceleration in viral clearance) within 7 days ○ Rates of viral clearance by treatment arm, as compared against REGN-COV2 (monoclonal antibody cocktail) within 7 days ○ Rates of hospitalization by treatment arm within 28 days
Starting date	30 September 2021
Contact information	Nicholas White Professor of Tropical Medicine at Mahidol University Phutthamonthon Thailand
Notes	• Recruitment status: recruiting

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NCT05041907 *(Continued)*

- Prospective completion date: August 2023
- Planned completion date more than 6 months ago: no
- Date last update posted: 12 January 2022
- Sponsor/funding: University of Oxford

NCT05060666

Study name	Prophylaxis of COVID-19 disease with ivermectin in COVID-19 contact persons
Methods	• Trial design: double-blind RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 412 • Setting: outpatient • Country: Germany • Language: English • Number of centres: 30 • Study purpose (treatment, prevention): prevention • Trial registration number: NCT05060666 • Date of registration: 19 September 2021

Participants	• Inclusion criteria
	  ○ > 18 years old
	  ○ Adult subject living in the same household as a related COVID-19 patient (index person)

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NCT05060666 *(Continued)*

	• Exclusion criteria ○ Index person has COVID-19 symptoms > 5 days at enrolment ○ Known past COVID-19 or current infection confirmed by positive SARS-CoV-2 PCR test at enrolment ○ Symptoms at enrolment indicating COVID-19 ○ Known contraindications to the use of the study medication ○ Known COPD ○ Known acute or chronic hepatitis B or C or other clinically recognizable or known liver dysfunction ○ Known HIV infection or AIDS ○ Known symptomatic allergic rhinitis ○ Current or planned therapy with non-steroidal anti-inflammatory drugs, other pain medication ○ Recent or planned therapy with systemic steroids ○ Recent or planned therapy with systemic immunosuppressive drugs ○ Known or clinically suspected disturbance of the blood-brain-barrier as well as history of neurotoxic effects by ivermectin or other substrates/inhibitors of the para-glycoprotein ○ Known hypersensitivity/intolerance to the study drug or any of its exicpients ○ Pregnancy or lactation ○ Women of child-bearing potential planning to become pregnant or not using effective mehods of contraception ○ Any other severe disorder, which in the opinion of the investigator would preclude the subject from trial participation ○ Previous or planned vaccination with any COVID-19 vaccine ○ Recent or planned therapy with ivermectin ○ Recent or planned therapy with drugs with evident or potential benefit in treating COVID-19 in alignment with Robert Koch Institute ○ Apparent unreliability or lack of compliance ○ Known alcohol or drug abuse ○ Participation in another clinical trial during the last 30 days or planned participation in another clinical trial during the next 30 days ○ Previous participation in this same clinical trial
Interventions	• Details of intervention of relevant arms ○ Type and dose: ivermectin 0.3 mg/kg, once daily at day 0 and day 2 ○ Route of administration: oral • Treatment details of control group ○ Placebo • Concomitant therapy: NR
Outcomes	• Primary study outcome ○ COVID-19 disease within 14 days • Relevant review outcomes planned ○ Adverse events and side effects within 14 days • Additional study outcomes ○ Adverse events and side effects within 14 days ○ Type, number and severity of symptoms within 14 days of study ○ Severity of COVID-19 disease within 14 days of study
Starting date	November 2021, postponed from September 2021
Contact information	InfectoPharm Arzneimittel und Consilium GmbH Von-Humboldt-Str. 1 64646 Heppenheim Deutschland

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NCT05060666 *(Continued)*

Notes	• Recruitment status: Not yet recruiting • Prospective completion date: March 2022 • Planned completion date more than 6 months ago: no • Date last update posted: 2 November 2021 • Sponsor/funding: Infectopharm Arzneimittel GmbH

NCT05155527

Study name	A double-blind randomized controlled trial of ivermectin with favipiravir in mild-to-moderate COVID-19 patients (IFCOV)
Methods	• Trial design: quadruple-blind RCT with 2 parallel arms • Sample size: 200 • Setting: outpatient • Country: Thailand • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: NCT05155527 • Date of registration: 13 December 2021

Participants	• Inclusion criteria
	  ○ Adult patient age between 18-65 years old
	  ○ Has confirmed SARS-CoV-2 infection by RT-PCR method using sample collected from nasopharyngeal swab and oropharyngeal swab
	  ○ Has been admitted for medical care at the investigational sites
	  ○ In case of symptomatic patient, date of symptom onset is ≤ 7 days prior to randomization. In case of asymptomatic patient, the first date of positive result from RT-PCR or antigen test kit for SARS-CoV-2 is ≤ 7 days prior to randomization
	  ○ Asymptomatic or has mild to moderate COVID-19
	  ○ Willing to participate in the study and able to provide written informed consent
	  ○ Women of childbearing potential must agree to either abstinence or use at least one primary form of contraception from the time of screening through day 28
	• Exclusion criteria
	  ○ Has severe or critical COVID-19
	  ○ Bedridden (totally confined to bed)
	  ○ Has elevated ALT or AST over 3 times ULN, or history of liver cirrhosis
	  ○ Females only: currently pregnant, as determined by positive β-human choriogonadotropin (HCG) test in urine, or breast-feeding
	  ○ Receiving other potential drugs for COVID-19 treatment prior to randomization
	  ○ Received ivermectin within 1 month prior to the randomization
	  ○ Receiving other immunosuppressive or immunomodulatory drugs for the treatment of other conditions (not including topical steroids)
	  ○ History of hypersensitivity to ivermectin or favipiravir or any components of the drugs
	  ○ Receiving medications that increase gamma-aminobutyric acid (GABA) potentiating activity
	  ○ Has history of hereditary xanthinuria
	  ○ Has hypouricemia (serum uric acid ≤ 1 mg/dL), uncontrolled gout or history of xanthine urolithiasis
	  ○ Participating in other clinical trials or participated in other clinical trials in a period of 1 month or < 5 half-lives of the study drug before screening

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NCT05155527 *(Continued)*

Interventions	• Details of intervention of relevant arms
	  ○ Type and dose: ivermectin 0.6 mg/kg, once daily for 5 days
	  ○ Route of administration: oral
	• Treatment details of control group
	  ○ Placebo
	• Concomitant therapy: standard of care (favipavir) administered in both study arms

Outcomes	• Primary study outcome:
	  ○ Rate of SARS-CoV-2 viral clearance within 6 days
	• Relevant review outcomes planned
	  ○ Rate of SARS-CoV-2 viral clearance within 6 days
	  ○ Mortality rate
	• Additional study outcomes
	  ○ Mortality rate
	  ○ Progression to severe disease within 28 days
	  ○ Duration of admission
	  ○ Oxygen requirement within 28 days
	  ○ Proportion of SARS-CoV-2 viral clearance within 6 days
	  ○ Safety of ivermectin in combination with favipiravir within 28 days
	  ○ Effect of variants and viral genetic repertoires on investigational drug efficacy
	  ○ Inflammatory cytokine response
	  ○ Immune response

Starting date	December 2021
Contact information	Mahidol University Phuttamonthon 4 Road 73170 Phutthamonthon Thailand
Notes	• Recruitment status: not yet recruiting • Prospective completion date: June 2022 • Planned complertion date more than 6 months ago: no • Date last update posted: 13 December 2021 • Sponsor/funding: Mahidol University

