# National Institute for Health and Care Excellence

# NICE COVID-19 rapid guideline: managing COVID-19

## [M] Evidence review for ivermectin

NICE guideline NG191

June 2022

Guideline version (Final)

## Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

## Copyright

# Objective

This evidence review aims to update existing NICE rapid guidance on the use of ivermectin for people in hospital and community with COVID-19, which was published in November 2021.

# Review question

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review question for this evidence review is:

1. What is the effectiveness and safety of ivermectin for acute symptoms and complications of COVID-19?

## Methodology

The evidence review was developed using NICE interim process and methods for guidelines developed in response to health and social care emergencies.

The original NICE recommendations on ivermectin were published in November 2021, based on an evidence review developed by NICE using the data provided by the National COVID-19 Australian Clinical Evidence Taskforce. Ongoing surveillance was conducted from publication to identify any new emerging evidence to be considered for inclusion in an update.

The searches for the effectiveness evidence were re-run on 21/04/2022. The following databases were searched: Central Register of Controlled Trials (Wiley), Cochrane Database of Systematic Reviews (Wiley), Embase (Ovid), MEDLINE ALL (Ovid). Full search strategies for each database are provided in Appendix B. A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy.

Ongoing surveillance also identified studies relevant to the PICO and hence studies identified via ongoing weekly surveillance (until 9th May 2022) were combined with the new search results to include the relevant studies. Furthermore, reference lists of the relevant systematic reviews were also searched to identify included studies.

## Analysis Plan

In the previous review, analysis was carried out based on hospital and community setting separately. In this update, this has been further split into two further categories based on dose regimen as follows: hospital setting with 1 dose of ivermectin per day for 2-5 days (multiple doses); hospital setting with one single dose of ivermectin; community setting with 1 dose of ivermectin per day for 2-5 days; community setting with one single dose of ivermectin. The reason for this analysis approach is to aim to further reduce methodological and clinical heterogeneity between the trials, now that more evidence is available to allow for analysis by ivermectin regimen. Multiple dose regimens will most likely increase the cumulative dosage and could influence the efficacy and safety outcomes of ivermectin differently and due to this diversity.

Dosing of ivermectin varied across the trials ranging from 200micrograms/kg to 1200micrograms/kg. To account for this in the analyses, a pragmatic approach to categorising doses was taken. These were doses of less than 400micrograms/kg, doses of greater than 400micrograms/kg and doses of greater than 1000micrograms/kg. These categories formed the subgroups used in the analyses to distinguish between the studies giving two higher doses compared to a more conservative dose.

### Included studies

Relevant references were screened against the protocol using their titles and abstracts and 7 full text references were obtained and assessed for relevance.

In total, 21 studies are included in this updated evidence review, 7 of which are new to this review and 15 of those were in the previous version of the evidence review. There were two pre-prints in the previous review, which are now included as peer-reviewed full text publication in the updated review (Bounfrate et al., 2022; Gonzalez et al., 2022). Pott-Junior 2021 was retracted since the previous review was conducted and has not been included in the updated analyses.

29 studies were excluded from this evidence review. Details of excluded studies are in appendix E. A summary of the included studies is shown in Table 1.

## Table 1: Summary of included studies

## Hospital setting – multiple doses of ivermectin

| Study details | COVID-19 Severity | Population | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|
| Lim et al., 2022 [New]<br><br>Open label randomised controlled trial (I-TECH)<br><br>Malaysia (20 hospitals)<br><br>Clinical Trial no: NCT04920942<br><br>Recruitment May 2021 – October 2021<br><br>No of participants 490 (241 in intervention and 249 in control arm) | Mild to moderate (Malaysian COVID-19 clinical severity stage 2 or 3; WHO clinical progression scale 2-4) within 7 days from symptom onset, with risk of severe disease progression | • RT-PCR confirmed COVID-19<br>• 50 years or older<br>• With at least 1 comorbidity<br><br>• within 7 days from symptom onset<br>Exclusion Criteria:<br>asymptomatic required supplemental oxygen or had pulse oximetry oxygen saturation level less than 95% at rest<br>pregnancy or breastfeeding, history of taking ivermectin or any antiviral drugs with reported activity against COVID-19 (favipiravir, hydroxychloroquine, lopinavir, and remdesivir) within 7 days before enrolment.<br><br>**Mean age ± SD (years):**<br>62.5 ± 8.7<br>**Average % female:**<br>54.5% | Ivermectin 0.4 mg/kg<br>body weight daily for 5 days, plus standard of care | Control group received standard of care alone.<br>The standard of care consisted of symptomatic therapy and monitoring for signs of early deterioration based on clinical findings, laboratory test results, and chest imaging. | Primary outcomes:<br>• Progression to severe disease<br>Secondary outcomes:<br>• time to progression to severe disease,<br>• 28-day in-hospital all-cause mortality,<br>• mechanical ventilation rate,<br>• intensive care unit admission,<br>• length of hospital stay after enrolment. |
| Manomaipiboon et al., 2022 [New]<br><br>Preprint | mild-to-moderate symptoms as defined by the WHO severity | • Adult men and women aged 18–80 years,<br>• non-pregnant or breast-feeding women,<br>Exclusion Criteria:<br>• allergic to ivermectin. | 12 mg per day of ivermectin for 5 days<br>plus standard care | standard care included favipiravir or andrographolide, corticosteroids, cetrizine and paracetamol | Primary Outcome:<br>• Negative RT-PCR at day 7 and 14<br>Secondary Outcomes: |