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

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PACTR202102848675636 *(Continued)*

	• 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 • 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 ○ Number developing severe or critical COVID-19 • Additional study outcomes ○ Number with serious adverse outcome within the study period ○ Number developing severe or critical COVID-19
Starting date	8 March 2021
Contact information	Olufemi Babalola Department of Surgery Bingham University Karu

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PACTR202102848675636 *(Continued)*

	Lagos Nigeria bablo57@gmail.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: October 2021 • Planned completion date more than 6 months ago: no • Date last update posted: 31 October 2021 • Sponsor/funding: Federal Government of Nigeria

SLCTR/2021/020

Study name	A randomized control trial to assess the efficacy and safety of ivermectin in the treatment of mild to moderate COVID 19 patients
Methods	• Trial design: double-blinded RCT with 2 parallel arms • Type of record: trial register entry • Sample size: 236 • Setting: inpatient • Country: Sri Lanka • Language: English • Number of centres: NR • Study purpose (treatment, prevention): treatment • Trial registration number: SLCTR/2021/020 • Date of registration: 19 July 2021

Participants	• Inclusion criteria
	  ○ > 18 years old
	  ○ Both gender
	  ○ Positive for SARS-CoV-2 by RT-PCR tests or antigen testing using nasopharyngeal swab/aspirate within 48 hours prior to randomization and is admitted for treatment to National Institute of Infectious Diseases
	  ○ Cycle threshold (Ct) value < 38 at the time of recruitment
	  ○ Mild to moderate COVID-19 infection
	  ○ Negative antibody test
	  ○ Within 4 days of onset of symptoms and RT-PCR positivity within 48 hours in asymptomatic patient
	• Exclusion criteria
	  ○ Pregnancy
	  ○ Breastfeeding mothers
	  ○ HIV co-infection
	  ○ Patients who are known to have allergy to ivermectin or anthelminths
	  ○ Patients with severe disease as indicated by $SpO_2 \leq 93\%$ on room air at sea level or $PaO_2/FiO_2 < 300$, respiratory rate ≥ 30/min, heart rate ≥ 125/min
	  ○ Patients with critical disease, i.e. those who require mechanical ventilation or anticipated impending need for mechanical ventilation
	  ○ Received the vaccine
	  ○ Recruited in any other trials simultaneously

Interventions	• Details of intervention of relevant arms
	  ○ Type and dose: ivermectin 24 mg, once daily for 5 days
	  ○ Route of administration: oral

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SLCTR/2021/020 *(Continued)*

	• Treatment details of control group ○ Placebo • Concomitant therapy: standard of care (no details provided) administered in both study arms

Outcomes	• Primary study outcome
	  ○ Reduction of viral burden (by 50%) based on the natural log Cycle threshold (Ct) value of the RT-PCR for SARS-COV-2
	  ○ Clinical progression of the patient using WHO Clinical Progression Scale
	  ○ Percentage of participants who experience side effects recorded by the patient on data sheet for assessment of symptoms and side effects.
	• Relevant review outcomes planned
	  ○ Clinical progression of the patient using WHO Clinical Progression Scale
	  ○ Percentage of participants who experience side effects recorded by the patient on data sheet for assessment of symptoms and side effects
	• Additional study outcomes
	  ○ Improvement of symptoms by 50% by day 6 and by 100% by day 10 of intervention
	  ○ 50% reduction of development of hypoxia (SPO_2 < 94%)
	  ○ 50% improvement of lymphopaenia by day 6

Starting date	26 July 2021
Contact information	Dr Ananda Wijewickrama Consultant Physician National Institute of Infectious Diseases Mandawila road, Angoda, Sri Lanka
Notes	• Recruitment status: recruiting • Prospective completion date: NR • Planned completion date more than 6 months ago: unclear • Date last update posted: 18 October 2021 • Sponsor/funding: National Institute of Infectious Diseases

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; CT: computer tomography; ESR: erythrocyte sedimentation rate; GFR: glomerular filtration rate; 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; RAT: rapid antigen test; 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; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SD: standard deviation; ULN: upper limit of normal; 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 at day 28

	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)						

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

Risk of bias for analysis 1.2 Worsening of clinical status at day 28: participants with new need for invasive mechanical ventilation or death

	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	~	~	✓	✓	~	~
Krolewiecki 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.3 Improvement of clinical status at day 28: participants discharged alive

	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)						
Gonzalez 2021	~	~	✓	✓	~	~

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Risk of bias for analysis 1.4 Serious adverse events during the study period

	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)						
Krolewiecki 2021	✓	✓	✓	~	~	~
Mohan 2021	✓	✓	✓	~	✓	~

Risk of bias for analysis 1.5 Any adverse events during the study period

	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)						
Krolewiecki 2021	✓	✓	✓	✗	✓	✗
Mohan 2021	✓	✓	✓	~	~	~
Pott-Junior 2021	✓	✓	✓	✗	~	✗

Risk of bias for analysis 1.6 Viral clearance at day 3

	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)						
Mohan 2021	✓	✓	✓	✓	✓	✓

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Risk of bias for analysis 1.7 Viral clearance at day 7

	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)						
Kirti 2021	✓	~	✗	✓	✓	✗
Mohan 2021	✓	✓	✓	✓	✓	✓
Pott-Junior 2021	✓	✗	✓	✓	~	✗

Risk of bias for analysis 2.1 All-cause mortality at day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Bounfrate 2021	✓	✓	✓	✓	✓	✓
Chaccour 2021	✓	✓	✓	✓	✓	✓
I-TECH 2022	✓	✓	✓	✓	✓	✓
López-Medina 2021	✓	~	✓	✓	✓	~
TOGETHER 2022	✓	✓	✓	✓	✓	✓
Vallejos 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.2 Worsening of clinical status within 28 days: admission to hospital or death

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

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

Risk of bias for analysis 2.3 Worsening of clinical status within 28 days: participants with need for ICU admission or death

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
I-TECH 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.4 Symptom resolution: all initial symptoms resolved (asymptomatic) at day 14

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

Risk of bias for analysis 2.5 Symptom resolution: all initial symptoms resolved (asymptomatic) at day 28

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

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Risk of bias for analysis 2.6 Quality of life (physical component) at up to 28 days

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
TOGETHER 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.7 Quality of life (mental component) at up to 28 days

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
TOGETHER 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.8 Serious adverse events during the study period

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Bounfrate 2021	✓	✓	✓	~	~	~
Chaccour 2021	✓	✓	✓	~	~	~
I-TECH 2022	✓	✓	✓	~	✓	~
López-Medina 2021	✓	~	✓	✓	✓	~
Vallejos 2021	✓	✓	✓	✓	✓	✓

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Risk of bias for analysis 2.9 Any adverse events during the study period

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Bounfrate 2021	✓	✓	✓	✓	~	~
Chaccour 2021	✓	✓	✓	✓	✓	✓
I-TECH 2022	✓	✓	✓	✗	✓	✗
López-Medina 2021	✓	~	✓	✓	✓	~
Vallejos 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.10 Viral clearance at day 3

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
TOGETHER 2022	✓	✓	~	✓	✓	~
Vallejos 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.11 Viral clearance at day 7

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chaccour 2021	✓	✓	✓	✓	✓	✓
TOGETHER 2022	✓	✓	~	✓	✓	~

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Risk of bias for analysis 2.12 Viral clearance at day 14

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

DATA AND ANALYSES

Comparison 1. Ivermectin for treating COVID-19 in inpatient settings with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality at day 28	3	230	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.14, 2.51]
1.1.1 Moderate disease (WHO 4 to 5)	3	230	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.14, 2.51]
1.2 Worsening of clinical status at day 28: participants with new need for invasive mechanical ventilation or death	2	118	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.33, 2.04]
1.2.1 Moderate disease (WHO 4 to 5)	2	118	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.33, 2.04]
1.3 Improvement of clinical status at day 28: participants discharged alive	1	73	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.78, 1.35]
1.3.1 Moderate disease (WHO 4 to 5)	1	73	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.78, 1.35]
1.4 Serious adverse events during the study period	2	197	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.07, 35.89]
1.4.1 Moderate disease (WHO 4 to 5)	2	197	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.07, 35.89]
1.5 Any adverse events during the study period	3	228	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.61, 1.79]
1.5.1 Moderate disease (WHO 4 to 5)	3	228	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.61, 1.79]
1.6 Viral clearance at day 3	1	125	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.33, 1.96]

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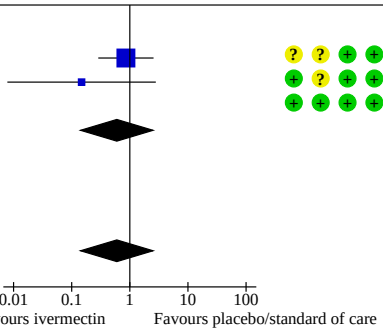
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6.1 Moderate disease (WHO 4 to 5)	1	125	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.33, 1.96]
1.7 Viral clearance at day 7	3	231	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.80, 1.58]
1.7.1 Moderate disease (WHO 4 to 5)	3	231	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.80, 1.58]

Analysis 1.1. Comparison 1: Ivermectin for treating COVID-19 in inpatient settings with moderate to severe disease, Outcome 1: All-cause mortality at day 28

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
1.1.1 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]	+	?	+	+	+	?
Krolewiecki 2021 (3)	0	30	0	15		Not estimable	+	+	+	+	+	+
Subtotal (95% CI)		**121**		**109**	**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)		**121**		**109**	**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)
(3) 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 (SoC)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

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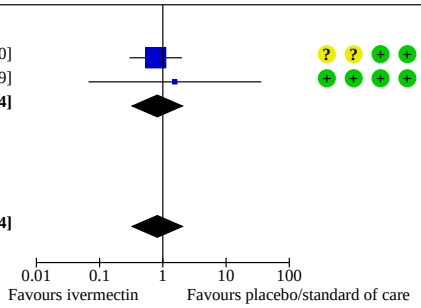
Analysis 1.2. Comparison 1: Ivermectin for treating COVID-19 in inpatient settings with moderate to severe disease, Outcome 2: Worsening of clinical status at day 28: participants with new need for invasive mechanical ventilation or death

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placeob/standard of care Events	Placeob/standard of care 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)	6	36	8	37	91.6%	0.77 [0.30 , 2.00]	?	?	+	+	?	?
Krolewiecki 2021 (2)	1	30	0	15	8.4%	1.55 [0.07 , 35.89]	+	+	+	+	+	+
Subtotal (95% CI)		**66**		**52**	**100.0%**	**0.82 [0.33 , 2.04]**						
Total events:	7		8									
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%												
Test for overall effect: Z = 0.43 (P = 0.67)												
Total (95% CI)		**66**		**52**	**100.0%**	**0.82 [0.33 , 2.04]**						
Total events:	7		8									
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%												
Test for overall effect: Z = 0.43 (P = 0.67)												
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 (30 days), participants (WHO 4 to 5), intervention (ivermectin 0.6 mg/kg/day, 3 mg or 6 mg daily for 5 days), comparator (SoC)

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions

(C) Bias due to missing outcome data

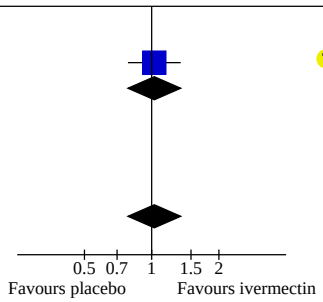
(D) Bias in measurement of the outcome

(E) Bias in selection of the reported result

(F) Overall bias

Analysis 1.3. Comparison 1: Ivermectin for treating COVID-19 in inpatient settings with moderate to severe disease, Outcome 3: Improvement of clinical status at day 28: participants discharged alive

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)												
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

(C) Bias due to missing outcome data

(D) Bias in measurement of the outcome

(E) Bias in selection of the reported result

(F) Overall bias

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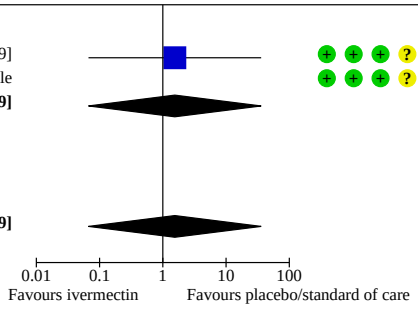
Analysis 1.4. Comparison 1: Ivermectin for treating COVID-19 in inpatient settings with moderate to severe disease, Outcome 4: Serious adverse events during the study period

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
1.4.1 Moderate disease (WHO 4 to 5)												
Krolewiecki 2021 (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 (SoC)

(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

(C) Bias due to missing outcome data

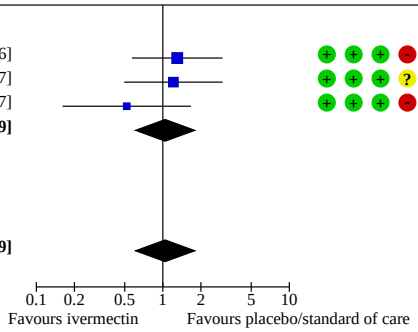
(D) Bias in measurement of the outcome

(E) Bias in selection of the reported result

(F) Overall bias

Analysis 1.5. Comparison 1: Ivermectin for treating COVID-19 in inpatient settings with moderate to severe disease, Outcome 5: Any adverse events during the study period

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
1.5.1 Moderate disease (WHO 4 to 5)												
Krolewiecki 2021 (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]	+	+	+	-	?	-
Subtotal (95% CI)		**157**		**71**	**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)		**157**		**71**	**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 (SoC)

(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 (SoC)

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions

(C) Bias due to missing outcome data

(D) Bias in measurement of the outcome

(E) Bias in selection of the reported result

(F) Overall bias

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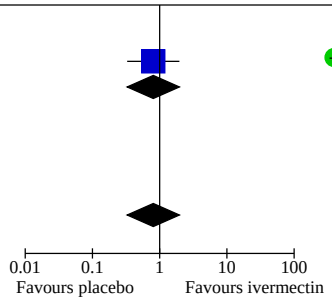
Analysis 1.6. Comparison 1: Ivermectin for treating COVID-19 in inpatient settings with moderate to severe disease, Outcome 6: Viral clearance at day 3