| | | | | | |
|---|---|---|---|---|---|
| Randomised double blind controlled trial<br><br>Recruitment: 1 September 2021 - 30 November 2021<br><br>Country: Thailand<br><br>No of participants 72 (36 in each arm) | score for COVID-19 | • had the potential for a drug-drug interaction with ivermectin, such as tamoxifen or warfarin.<br>• were previously treated with ivermectin in the last 7 days or received herbal medicine<br>• had severe chronic illness (severe congestive heart failure, chronic kidney disease stage 4–5, chronic liver disease, terminal cancer) or bacterial infection<br>**Mean age ± SD (years)**<br>Control: 47.72± 15.45 years<br>Intervention: 49.42± 29 years,<br>**Average Female %**<br>Control: 63.9%<br>Intervention: 61.1%, | | | • Duration of hospitalisation,<br>• frequency of clinical worsening,<br>• survival on day 28,<br>• adverse events |
| Abd-Elsalam 2021<br><br>RCT<br><br>Study dates March 2020 to October 2020<br><br>Egypt<br><br>**No. of participants: 164** | Mild/moderate | Adults<br><br>PCR confirmed COVID-19<br><br>Exclusions: pregnancy/lactation, allergy or contraindication to the drugs in the study, pregnant and lactating mothers, and patients with cardiac problems.<br><br>**Mean age ± SD (years):**<br>Intervention - 42.38 ± 16.02<br>Comparator - 39.38 ± 16.92<br><br>**Average % female:**<br>Intervention - 54.9<br>Comparator - 45.1 | Oral ivermectin 12 mg once daily for 3 days<br><br>Standard care<br><br>Antibiotics | Standard care included: paracetamol, oxygen, fluids (according to the condition of the patient), empiric antibiotic, oseltamivir if needed (75 mg/12h for 5 days), and invasive mechanical ventilation with hydrocortisone for severe cases if PaO2 less than 60 mm Hg, O2 saturation less than | Mortality<br><br>Invasive mechanical ventilation<br><br>Adverse events<br><br>Hospital length of stay |

| | | | | | |
|---|---|---|---|---|---|
| | | | | 90% despite oxygen or non-invasive ventilation, progressive hypercapnia, respiratory acidosis (pH < 7.3), and progressive or refractory septic shock. | |
| Ahmed 2020<br><br>RCT<br>Multi-arm trial<br><br>Bangladesh<br><br>**No. of participants: 68** | Mild symptoms | Adults<br><br>PCR confirmed COVID-19<br><br>Exclusions: pregnancy/lactation, allergic to ivermectin/ doxycycline, or if there was the potential for a drug–drug interaction with ivermectin or doxycycline; chronic illness; received ivermectin and/or doxycycline in the last 7 days; or had participated in any other clinical trial within the last month.<br><br>**Average age (years):**<br>42<br><br>**Average % female:**<br>54 | 1) oral ivermectin 12mg once daily (5 days)<br><br>2) oral ivermectin 12 mg single dose and 200 mg doxycycline on day 1, followed by 100 mg doxycycline every 12h for the next 4 days | Placebo control group | Duration to Virological clearance |
| Krolewiecki 2020<br><br>RCT<br><br>Argentina | Mild/Moderate (WHO ordinal scale score of 3 or 4) | Adults<br><br>PCR confirmed COVID-19<br><br>Exclusions: pregnancy/lactation, pre-existing | Oral ivermectin 600microgram/kg (5 days) | Standard care (included hospitalisation of all symptomatic cases) | Invasive mechanical ventilation<br><br>Adverse events<br><br>Clinical evolution |

| | | | | | |
|---|---|---|---|---|---|
| **No. of participants: 32** | | hypersensitivity/allergy to ivermectin, use of immunomodulators within 30 days, poorly controlled comorbidities.<br><br>**Mean age ± SD (years):**<br>Intervention<br>Ivermectin <160ng/mL – 50.9 ± 12.3<br>Ivermectin >160ng/mL – 39.8 ± 10.2<br>Comparator – 37.3 ± 12.7<br><br>**Average % female:**<br>Intervention<br>Ivermectin <160ng/mL -– 45<br>Ivermectin >160ng/mL – 56<br>Comparator - 42 | | | |
| Mohan 2021<br><br>RCT<br><br>India<br><br>**No. of participants: 125** | Mild/moderate (WHO ordinal scale score of 3 or 4) (SpO2) >90%, and with no hypotension or requirement of mechanical ventilation | Adults<br><br>Diagnosis of COVID-19 based on positive result on either PCR or a rapid antigen test.<br><br>Exclusions: pregnancy/lactation, known hypersensitivity to ivermectin, chronic kidney disease with creatinine clearance <30 mL/min, elevated transaminase levels (>5x upper limit of normal), myocardial infarction or heart failure within 90 days prior to enrolment, prolonged corrected QT interval (>450 ms) on electrocardiogram, any other severe comorbidity, or | Oral ivermectin by subgroup<br><br>1) 24mg<br>2) 12mg | Placebo | Mortality<br><br>Invasive mechanical ventilation<br><br>Adverse events<br><br>Hospital discharge<br><br>Symptom resolution<br><br>Virological clearance<br><br>Clinical worsening<br><br>Note: primary outcomes were assessed in PCR confirmed group |

| | | | | | |
|---|---|---|---|---|---|
| | | enrolment in a concomitant clinical trial.<br><br>**Mean age ± SD (years):**<br>Intervention<br>Ivermectin 24mg – 34.3 ± 10.45<br>Ivermectin 12mg – 36.3 ± 10.54<br>Comparator - 35.3 ± 10.52<br><br>**Average % female:**<br>Intervention<br>Ivermectin 24mg – 7.5<br>Ivermectin 12mg – 12.5<br>Comparator – 13.3 | | | only (modified ITT group). Safety outcomes assessed in ITT population. |
| Ravikirti 2021<br><br>RCT<br><br>India<br><br>**No. of participants: 112** | Mild/Moderate disease as defined by the Ministry of Health and Family Welfare (MOHFW), Government of India (GOI) guidelines<br><br>Mild: No evidence of breathlessness or hypoxia (normal saturation)<br>Moderate: Breathlessness and/or hypoxia (saturation 90-94% on room | Adults<br><br>Diagnosis of COVID-19 based on positive result on either PCR or a rapid antigen test.<br><br>Exclusions: pregnancy/lactation, known allergy to or adverse drug reaction with Ivermectin; unwillingness or inability to provide consent to participate in the study; prior use of ivermectin during the course of this illness.<br><br>**Mean age ± SD (years):**<br>Intervention - 50.7 ± 12.7<br>Comparator - 54.2 ± 16.3<br><br>**Average % female:**<br>Intervention - 27.3<br>Comparator - 28.1 | Oral ivermectin 12 mg daily for 2 days<br><br>Hydroxychloroquine<br><br>Antibiotics<br><br>Tocilizumab (7% of patients)<br><br>Remdesivir (22% of patients) | Placebo<br><br>Hydroxychloroquine<br><br>Antibiotics<br><br>Tocilizumab (5% of patients)<br><br>Remdesivir (19% of patients) | Mortality<br><br>Invasive mechanical ventilation<br><br>Admission to ICU<br><br>Hospital discharge<br><br>Symptom resolution<br><br>Virological clearance |