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
1.6.1 Moderate disease (WHO 4 to 5)							
Mohan 2021 (1)	10	80	7	45	100.0%	0.80 [0.33 , 1.96]	+ + + + + +
Subtotal (95% CI)		**80**		**45**	**100.0%**	**0.80 [0.33 , 1.96]**	
Total events:	10		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.48 (P = 0.63)							
Total (95% CI)		**80**		**45**	**100.0%**	**0.80 [0.33 , 1.96]**	
Total events:	10		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.48 (P = 0.63)							
Test for subgroup differences: Not applicable							



Footnotes

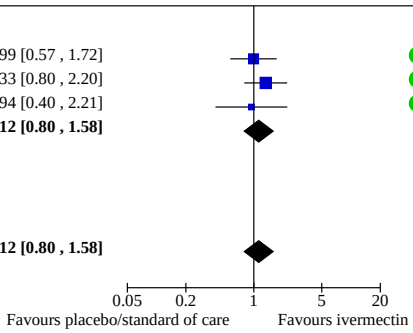
(1) Time point (3 days), participants (WHO 4 to 5 incl. asymptomatic people), intervention (ivermectin 12 mg and 24 mg, single dose), comparator (placebo)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.7. Comparison 1: Ivermectin for treating COVID-19 in inpatient settings with moderate to severe disease, Outcome 7: Viral clearance at day 7

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)							
Kirti 2021 (1)	13	32	18	44	38.6%	0.99 [0.57 , 1.72]	+ ? - + + -
Mohan 2021 (2)	33	80	14	45	45.3%	1.33 [0.80 , 2.20]	+ + + + + +
Pott-Junior 2021 (3)	17	27	2	3	16.1%	0.94 [0.40 , 2.21]	+ - + + ? -
Subtotal (95% CI)		**139**		**92**	**100.0%**	**1.12 [0.80 , 1.58]**	
Total events:	63		34				
Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 2 (P = 0.68); I² = 0%							
Test for overall effect: Z = 0.66 (P = 0.51)							
Total (95% CI)		**139**		**92**	**100.0%**	**1.12 [0.80 , 1.58]**	
Total events:	63		34				
Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 2 (P = 0.68); I² = 0%							
Test for overall effect: Z = 0.66 (P = 0.51)							
Test for subgroup differences: Not applicable							



Footnotes

(1) Time point (6 days), participants (WHO 4 to 5), intervention (ivermectin 12 mg daily for 2 days), comparator (placebo)
(2) Time point (5 days), participants (WHO 4 to 5 incl. asymptomatic people), intervention (ivermectin 12 mg and 24 mg, single dose, oral), comparator (placebo)
(3) 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 (SoC)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

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Comparison 2. Ivermectin for treating COVID-19 in outpatient settings with asymptomatic or mild disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality at day 28	6	2860	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.47, 1.25]
2.2 Worsening of clinical status within 28 days: admission to hospital or death	2	590	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.20, 6.02]
2.3 Worsening of clinical status within 28 days: participants with need for ICU admission or death	1	490	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.27, 1.51]
2.4 Symptom resolution: all initial symptoms resolved (asymptomatic) at day 14	2	478	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.60, 1.36]
2.5 Symptom resolution: all initial symptoms resolved (asymptomatic) at day 28	2	478	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.94, 1.13]
2.6 Quality of life (physical component) at up to 28 days	1	1358	Mean Difference (IV, Random, 95% CI)	0.00 [-0.98, 0.98]
2.7 Quality of life (mental component) at up to 28 days	1	1358	Mean Difference (IV, Random, 95% CI)	0.00 [-1.08, 1.08]
2.8 Serious adverse events during the study period	5	1502	Risk Ratio (M-H, Random, 95% CI)	2.27 [0.62, 8.31]
2.9 Any adverse events during the study period	5	1502	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.87, 1.76]
2.10 Viral clearance at day 3	2	819	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.78, 1.12]
2.11 Viral clearance at day 7	2	331	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.69, 1.48]
2.12 Viral clearance at day 14	2	588	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.90, 1.03]

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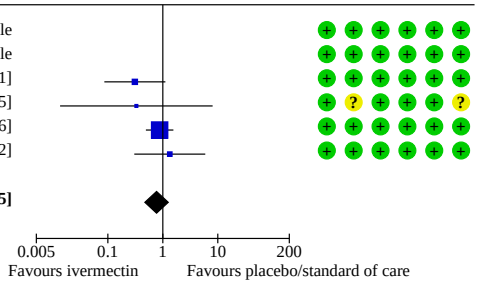
Analysis 2.1. Comparison 2: Ivermectin for treating COVID-19 in outpatient settings with asymptomatic or mild disease, Outcome 1: All-cause mortality at day 28

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
Bounfrate 2021 (1)	0	58	0	31		Not estimable
Chaccour 2021 (2)	0	12	0	12		Not estimable
I-TECH 2022 (3)	3	241	10	249	14.7%	0.31 [0.09 , 1.11]
López-Medina 2021 (4)	0	200	1	198	2.3%	0.33 [0.01 , 8.05]
TOGETHER 2022 (5)	21	679	24	679	72.2%	0.88 [0.49 , 1.56]
Vallejos 2021 (6)	4	250	3	251	10.8%	1.34 [0.30 , 5.92]
Total (95% CI)		**1440**		**1420**	**100.0%**	**0.77 [0.47 , 1.25]**
Total events:	28		38			

Heterogeneity: Tau² = 0.00; Chi² = 2.96, df = 3 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.05 (P = 0.29)
Test for subgroup differences: Not applicable



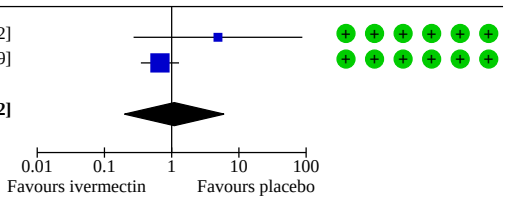
Footnotes
(1) Time point (30 days), participants (WHO 1 to 3), intervention (ivermectin 0.6 mg/kg and 1.2 mg/kg daily for 5 days), comparator (placebo)
(2) Time point (28 days), participants (WHO 2 to 3), intervention (ivermectin 0.4 mg/kg, single dose), comparator (placebo)
(3) Time point (28 days), participants (WHO 2 to 4), intervention (ivermectin 0.4 mg/kg daily for 5 days), comparator (SoC)
(4) 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)
(5) Time point (28 days), participants (WHO 2 to 3), intervention (ivermectin 0.4 mg/kg daily for 3 days), comparator (placebo)
(6) Time point (30 days), participants (WHO 1 to 3), intervention (ivermectin 12 to 24 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
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.2. Comparison 2: Ivermectin for treating COVID-19 in outpatient settings with asymptomatic or mild disease, Outcome 2: Worsening of clinical status within 28 days: admission to hospital or death

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Bounfrate 2021 (1)	4	58	0	31	24.7%	4.88 [0.27 , 87.82]
Vallejos 2021 (2)	14	250	21	251	75.3%	0.67 [0.35 , 1.29]
Total (95% CI)		**308**		**282**	**100.0%**	**1.09 [0.20 , 6.02]**
Total events:	18		21			

Heterogeneity: Tau² = 0.89; Chi² = 1.78, df = 1 (P = 0.18); I² = 44%
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable



Footnotes
(1) Time point (30 days), participants (WHO 1 to 3), intervention (ivermectin and, 0.6 mg/kg and 1.2 mg/kg daily for 5 days), comparator (placebo)
(2) Time point (30 days), participants (WHO 1 to 3), intervention (ivermectin 12 to 24 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
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

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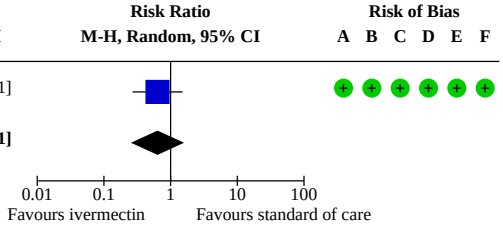
Analysis 2.3. Comparison 2: Ivermectin for treating COVID-19 in outpatient settings with asymptomatic or mild disease, Outcome 3: Worsening of clinical status within 28 days: participants with need for ICU admission or death

Study or Subgroup	Ivermectin Events	Ivermectin Total	Standard of care Events	Standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI
I-TECH 2022 (1)	8	241	13	249	100.0%	0.64 [0.27 , 1.51]
Total (95% CI)		**241**		**249**	**100.0%**	**0.64 [0.27 , 1.51]**
Total events:	8		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable



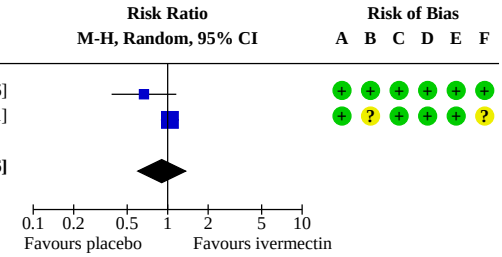
Footnotes
(1) Time point (28 days), participants (WHO 2 to 4), intervention (ivermectin 0.4 mg/kg daily for 5 days), comparator (SoC)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.4. Comparison 2: Ivermectin for treating COVID-19 in outpatient settings with asymptomatic or mild disease, Outcome 4: Symptom resolution: all initial symptoms resolved (asymptomatic) at day 14

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Bounfrate 2021 (1)	17	53	13	27	31.7%	0.67 [0.38 , 1.16]
López-Medina 2021 (2)	126	200	120	198	68.3%	1.04 [0.89 , 1.21]
Total (95% CI)		**253**		**225**	**100.0%**	**0.90 [0.60 , 1.36]**
Total events:	143		133			

Heterogeneity: Tau² = 0.06; Chi² = 2.33, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 0.49 (P = 0.62)
Test for subgroup differences: Not applicable



Footnotes
(1) Time point (14 days), participants (WHO 1 to 3), intervention (ivermectin and, 0.6 mg/kg and 1.2 mg/kg daily for 5 days), comparator (placebo)
(2) 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
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

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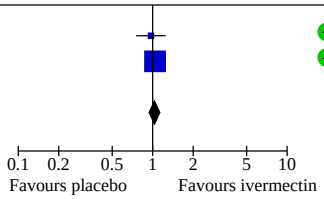
Analysis 2.5. Comparison 2: Ivermectin for treating COVID-19 in outpatient settings with asymptomatic or mild disease, Outcome 5: Symptom resolution: all initial symptoms resolved (asymptomatic) at day 28

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Bounfrate 2021 (1)	40	53	21	27	12.8%	0.97 [0.75 , 1.25]
López-Medina 2021 (2)	164	200	156	198	87.2%	1.04 [0.94 , 1.15]
Total (95% CI)		**253**		**225**	**100.0%**	**1.03 [0.94 , 1.13]**
Total events:	204		177			

Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable



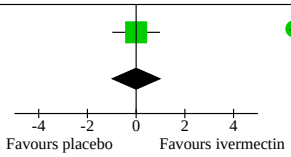
Footnotes
(1) Time point (30 days), participants (WHO 1 to 3), intervention (ivermectin and, 0.6 mg/kg and 1.2 mg/kg daily for 5 days), comparator (placebo)
(2) Time point (21 days), participants (WHO 2 to 5, < 1% participants at WHO 4 and 5), intervention (ivermectin 0.3 mg/kg daily for 5 days), comparator (placebo)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.6. Comparison 2: Ivermectin for treating COVID-19 in outpatient settings with asymptomatic or mild disease, Outcome 6: Quality of life (physical component) at up to 28 days

Study or Subgroup	Ivermectin Mean	Ivermectin SD	Ivermectin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
TOGETHER 2022 (1)	49.6	7.8	679	49.6	10.4	679	100.0%	0.00 [-0.98 , 0.98]
Total (95% CI)			**679**			**679**	**100.0%**	**0.00 [-0.98 , 0.98]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Footnotes
(1) Time point (28 days), participants (WHO 2 to 3), intervention (ivermectin 0.4 mg/kg daily for 3 days), comparator (placebo)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

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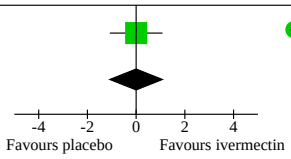
Analysis 2.7. Comparison 2: Ivermectin for treating COVID-19 in outpatient settings with asymptomatic or mild disease, Outcome 7: Quality of life (mental component) at up to 28 days

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
TOGETHER 2022 (1)	52.5	11.2	679	52.5	9	679	100.0%	0.00 [-1.08 , 1.08]	+ + + + + +
Total (95% CI)			**679**			**679**	**100.0%**	**0.00 [-1.08 , 1.08]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



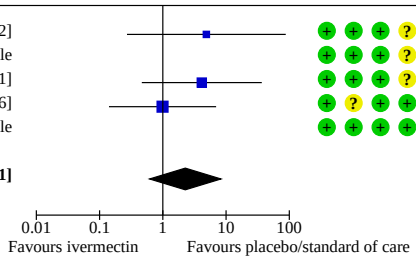
Footnotes
(1) Time point (28 days), participants (WHO 2 to 3), intervention (ivermectin 0.4 mg/kg daily for 3 days), comparator (placebo)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.8. Comparison 2: Ivermectin for treating COVID-19 in outpatient settings with asymptomatic or mild disease, Outcome 8: Serious adverse events during the study period

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
Bounfrate 2021 (1)	4	58	0	31	20.2%	4.88 [0.27 , 87.82]	+ + + ? ? ?
Chaccour 2021 (2)	0	12	0	12		Not estimable	+ + + ? ? ?
I-TECH 2022 (3)	4	241	1	249	35.4%	4.13 [0.47 , 36.71]	+ + + ? + ?
López-Medina 2021 (4)	2	200	2	198	44.4%	0.99 [0.14 , 6.96]	+ ? + + + ?
Vallejos 2021 (5)	0	250	0	251		Not estimable	+ + + + + +
Total (95% CI)		**761**		**741**	**100.0%**	**2.27 [0.62 , 8.31]**	
Total events:	10		3				

Heterogeneity: Tau² = 0.00; Chi² = 1.28, df = 2 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.23 (P = 0.22)
Test for subgroup differences: Not applicable