| | | | | | |
|---|---|---|---|---|---|
| | air), respiratory rate of 24 or more and no features of severe disease | | | | |
| Shakhsi Niaee 2020<br><br>RCT<br><br>Iran<br><br>**No. of participants: 180** | Mild/Moderate/ Severe<br><br>Disease severity was based on CT scan for all participants. | Adults<br><br>COVID-19 confirmed by PCR or chest image tests.<br><br>80% of intervention groups diagnosed by PCR.<br><br>53% of control groups diagnosed by PCR.<br>Exclusions: pregnancy/lactation, known allergic reaction to intervention drugs, severe immunosuppression, chronic kidney disease, cancer, severe COVID-19 patients and indications patients were unable and/or unlikely to comprehend and/or follow the protocol.<br><br>**Median age, IQR (years):**<br><br>Ivermectin<br>Arm 1: 61 (42, 68)<br>Arm 2: 53 (42, 65)<br>Arm 3: 54 (47, 60)<br>Arm 4: 54 (46, 65)<br>Comparator<br>Standard care: 55 (45, 70)<br>Standard care + placebo: 58 (45, 68)<br><br>**Average % female:** | Subgroups<br><br>Oral ivermectin (duration 5 days):<br><br>Arm 2: three low interval doses of ivermectin (200, 200, 200 micrograms/kg)<br>Arm 4: three high interval doses of ivermectin (400, 200, 200 micrograms/kg).<br><br>All groups:<br><br>Hydroxychloroquine 200 mg twice per day | Group 1: hydroxychloroquine 200 mg/kg twice per day<br><br>Group 2: placebo plus hydroxychloroquine 200 mg/kg twice per day<br><br>All groups received standard regimen as hydroxychloroquine 200mg twice per day and a heparin prophylaxis with supplemental oxygen | Mortality<br><br>Duration of hospital stay |

| | | | | | |
|---|---|---|---|---|---|
| | | Ivermectin<br>Arm 1: 60<br>Arm 2: 36.7<br>Arm 3: 46.7<br>Arm 4: 56.7<br>Comparator<br>Standard care: 46.7<br>Standard care + placebo: 53.3 | | | |

See appendix F for full evidence tables.

## Hospital setting – Single dose of ivermectin

COVID severity was not defined in all studies. Where it has been defined, this information has been included in the tables below.

| Study & Country | COVID-19 severity | Population | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|
| Shah Bukhari 2021<br><br>RCT<br>Pakistan<br><br>**No. of participants: 86** | Mild/moderate - severity was defined by WHO guidelines<br><br>Chest x-ray was used to support "moderate" severity and if these patients had oxygen requirements equivalent to FiO2 ≥ | Adults and children 15 and above<br><br>PCR confirmed COVID-19<br><br>Exclusions: pregnancy, severe symptoms, uncontrolled co-morbidities and immunocompromised, history of ivermectin allergy, patients taking CY3A4 inhibitors.<br><br>**Mean age ± SD (years):**<br>Intervention - 42.24 ± 12.0<br>Comparator - 38.98 ± 12.61 | Oral ivermectin 12mg single dose | Standard care included oral vitamin C 500mg once daily, oral vitamin D3 200,000 IU once weekly, and oral paracetamol 500 mg SOS. | Adverse events<br><br>Virological clearance |

| Study & Country | COVID-19 severity | Population | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|
| | 50%, they were excluded. | **Average % female:**<br>Intervention - 9.8<br>Comparator - 20 | | | |
| Gonzalez et al., 2022<br>[New]<br>Randomised, double blind trial<br><br>Mexico<br><br>Clinical trial no: NCT04391127<br><br>August 2020<br><br>No of participants: 73 | • : severity of clinical presentation,<br>• need for supplemental oxygen,<br>• comorbidities, and laboratory markers suggesting a poor prognosis (High D-Dimer, Ferritin, Troponin, Creatinine) | Patients fulfilling criteria of a suspected or confirmed COVID-19 case as well as the pneumonia by American Thoracic Society criteria pneumonia, diagnosed by an X-ray or high-resolution chest CT scan recently established hypoxemic respiratory failure or acute clinical deterioration of pre-existing lung or heart disease.<br>Exclusion Criteria:<br>if required high oxygen volumes (face mask > 10 L/ min), or mechanical ventilation<br>if they had predictors of a poor response to high-flow oxygen nasal prong therapy,<br><br>**Average age (years):**<br>Intervention: 56 (±16.5)<br>Control: 53.8 (±16.9)<br>**Average % male:**<br>Intervention: 21 (58.3%)<br>Control: 23 (62.1%) | Ivermectin 12 mg in patients with weight<80 kg and 18mg in patients with weight>80kg (n=36) | Calcium citrate as placebo: 2 tablet every 12h on first day followed by one tablet every 12h for next 4 days (n=37)<br><br>All patients received pharmacological thromboprophylaxis with low molecular weight heparin or unfractionated heparin<br><br>Since last week of June 2020, patients requiring oxygen therapy also received dexamethasone, 6mg IV every 24h for 10 days or until discharge | Efficacy outcomes:<br>• duration of hospitalisation<br>• respiratory deterioration<br>• death<br><br>Safety outcomes:<br>• adverse events |
| Kishoria 2020<br><br>India<br>RCT<br>**No. of participants: 32** | Mild/asymptomatic. Mild illness stated to be 'as per WHO'. | Adults<br><br>PCR confirmed COVID-19 (positive after standard care treatment)<br><br>Exclusions: pregnancy/lactation, allergy or hypersensitivity to | Oral ivermectin 12 mg single dose<br><br>Hydroxychloroquine 400 mg twice a day for 5 days | Hydroxychloroquine 400mg twice a day for 5 days<br><br>Paracetamol 500mg as required | Hospital discharge<br><br>Virological clearance |

| Study & Country | COVID-19 severity | Population | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|
| | | ivermectin; respiratory distress/requiring intensive care; used immunosuppressants in the last 30 days; known HIV infection with CD4 count <300 cell/ L; medical conditions such as mal-absorption syndromes; autoimmune disease and/or decompensated chronic diseases; Uncontrolled, intercurrent diseases including renal impairment, hepatic impairment, symptomatic congestive heart failure, unstable chest angina or heart arrhythmia); treated in any other study in the previous 30 days.<br><br>**Average age (years):**<br>Intervention – 39.5<br>Comparator – 37.0<br><br>**Average % female:**<br>Intervention – 26.3<br>Comparator – 30.7 | Paracetamol 500mg as required<br><br>Vitamin C 1 tab twice a day | Vitamin C 1 tab twice a day | |
| Shahbaznejad 2021<br><br>RCT<br>Iran<br><br>**No. of participants: 69** | Moderate/ Severe<br><br>Severe disease was defined as tachypnea (respiratory rate of ≥24 breaths/min), need for mechanical ventilation, need | Adults and children aged above 5 years<br><br>Diagnostic criteria for COVID-19 included any of the following:<br>positive result on PCR test:<br>clinical symptoms of COVID-19, with a history of contact with a patient | Oral ivermectin single dose 200microgram/kg<br><br>Hydroxychloroquine as part of standard care.<br><br>Lopinavir-ritonavir (77% of patients) | Standard care<br><br>Hydroxychloroquine as part of standard care.<br><br>Lopinavir-ritonavir (82% of patients)<br><br>Azithromycin (50% of patients) | Invasive mechanical ventilation<br><br>Adverse events<br><br>Length of hospital stay<br><br>Supplemental oxygen |

| Study & Country | COVID-19 severity | Population | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|
| | for supplemental oxygen, and oxygen saturation of <94% in the ambient air.<br><br>All other patients were considered to have moderate disease. | with COVID-19; and/or abnormalities on CT scan compatible with COVID-19.<br><br>Exclusions: pregnancy/lactation, Chronic liver and/or renal disease; warfarin treatment, an angiotensin-converting enzyme inhibitor, or a angiotensin II receptor antagonist; and acquired immunodeficiency.<br><br>**Mean age ± SD age (years):**<br>Intervention - 47.63 ± 22.20<br>Comparator – 45.18 ± 23.20<br><br>**Average % female:**<br>Intervention - 48.6<br>Comparator – 47.1 | Azithromycin (66% of patients)<br><br>Antibiotics as indicated (91% of patients). | Antibiotics as indicated (88% of patients). | Duration of symptoms<br><br>Virological clearance |
| Mohan 2021<br><br>RCT<br><br>India<br><br>**No. of participants: 125** | Mild/moderate (WHO ordinal scale score of 3 or 4)<br>(SpO2) >90%, and with no hypotension or requirement of mechanical ventilation | Adults<br><br>Diagnosis of COVID-19 based on positive result on either PCR or a rapid antigen test.<br><br>Exclusions: pregnancy/lactation, known hypersensitivity to ivermectin, chronic kidney disease with creatinine clearance <30 mL/min, elevated transaminase levels (>5x upper limit of normal), myocardial infarction or heart failure within 90 days prior to enrolment, prolonged corrected QT interval | Oral ivermectin by subgroup<br><br>3) 24mg<br>4) 12mg | Placebo | Mortality<br><br>Invasive mechanical ventilation<br><br>Adverse events<br><br>Hospital discharge<br><br>Symptom resolution<br><br>Virological clearance<br><br>Clinical worsening<br><br>Note: primary outcomes were |

| Study & Country | COVID-19 severity | Population | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|
| | | (>450 ms) on electrocardiogram, any other severe comorbidity, or enrolment in a concomitant clinical trial.<br><br>**Mean age ± SD (years):**<br>Intervention<br>Ivermectin 24mg – 34.3 ± 10.45<br>Ivermectin 12mg – 36.3 ± 10.54<br>Comparator - 35.3 ± 10.52<br><br>**Average % female:**<br>Intervention<br>Ivermectin 24mg – 7.5<br>Ivermectin 12mg – 12.5<br>Comparator – 13.3 | | | assessed in PCR confirmed group only (modified ITT group). Safety outcomes assessed in ITT population. |
| Shakhsi Niaee 2020<br><br>RCT<br><br>Iran<br><br>**No. of participants: 180** | Mild/Moderate/ Severe<br><br>Disease severity was based on CT scan for all participants. | Adults<br><br>COVID-19 confirmed by PCR or chest image tests.<br><br>80% of intervention groups diagnosed by PCR.<br><br>53% of control groups diagnosed by PCR.<br>Exclusions:<br>pregnancy/lactation, known allergic reaction to intervention drugs, severe immunosuppression, chronic kidney disease, cancer, severe COVID-19 patients and indications patients were unable and/or unlikely to comprehend and/or follow the protocol. | Subgroups<br><br>Oral ivermectin:<br><br>Arm 1:<br>single dose ivermectin (200 micrograms/kg)<br>Arm 3: single dose ivermectin (400 micrograms/kg)<br><br>All groups:<br>Hydroxychloroquine 200 mg twice per day | Group 1: hydroxychloroquine 200 mg/kg twice per day<br><br>Group 2: placebo plus hydroxychloroquine 200 mg/kg twice per day<br><br>All groups received standard regimen as hydroxychloroquine 200mg twice per day and a heparin prophylaxis with supplemental oxygen | Mortality<br><br>Duration of hospital stay |