Footnotes
(1) Time point (30 days), participants (WHO 1 to 3), intervention (ivermectin and, 0.6 mg/kg and 1.2 mg/kg daily for 5 days), comparator (placebo)
(2) Time point (28 days), participants (WHO 2 to 3), intervention (ivermectin 0.4 mg/kg, single dose), comparator (placebo)
(3) Time point (28 days), participants (WHO 2 to 4), intervention (ivermectin 0.4 mg/kg daily for 5 days), comparator (SoC)
(4) 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)
(5) Time point (median 12 days), participants (WHO 1 to 3), intervention (ivermectin 12 to 24 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
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

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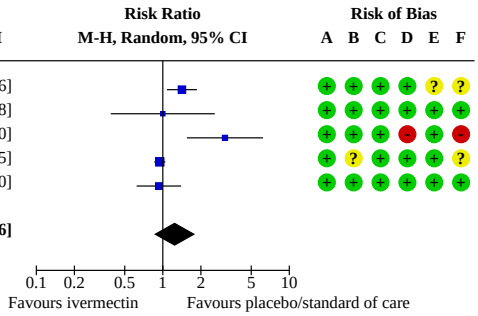
Analysis 2.9. Comparison 2: Ivermectin for treating COVID-19 in outpatient settings with asymptomatic or mild disease, Outcome 9: Any adverse events during the study period

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
Bounfrate 2021 (1)	53	58	20	31	25.6%	1.42 [1.08 , 1.86]
Chaccour 2021 (2)	5	12	5	12	9.4%	1.00 [0.39 , 2.58]
I-TECH 2022 (3)	30	241	10	249	13.8%	3.10 [1.55 , 6.20]
López-Medina 2021 (4)	154	200	161	198	29.6%	0.95 [0.86 , 1.05]
Vallejos 2021 (5)	38	250	41	251	21.6%	0.93 [0.62 , 1.40]
Total (95% CI)		**761**		**741**	**100.0%**	**1.24 [0.87 , 1.76]**
Total events:	280		237			

Heterogeneity: Tau² = 0.11; Chi² = 19.87, df = 4 (P = 0.0005); I² = 80%
Test for overall effect: Z = 1.20 (P = 0.23)
Test for subgroup differences: Not applicable



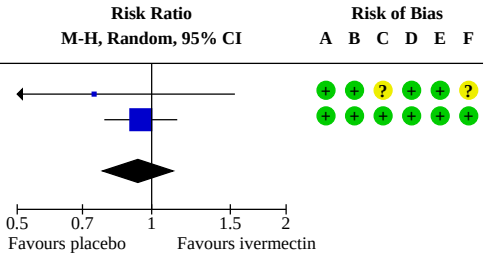
Footnotes
(1) Time point (30 days), participants (WHO 1 to 3), intervention (ivermectin and, 0.6 mg/kg and 1.2 mg/kg daily for 5 days), comparator (placebo)
(2) Time point (28 days), participants (WHO 2 to 3), intervention (ivermectin 0.4 mg/kg, single dose), comparator (placebo)
(3) Time point (28 days), participants (WHO 2 to 4), intervention (ivermectin 0.4 mg/kg daily for 5 days), comparator (SoC)
(4) 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)
(5) Time point (median 12 days), participants (WHO 1 to 3), intervention (ivermectin 12 to 24 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
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.10. Comparison 2: Ivermectin for treating COVID-19 in outpatient settings with asymptomatic or mild disease, Outcome 10: Viral clearance at day 3

Study or Subgroup	Ivermectin Events	Ivermectin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
TOGETHER 2022 (1)	11	148	17	170	6.3%	0.74 [0.36 , 1.54]
Vallejos 2021 (2)	113	250	120	251	93.7%	0.95 [0.78 , 1.14]
Total (95% CI)		**398**		**421**	**100.0%**	**0.93 [0.78 , 1.12]**
Total events:	124		137			

Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable



Footnotes
(1) Time point (3 days), participants (WHO 2 to 3), intervention (ivermectin 0.4 mg/kg daily for 3 days), comparator (placebo)
(2) Time point (3±1 days), participants (WHO 1 to 3), intervention (ivermectin 12 to 24 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
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

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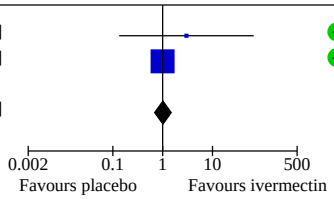
Analysis 2.11. Comparison 2: Ivermectin for treating COVID-19 in outpatient settings with asymptomatic or mild disease, Outcome 11: Viral clearance at day 7

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	1.5%	3.00 [0.13 , 67.06]	+	+	+	+	+	+
TOGETHER 2022 (2)	36	142	42	165	98.5%	1.00 [0.68 , 1.46]	+	+	?	+	+	?
Total (95% CI)		**154**		**177**	**100.0%**	**1.01 [0.69 , 1.48]**						
Total events:	37		42									

Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable



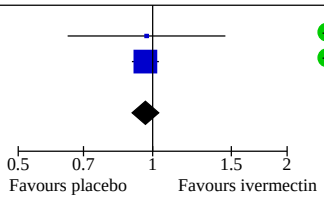
Footnotes
(1) Measured by E-gene clearance, time point (7 days), participants (WHO 2 to 3), intervention (ivermectin 0.4 mg/kg, single dose), comparator (placebo)
(2) Time point (7 days), participants (WHO 2 to 3), intervention (ivermectin 0.4 mg/kg daily for 3 days), comparator (placebo)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.12. Comparison 2: Ivermectin for treating COVID-19 in outpatient settings with asymptomatic or mild disease, Outcome 12: Viral clearance at day 14

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
Bounfrate 2021 (1)	31	58	16	29	2.8%	0.97 [0.65 , 1.45]	+	+	+	+	+	+
Vallejos 2021 (2)	212	250	221	251	97.2%	0.96 [0.90 , 1.03]	+	+	+	+	+	+
Total (95% CI)		**308**		**280**	**100.0%**	**0.96 [0.90 , 1.03]**						
Total events:	243		237									

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.07 (P = 0.28)
Test for subgroup differences: Not applicable



Footnotes
(1) Time point (14 days), participants (WHO 1 to 3), intervention (ivermectin and, 0.6 mg/kg and 1.2 mg/kg daily for 5 days), comparator (placebo)
(2) Time point (12±2 days), participants (WHO 1 to 3), intervention (ivermectin 12 to 24 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
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

ADDITIONAL TABLES

Table 1. Changed decisions in study eligibility assessment

Study ID	Status in this review update	Status in the previous review	Reason for change of decision

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Table 1. Changed decisions in study eligibility assessment *(Continued)*

Faisal 2020	Excluded	Awaiting classification	**Study did not pass research integrity check*, due to lack of trial registration**; author did not provide clarification regarding the trial design. Presumably, it is not a RCT.
Samaha 2021	Excluded	Awaiting classification	**Trial did not pass research integrity check*, due to published retraction notice**
Abd-Elsalam 2021	Excluded	Ongoing	**Trial did not pass research integrity check*, due to retrospective trial registration**
Biber 2021	Excluded	Ongoing	**Trial did not pass research integrity check*, due to retrospective trial registration**
Ahmed 2020	Excluded	Included	**Trial did not pass research integrity check*, due to lack of trial registration**
Chachar 2020	Excluded	Included	**Trial did not pass research integrity check*, due to retrospective trial registration**
Kishoria 2020	Excluded	Included	**Trial did not pass research integrity check*, due to lack of trial registration**
Okumuş 2021	Excluded	Included	**Trial did not pass research integrity check*, due to retrospective trial registration**
Podder 2020	Excluded	Included	**Trial did not pass research integrity check*, due to lack of trial registration**
Shah Bukhari 2021	Excluded	Included	**Trial did not pass research integrity check*, retrospective trial registration**
Shouman 2021	Excluded	Included	**Trial did not pass research integrity check*, due to wrong study design**; direct contact with the author revealed that the study is not a RCT.
Vallejos 2021	Included	Ongoing	**New full-text journal publication**
Bounfrate 2021	Included	Ongoing	**New preprint and pre-proof journal publication**
IRC-T20190624043993N2	Awaiting classification	Ongoing	**Meanwhile completed, no results published**
IRC-T20200404046937N4	Awaiting classification	Ongoing	**Meanwhile completed, no results published**
NCT04602507	Awaiting classification	Ongoing	**Meanwhile terminated, interim results might be published in the future**
NCT04673214	Awaiting classification	Ongoing	**Trial did not pass research integrity check* yet,** because relevant information to assure trustworthiness is missing. Trialist was contacted for clarification. Only a partial response was received which could not fully clarify the issue up until now.
NCT04894721	Awaiting classification	Ongoing	**Meanwhile completed, no results published**

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Table 1. Changed decisions in study eligibility assessment *(Continued)*

PACTR20210258877759A	Awaiting classification	Ongoing	**Meanwhile terminated, interim might be published in the future**
IRC-T20111224008507N4	Awaiting classification	Ongoing	**Meanwhile completed, no results published**
TOGETHER 2022	Included	Ongoing	**New full-text journal publication**

*Details of the research integrity check can be found in Figure 1 and Supplementary File_Ivermectin_Research Integrity.
RCT: randomized controlled trial.

APPENDICES

Appendix 1. Search strategies

Cochrane COVID-19 Study Register (CCSR)

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 design": "Parallel/Crossover" AND "Unclear" OR
3) "Study type": "Adaptive/Platform"
= 160

Web of Science Core Collection (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

#4 TI=(random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII") OR AB=(random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

#5 #3 AND #4
Indexes=SCI-EXPANDED, ESCI
= 134

WHO COVID-19 Global literature on coronavirus disease

Title, abstract, subject: (ivermectin* OR stromectol* OR mectizan* OR "MK 933" OR MK933 OR eqvalan* OR soolantra* OR sklice* OR stromectal* OR ivomec*) AND (random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")
= 270

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HTA database
ALL: ivermectin*
= 3

Selections on the CCSR used to monitor RCTs on a weekly basis:
Results available: "Report Results"
Study type: "Interventional"
Intervention assignment: "Randomised" or "Quasi Randomised"

Appendix 2. Critical and important criteria for the research integrity assessment of RCTs investigating ivermectin

We applied the research integrity hierarchy to assess potentially-eligible RCTs we had identified during screening. We considered the domains of: retraction, lack of prospective registration, lack of adequate ethical approval with informed written consent, implausible study authorship, lack of truthful randomization, and implausible study results to inform decisions to exclude a RCT. Concerns with a RCT in any domain put the study in 'awaiting classification' and led to further investigations. If we had no concerns in any domain or we could clarify concerns, e.g. in correspondence with study authors, the RCT met the inclusion criteria for the review, and we processed it further. For the next review update, we will need to reassess included RCTs and RCTs 'awaiting classification' for retraction notices.

Domain		Signalling questions to critical and important criteria	Assessment	Decision
1	**Retraction or expression of concern**	Is the study retracted?	Check for post-publication amendments in the systematic search for studies and on the Retraction Watch Database (retractiondatabase.org/RetractionSearch.aspx?)	If study is retracted, **exclude** the study
		Is there an expression of concern published elsewhere?	Check for expressed concerns on the journal homepage or preprint server	If expression of concerns are published: (1) send a request to the authors or the journal editors or wait until resolution of the concerns, and (2) hold the study in **awaiting classification** until clarification
2	**Trial registration**	Does the study report a trial registry number?	Check in the publication or study report	If study is not prospectively registered, **exclude** the study
		Is the study prospectively registered?	Check in the trials register the date of protocol submission and first posted. Prospective registration is defined as registration of a trial before enrolment of the first participant as defined by the WHO. It must be determined whether the registers registered (date first posted) without delay at this point in the pandemic. In case of doubt, check for the date first submitted or the authors must be asked for the submission date.	

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(Continued)

		Are there any inconsistencies in details such as dates and study methods reported in the publication and in the registration documents?	Compare study dates (enrolment, duration, completion) and methods (study type, allocation, masking) between publication and protocol.	If date of registration is unclear or if prospectively registered, but with inconclusive information: (1) send a request to the authors, and (2) hold the study in **awaiting classification** until clarification
3	**Ethics approval**	Is an ethics approval reported in the publication?	For example, the study was authorized by the ethics committee XY located in XY.	If ethics approval or participants' consent is not adequate, **exclude** the study. If ethics approval or participants' consent is unclear or incomplete: (1) send a request to the authors, and (2) hold the study in **awaiting classification** until clarification.
		Is an ethics approval number reported?	Check in the publication, study report, and study protocol	
		Is the name and location of the ethics committee reported?	Check in the publication, study report, and study protocol	
		Does a nationally-recognized ethics committee, as defined in the country's clinical trial regulations, give the ethics committee approval?	Check the ethics committee on the WHO list of national ethics committees (apps.who.int/ethics/national-committees) and the specific regulations for the country on NIH Clinical Trials Regulation website (clinregs.niaid.nih.gov/country/mexico#_top).	
		Does the study require written informed consent from participants?	Check in the publication, study report, and study protocol	
4	**Study authorship**	Are the authors' affiliations and countries the study is reported to have taken place in consistent?	Check in the publication, study report, and study protocol	If study authorship is unclear: (1) send a request to the authors and (2) hold the study in **awaiting classification** until clarification. If study authorship is still not plausible after contacting the authors, **exclude** the study.
		Are countries specified in different parts of the article, or as compared to the trials registry, consistent?	Check in the publication, study report, and study protocol	
		Is the number of authors plausible for the study design (e.g. a single author article reporting a RCT is impossible)?	Check in the publication, study report, and study protocol	
5	**Methods reporting**	Is the study design (e.g. randomization) reported in sufficient detail?	It has to be clear that the study was truthfully randomized. The method used for randomization must be described and the process must lead to a random allocation of participants. The sole des-	If study design is not reported in sufficient detail: (1) send a request to the authors, and (2) hold the study in **awaiting classification** until clarification.