| Study & Country | COVID-19 severity | Population | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|
| | | **Median age, IQR (years):**<br><br>Ivermectin<br>Arm 1: 61 (42, 68)<br>Arm 2: 53 (42, 65)<br>Arm 3: 54 (47, 60)<br>Arm 4: 54 (46, 65)<br>Comparator<br>Standard care: 55 (45, 70)<br>Standard care + placebo: 58 (45, 68)<br><br>**Average % female:**<br>Ivermectin<br>Arm 1: 60<br>Arm 2: 36.7<br>Arm 3: 46.7<br>Arm 4: 56.7<br>Comparator<br>Standard care: 46.7<br>Standard care + placebo: 53.3 | | | |

## Community setting – Multiple doses (2-5) of ivermectin

| Study | COVID-19 severity | Population | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|
| Biber 2021<br><br>Randomised Controlled trial<br>Israel<br><br>**No. of participants: 89** | Asymptomatic/ mild/moderate | Adults<br><br>PCR confirmed COVID-19<br><br>Exclusions: pregnancy/lactation, weighed below 40kg, known allergy to the drugs, unable to take oral medication, participating in another RCT for treatment of | Oral ivermectin 200microgram/kg (daily for 3 days) | Placebo | Adverse events<br><br>Hospitalisation<br><br>Supplemental oxygen<br><br>Virological clearance |

| Study | COVID-19 severity | Population | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|
| | | COVID-19. In addition, patients who had RT-PCR results with Ct (cycle threshold) value >35 in first two consecutive were excluded. Patients with comorbidities of cardiovascular disease, diabetes, chronic respiratory disease (excluding mild intermittent asthma), hypertension, and or cancer were defined as high-risk patients.<br><br>**Median age, IQR (years):**<br>Intervention - 36.0 (32·0-50·0)<br>Comparator – 33.5 (26·0-47·0)<br>**Average % female:**<br>Intervention - 21.7<br>Comparator – 21.4 | | | |
| Buonfrate D. et al., 2022<br>[New]<br>Randomised double-blind Phase II trial<br><br>Clinical trial no: NCT04438850<br><br>Italy<br><br>Recruitment: July 2020 to May 2021<br><br>No of participants: 93 | COVID-19 severity score <3 defined by published article on endpoints of RCTs in COVID-19 treatments | Adults≥18 years with confirmed SARS-CoV-2 infection by PCR<br><br>Exclusion criteria:<br>• pregnant or lactating women<br>• Central nervous system disease<br>• patients on dialysis<br>• any severe medical condition with a prognosis of <6 months<br>• treatment with either warfarin, antiviral, chloroquine phosphate or hydroxychloroquine<br><br>**Median age overall:**<br>47.0 (31.0–58.0)<br>**Female n(%):** | Arm B: single dose ivermectin 600 micrograms/kg plus placebo for 5 days (n=29)<br><br>Arm C: single dose ivermectin 1200 micrograms/kg for 5 days (n=32) | Placebo (n=32) | Primary Outcomes:<br>• Serious adverse events<br>• change in viral load at day 7 from baseline<br><br>Secondary Outcomes:<br>• Time to clinical resolution<br>• Virological clearance at day 14 and 30<br>• Hospitalisation rate<br>COVID-19 severity score at day 14 and 30 |

| Study | COVID-19 severity | Population | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|
| | | 39 (41.9) | | | |
| Reis et al., 2022 [New]<br><br>Randomised controlled trial<br><br>Brazil (12 sites)<br><br>Clinical Trial no: NCT04727424<br><br>Recruitment: 23 March 2021 to 6th August, 2021<br><br>**No of participants: 1358** | | 1. age of 18 years or older<br>2. an acute clinical condition consistent with Covid-19 within 7 days after symptom onset; and<br>3. at least one high-risk criterion for progression of Covid-19<br>Patients with SARS CoV-2 vaccine were also eligible<br><br>Median age:<br>49 (38–57)<br>Female n(%)<br>791 (58.2) | ivermectin 400 micrograms/kg for 3 days | Placebo since the day of randomisation, once per day<br><br>Duration: 1, 3, 10 or 14 depending on various comparators in the trial<br><br>All the patients received usual standard care in Brazil | Primary Outcomes:<br>• hospitalisation<br>• proxy for hospitalisation,<br>• observation in a Covid-19 emergency setting for more than 6 hours<br>Secondary Outcomes (28 days):<br>• SARS-CoV-2 viral clearance at day 3 and day 7<br>• Hospitalisation for any cause<br>• Time to hospitalisation<br>• Duration of hospitalisation<br>• Time to clinical recovery (WHO clinical progression scale)<br>• Death from any cause<br>• Time to death<br>• Receipt of mechanical ventilation<br>• Health related quality of life (PROMIS Global-10 score)<br>• Adverse reaction to ivermectin or placebo |
| Abbas et al., 2022 [New]<br><br>Short communication | Mild COVID-19 | • Patients with COVID-19 aged 18 to 50 years<br><br>Exclusion criteria | Ivermectin 300 µg/ kg body weight per day for 5 days | Placebo: a mixture of 5 % dextrose in saline and 5 % | Primary outcomes:<br>• Time to resolution of symptoms<br>• Symptoms resolved<br>Secondary outcomes: |

| Study | COVID-19 severity | Population | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|
| Double blind randomised clinical trial<br><br>China<br><br>Recruitment: May 2021 – August 2021<br><br>No of participants: 202 | | • history of treatment with steroids<br>during the last week,<br>• concomitant use of anticoagulants,<br>• history of any allergies to the studied drugs,<br>recent bleeding for any reason,<br>• patients with chronic diseases such as cardiovascular disease<br><br>Mean ± SD<br>Ivermectin: 38.33±6.84 Control: 37.33±5.84<br><br>Female n(%)<br>Ivermectin: 52 (52.6 %) Control: 60 (57.7 %) | | dextrose in distilled water | • Deterioration of 2 or more points on 8 points score WHO<br>• Escalation of care<br>• Developing fever<br>• Death<br>• Adverse events |
| López-Medina 2021<br><br>RCT<br><br>Colombia<br><br>**No. of participants: 398** | Mild disease defined as being at home or hospitalised but not receiving high-flow nasal oxygen or mechanical ventilation (invasive or non-invasive) | Adults<br><br>PCR confirmed COVID-19<br><br>Exclusions: pregnancy/lactation, asymptomatic, severe pneumonia, received ivermectin within the previous 5 days, or had hepatic dysfunction or liver function test results more than 1.5 times the normal level.<br><br>**Median age (IQR) (years):**<br>Intervention - 37 (29 - 47.7)<br>Comparator – 37 (28.7- 49.2) | Oral ivermectin 300 microgram/kg for 5 days<br><br>Glucocorticoids (3% of patients)<br><br>Antibiotics (7% of patients) | Placebo<br><br>Glucocorticoids (6% of patients)<br><br>Antibiotics (6% of patients) | Mortality<br><br>Adverse events<br><br>Clinical deterioration<br><br>Symptom resolution |

| Study | COVID-19 severity | Population | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|
| | | **Average % female:**<br>Intervention - 61<br>Comparator - 55 | | | |
| Vallejos 2021<br><br>RCT<br><br>Argentina<br><br>**No. of participants: 501** | Mild/moderate<br><br>No scale used to determine severity. | Adults<br><br>PCR confirmed COVID-19<br><br>Exclusions: pregnancy/lactation, If patients required current home oxygen use or required hospitalisation for COVID-19 at time of diagnosis; history of hospitalisation for COVID-19; allergy to ivermectin, presence of mal-absorptive syndrome, any concomitant acute infectious disease, severe liver disease or need for dialysis.<br><br>**Mean age ±SD (years):**<br>Intervention – 42.58 ± 15.29<br>Comparator – 42.40 ± 15.75<br><br>**Average % female:**<br>Intervention – 44.4<br>Comparator – 50.2 | Oral ivermectin 2 doses in 2 days<br><br>12mg (≥80kg), 18mg (80-110kg), 24mg (≥110kg)<br><br>Antibiotics (6% of patients) | Standard of care in accordance with the recommendations of the Argentine Ministry of Health<br><br>Placebo<br><br>Antibiotics (6% of patients) | Mortality<br><br>Hospitalisation<br><br>Invasive mechanical ventilation<br><br>Adverse events<br><br>Negative nasal swab |
| Chachar 2020<br><br>RCT<br><br>Pakistan<br><br>**No. of participants: 50** | Mild | Adults<br><br>PCR confirmed COVID-19<br><br>Exclusions: pregnancy/lactation, known severe allergic reactions to Ivermectin, severe symptoms likely attributed to Cytokine Release Storm, malignant diseases, chronic kidney disease, cirrhosis liver with Child class B or | Ivermectin 12mg loading dose and 12mg; 12 and 24 hours after initial dose and symptomatic treatment.<br><br>Method of administration not reported. | Standard care – symptomatic treatment. | Adverse events<br><br>Symptom resolution |

| Study | COVID-19 severity | Population | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|
| | | C<br><br>**Mean age ±SD (years):**<br>Intervention – 40.60± 17<br>Comparator – 43.08 ± 14.8<br><br>**Average % female:**<br>Intervention - 16<br>Comparator - 22 | | | |

## Community setting – Single dose of ivermectin

| Study details | COVID-19 severity | Population | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|
| Podder 2020<br><br>RCT<br>Bangladesh<br><br>No. of participants: 62 | Mild/moderate according to WHO COVID-19 disease severity classification | Adults<br><br>PCR confirmed COVID-19<br><br>Exclusions: pregnancy/lactation, pre-existing hypersensitivity to ivermectin, patients taking other antimicrobials or hydroxychloroquine.<br><br>Mean age ±SD (years):<br>Intervention – 38.41 ± 11.02<br>Comparator – 39.97 ± 13.24 | Oral ivermectin 200 microgram/kg single dose.<br><br>Symptomatic treatment included antipyretics, cough suppressants, capsule doxycycline (100 mg every 12 hours for seven days). | Standard care<br><br>Symptomatic treatment included antipyretics, cough suppressants, capsule doxycycline (100 mg every 12 hours for seven days). | Symptom resolution<br><br>Viral clearance (7-10 days) |

| | | | | | |
|---|---|---|---|---|---|
| | | Average % female:<br>Intervention – 28.1<br>Comparator – 30.0 | | | |
| Chaccour 2021<br><br>RCT<br>Spain<br><br>No. of participants: 24 | Non-severe disease | Adults<br><br>PCR confirmed COVID-19<br><br>Exclusions: pregnancy; known history of Ivermectin allergy; hypersensitivity to any component of Stromectol® ; COVID-19 Pneumonia:<br>• Diagnosed by the attending physician<br>• Identified in a chest X-ray<br>Fever or cough present for more than 72 hours; Positive IgG against SARS-CoV-2 by rapid test; following co-morbidities: immunosuppression, COPD, diabetes, hypertension, obesity, acute/ chronic renal failure, history of coronary disease, history of cerebrovascular disease, current neoplasm; recent travel history to countries that are endemic for Loa loa; current use of CYP 3A4 or P-gp inhibitor drugs/use of critical CYP3A4 substrate drugs such as warfarin. | Oral ivermectin 400 microgram/kg single dose | Placebo | Adverse events<br><br>Virological clearance |

| | | | | | |
|---|---|---|---|---|---|
| | | Age, median (IQR) [range] (years):<br>Intervention - 26 (19-36) [18-54]<br>Comparator – 26 (21-44) [18-54]<br><br>Average % female:<br>Intervention - 42<br>Comparator – 58 | | | |

See appendix F for full evidence tables.