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			ignation "randomized study" is not sufficient.	If study turns out to be non-randomized following author contact, **exclude** the study.
		Are baseline details reported in sufficient detail to assess whether randomization worked properly?	Check whether participant characteristics, e.g. risk factors for COVID-19 (age, gender, comorbidities) and co-interventions, are reported	
6	**Results**	Is the number of patients recruited within the timeframe with the condition plausible?	Check in the publication. Justify the decision based on clinical experience. The decision should be verifiable.	If study results are not plausible: (1) send a request to the authors, and (2) hold the study in **awaiting classification** until clarification. If, after contacting the author, it turns out that study results are not plausible or fabricated, **exclude** the study.
		Is there a realistic response rate or number of participants lost to follow-up? In cases with zero losses to follow-up, is there a plausible explanation (e.g. small number of participants, short-term follow-up)?		
		Is the study free from results that could be implausible (e.g. massive risk reduction, unexpected outlier data, unusual frequency of an outcome)?		
		Does the number of participants (e.g. women) in each group coincide with the reported randomization method (e.g. block randomization)?	Check in the publication, study report, and study protocol	
		Is there no noteworthy overlap in text/data with other published articles by the same or different authors without explanation?		
		Is there no excessive similarity or difference in the characteristics of the study participants between groups?		
		Are there no discrepancies between data reported in figures, tables, and text?		
		Are there no calculation errors (e.g. number of participants, percentages, proportions)?		

COVID-19: coronavirus disease 2019; **NIH**: National Institutes of Health; **RCT**: randomized controlled trial; **WHO**: World Health Organization.

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WHAT'S NEW

Date	Event	Description
22 June 2022	Amended	Corrected minor typo in Plain Language Summary section

HISTORY

Protocol first published: Issue 4, 2021
Review first published: Issue 7, 2021

Date	Event	Description
16 June 2022	New citation required and conclusions have changed	The authors' confidence in the evidence, especially for outpatients, improved since the last review version, because they could look at more participants included in high-quality trials. Although they are quite certain regarding results on risk of people dying and quality of life, the confidence in the evidence is still low for many other outpatient and inpatient outcomes because there were only a few events measured.
16 June 2022	New search has been performed	The review authors reappraised eligible trials for research integrity: only RCTs prospectively registered in a trial registry according to World Health Organizatin (WHO) guidelines for clinical trial registration were eligible for inclusion.
17 August 2021	Amended	Corrected minor typographical errors; the minor corrections have not changed the review findings

CONTRIBUTIONS OF AUTHORS

MP: conception of the review; design of the review; search and selection of trials for inclusion in the review; collection of data for the review; assessment of risk of bias in included trials; analysis of data; assessment of certainty in the body of evidence; interpretation of data; and writing of the review.

SR: search and selection of trials for inclusion in the review; collection of data for the review; assessment of risk of bias in included trials; analysis of data; and assessment of certainty in the body of evidence.

SS: collection of data for the review; assessment of risk of bias in included trials; analysis of data; and assessment of certainty in the body of evidence.

RIH: collection of data for the review; assessment of risk of bias in included trials; analysis of data; and assessment of certainty in the body of evidence.

MS: conception of the review; design of the review; interpretation of data; and writing and proofreading of the review.

MIM: search strategy design; conduct of search; and writing of the review.

PK: conception of the review; design of the review; interpretation of data; and proofreading of the review.

PM: conception of the review; design of the review; interpretation of data; and proofreading of the review.

NS: conception of the review; design of the review; interpretation of data; and proofreading of the review.

SW: conception of the review; design of the review; co-ordination of the review; search and selection of trials for inclusion in the review; collection of data for the review; assessment of risk of bias in included trials; analysis of data; assessment of certainty in the body of evidence; interpretation of data; and writing of the review.

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DECLARATIONS OF INTEREST

MP: is partly 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).

SR: none

SS: none

RIH: none

MS: none

MIM: none

PK: none

PM: none

NS: none

SW: is partly 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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  Project number 300342-104

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between protocol and review[1], and between review and first review update[2] are transparently shown in the following overview table.

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	Study design	Participants (inclusion and exclusion)	Intervention	Comparator	Outcomes	Method changes	Results	Authors' conclusion
Protocol (20 April 2021; Popp 2021a)								
Differences[1]	None	None	None	None	1. We added a new outcome: 'patients discharged without respiratory deterioration or death at 28 days' 2. We changed the timing of outcome measurement for serious adverse events and adverse events ('within 14 days' to 'within 28 days')	New added a new methods section: 'methods for future updates'	Not applicable	Not applicable
Review (28 July 2021; Popp 2021b)								
Differences[2]	New exclusion criteria - we excluded trials if they were: 1. not prospectively registered; or 2. had concerns regarding research integrity	Trials investigating prevention of infection have to report on the vaccination status of included participants.	For clarity, we named the intervention group 'ivermectin plus standard of care'.	For clarity, we named the comparator group 'standard of care plus/minus placebo'.	New outcome sets for: 1. inpatients; 2. outpatients; 3. prevention of an infection. Core outcomes are in accordance with the Core Outcome Measures in Effectiveness Trials (COMET) Initiative for COVID-19 patients (COMET 2020; Marshall 2020). Additional outcomes have been prioritized by consumer representatives and the German guideline panel for inpatient therapy	1. Research integrity check of trials as part of the eligibility screening 2. No differentiation between primary and secondary analyses based on risk of bias ratings; all included trials were eligible for the main analyses which informed the summary of findings tables 3. New data extraction items ('vaccination status', 'start of treatment since symptom onset') 4. Data synthesis methods added for time-to-event outcomes	1. Six trials included in the original review were not prospectively registered, and one additional trial was found to be non-randomized; we had to exclude all 7 trials. The remaining 7 trials from the original review plus 4 newly-identified trials resulted in a new pool of 11 trials. 2. Direction of effect moved closer to 1 (no effect) for 1 inpatient and	The conclusion did not change, however gained some strength regarding certainty of the evidence: "Overall, the reliable evidence available not support the use of ivermectin for treatment or prevention of COVID-19 outside of well-

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	of people with COVID-19 (German AWMF Guideline 2021a) and for outpatient therapy (German AWMF Guideline 2021b). Changes to the outcomes were necessary due to the risk of competing events associated with the original outcome set. This review update no longer has secondary outcomes. We treated all outcomes as primary outcome sets which informed the summary of findings tables.	5. We no longer performed the subgroup analysis 'severity of condition at baseline' independent of heterogeneity. In case of heterogeneity, we planned different subgroup analyses. 6. We added new sensitivity analyses considering risk of bias, vaccination status, and starting time point of treatment. 7. The summary of findings tables included the new outcome sets.	1 outpatient outcome. 3. Certainty of evidence increased from very low to low for 2 inpatient outcomes and 1 outpatient outcome. We could evaluate certainty of evidence for the first time for 1 inpatient outcome and 2 outpatient outcomes. Overall, we included more participants for outpatient outcomes.	designed randomized controlled trials (RCTs). "
First review update (June 2022)					

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INDEX TERMS

Medical Subject Headings (MeSH)

Antiparasitic Agents [adverse effects] [*therapeutic use]; Antiviral Agents [adverse effects] [*therapeutic use]; Cause of Death; COVID-19 [*drug therapy] [mortality] [prevention & control] [virology]; Ivermectin [adverse effects] [*therapeutic use]; Placebos [therapeutic use]; Post-Exposure Prophylaxis; Randomized Controlled Trials as Topic; Respiration, Artificial [statistics & numerical data]; SARS-CoV-2 [drug effects]; Time Factors; Treatment Outcome

MeSH check words

Humans

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