## Results

**Review question: What are the effectiveness and safety of ivermectin for acute symptoms and complications of COVID-19?**

## Key Updates

- 7 new RCTs were included in this update including 2 peer-reviewed publications which were previously included as preprints.

- Due to the addition of new trials, there has been a wide range of ivermectin dose and regimen used across trials. Data analysis was updated by splitting into four subgroups based on ivermectin regimen and study setting (2-5 doses of ivermectin in hospital setting, single dose of ivermectin in hospital setting, 2-5 doses of ivermectin in community setting, single dose of ivermectin in community setting). Cumulative dose of ivermectin ranged from 12mg to 378mg across trials. Therefore the analyses were further split by "lower/higher" doses of ivermectin, where applicable.

## Comparison: Ivermectin (multiple doses) vs placebo, standard care or placebo plus standard care in hospital setting

### Key result

Compared to standard care, ivermectin administered for 2-5 days significantly reduced mortality. However, after excluding two studies with high risk of bias, there was no statistically significant reduction in mortality compared to control group. There was statistically significant increase in adverse events in ivermectin group compared to control group.

### What is the evidence informing this conclusion?

Evidence comes from 8 randomised controlled trials (n=1174) that compared ivermectin (administered daily for 2-5 days) to standard care, placebo or standard care plus placebo in hospitalised for COVID-19 (Mohan 2021, Abd-Elsalam 2021, Mainomaipiboon 2022, Shakhsi Niaee 2020, Ravikirti 2021, Lim 2022, Ahmed 2020, Krolewiecki 2020). Two new trials were added in this update (Mainomaipiboon 2022 and Lim 2022). Studies were conducted in Bangladesh, Malaysia, Thailand, Egypt,

Argentina, India, Iran. Two trials were multi-arms studies and compared two different dosage regimens of ivermectin (Mohan 2021 and Niaee 2020); less than 400 micrograms/kg (micrograms/kg) and more than 400 micrograms/kg. 6 other RCTs used either a dose of more than 400 micrograms/kg or less than 400 micrograms/kg (Abd-Elsalam 2021, Mainomaipiboon 2022, Ravikirti 2021, Lim 2022, Ahmed 2020, Krolewiecki 2020).

Subgroup analyses were conducted based on less than 400micrograms/kg and greater than 400 micrograms/kg to highlight the differences in COVID-19 outcomes.

**Publication status**

All trials were full peer-reviewed publications except Mainomaipiboon 2022, which was a preprint and not peer-reviewed.

**Study characteristics**

Severity of COVID across trials was mild to moderate COVID-19. Standard care varied between trials.

Lim 2022 included people 50 years or older with at least one comorbidity and had mild to moderate COVID-19. RCT by Abd-Elsalam 2021 had mean age of 42.38 ± 16.02 years in ivermectin and 39.38 ± 16.92 in control group. The mean age of people was 38.33±6.84 in the ivermectin group and 37.33±5.84 in the control group in Abbas 2022. The mean age in trial by Mainomaipiboon 2022 was 48.57± 14.80 years.

The median age varied from 53 to 61 years in different arms of trial by Shakhsi Niaee 2020. A trial by Ravikirti 2021 had mean age of 50.7 ± 12.7 in ivermectin and 54.2 ± 16.3 in comparator group. The mean age was 42.3 ± 12.8 in ivermectin and 38.1 ± 11.7 in control group in Krolewiecki 2020. A study by Mohan 2021 had mean age of 34.3 ± 10.45 in Ivermectin 24mg, 36.3 ± 10.54 in Ivermectin 12mg and 35.3 ± 10.52 in comparator group. Percentage of females varied from 7.5% to 61% across trials. Cumulative ivermectin dose ranged from 12mg to 189mg across trials.

Hydroxychloroquine was part of standard care in two trials (Shakhsi Niaee 2021, Ravikirti 2021) which is not part of UK standard care. Some trials also used antivirals other than remdesivir which differ from current UK practice.

**What are the main results?**

All-cause mortality – [Updated]

Data on all-cause mortality from 6 trials (n=958) were included in the meta-analysis. The analysis found a statistically significant reduction in all-cause mortality at 28 days for ivermectin compared to standard care in people hospitalised with mild-moderate COVID-19 (RR 0.40 (CI 95% 0.20 — 0.82). However, the certainty of evidence was very low due to different standard of care within studies and risk of bias concerns. Two studies had high risk of bias due to inappropriate randomisation across control group and ivermectin group (Shakhsi Niaee 2020) and inconclusive RT-PCR reports for a high proportion of included participants (Ravikirti 2020). There were participants with negative RT-PCR included in the randomisation process and a relatively larger proportion of negative RT-PCR people were in control group, which resulted in the imbalance in randomisation (Shakhsi Niaee 2020). Due to the high risk of bias concerns, a sensitivity analysis was performed removing these two studies from the analysis. As a result, all-cause mortality was no longer statistically significant in favour of ivermectin compared with control (RR 0.45 (CI 95% 0.17 - 1.19)).

Viral clearance at day 1-6 and day 7-14 – [Updated]

Viral clearance has no statistically significant difference between 2-5 doses of ivermectin and control at day 1-6 [RR 0.75 (CI 95% 0.41 — 1.38)] and 7-14 [RR 1.17 (CI 95% 0.43 — 3.13)] in hospital setting.

Duration of hospitalisation - [Updated]

The meta-analysis did not show a statistically significant difference in duration of hospitalisation in people who received 2-5 doses of ivermectin in hospital setting (n=699; 3 studies).

Discharge from hospital

The meta-analysis did not show a statistically significant difference in discharge from the hospital between 2-5 doses of ivermectin and comparator group.

Admission to ICU

There was no statistically significant difference in admission to ICU between 2-5 doses of ivermectin and comparator group.

Invasive mechanical ventilation

The meta-analysis did not show a statistically significant difference in invasive mechanical ventilation between 2-5 doses of ivermectin and comparator group.

Clinical progression

The meta-analysis did not show a statistically significant difference in clinical progression between 2-5 doses of ivermectin and control group.

Symptom resolution

Data from updated meta-analysis showed no statistically significant findings for symptom resolution in people who received 2-5 doses of ivermectin compared to control group.

Time to progression to severe disease

No statistically significant difference was observed after the update on the meta-analysis for time to progression to severe disease.

Serious adverse events

Serious adverse events were non-statistically higher in 2-5 doses of ivermectin group compared to control group with, RR 3.00 (CI 95% 0.50 - 18.05) in 3 trials n=580.

Adverse events - Updated

A statistically significant increase was observed in adverse events in people who received 2-5 doses of ivermectin compared to those who received placebo based on data from 5 studies (n=816), with RR 2.34 (CI 95% 1.05 - 5.22).

Our confidence in the results

Studies are heterogenous with both clinical and methodological diversity. Most studies were assessed as being at unclear risk of bias. Other reasons for downgrading evidence included inconsistency (for example, when point estimates varied widely between studies) and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). The variance in duration of symptoms prior to randomisation across the studies may impact the certainty in outcomes such as viral clearance. Certainty of evidence was moderate, low or very low for all outcomes.

## Comparison: Ivermectin (single) vs placebo, standard care or placebo plus standard care in hospital setting

### Key result

Compared to standard care, single dose of ivermectin did not reduce all-cause mortality, viral clearance, need for invasive mechanical ventilation, admission to ICU, duration of hospitalisation and symptoms of COVID-19 in people hospitalised for COVID-19.

### What is the evidence informing this conclusion?

Data from 6 trials (n=598) were included in this comparison, where single dose of ivermectin was given to people hospitalised for COVID-19 (Gonzalez 2022, Kishoria 2020, Mohan 2021, Niaee 2020, Shah Bukhari 2021, Shahbaznejad 2021). One new trial was included in this update (Gonzalez 2022). Studies were conducted in Iran, India, Mexico and Pakistan. There were different dosage regimen within two trials by Mohan 2021 and Niaee 2020; less than 400 micrograms/kg (micrograms/kg) and more than 400 micrograms/kg. Other trials administered one or the other dose regimen.

Subgroup analyses were conducted based on less than 400micrograms/kg and greater than 400 micrograms/kg to highlight the differences in COVID-19 outcomes.

**Publication status**

All trials were full peer-reviewed publications.

**Study characteristics**

The mean age varied from 34.3 to 48.0 in 6 trials in this comparison except for Shakhsi Niaee 2021, where median age varied from 42 to 70 across multiple arms of the trial. The proportion of females varied from 7.5% to 61% in the trials. People with mild to moderate COVID-19 were included in Kishoria 2020, Mohan 2021, Shahbaznejad 2021, Shakhsi Niaee 2020. A study by Gonzalez 2022 recruited patients with severe COVID-19. Standard care varied between trials. Hydroxychloroquine was administered in comparator group in Kishoria 2020, Shakhsi Niaee 2020 and Shahbaznejad 2021. Placebo was given to control group in Mohan 2021 and calcium citrate as placebo in Gonzalez 2022.

The mean age was 39.5 in ivermectin group and 37.0 in control group in trial by Kishoria 2020. Mohan 2021 had mean age of 34.3 in >400ug/kg ivermectin and 36.3 in <400ug/kg ivermectin, and control group 35.3, while average age was above 50 years in Gonzalez 2022. Cumulative ivermectin dose ranged from 12mg to 25mg across trials.

**What are the main results?**

All-cause mortality

A meta-analysis of five studies showed no statistically significant difference in all-cause mortality in people who received single dose of ivermectin compared to control group in hospital setting, RR 0.26 (CI 95% 0.04 - 1.79). Data from 3 studies were included (n=345).

Viral clearance day 1-6 and day 7-14 - [Updated]

No statistically significant difference was observed between single dose ivermectin and control group in viral clearance at day 1-6, viral clearance day 7-14 based on data from 4 trials.

Discharge from hospital

No statistically significant difference was observed in discharge from hospital between single dose ivermectin group and control group.

Need for supplemental oxygen

No statistically significant difference was observed in need for supplemental oxygen between single dose ivermectin and comparator group.

Invasive mechanical ventilation

No statistically significant difference was observed for invasive mechanical ventilation between single dose of ivermectin and control group.

Clinical progression of COVID-19 severity

No statistically significant difference was observed for clinical progression of COVID-19 between single dose of ivermectin and control group.

Clinical improvement

No statistically significant difference was observed in clinical improvement between single dose of ivermectin and control group.

Duration of hospitalisation

No difference was observed for duration of hospitalisation between single dose ivermectin group and control group.

Time to resolution of symptoms

No statistically significant difference was observed in time to resolution of symptoms of COVID-19 between single dose ivermectin group and control group.

Duration of symptoms

A statistically significant reduction was observed in duration of symptoms in single dose ivermectin group compared to control group (RR -1.00(CI 95% -1.14 to -0.86)). However, it is worth noting that only one study reported duration of symptoms n=69 (Shahbaznejad 2021) which had unclear risk of bias, with incomplete information on randomisation and allocation procedure.

Adverse events

Adverse events had no statistically significant difference between single dose ivermectin and control group, RR 1.21 (CI 95% 0.49 - 2.97). Data from 4 trials were included (n=307).

**Our confidence in the results**

Studies are heterogenous with both clinical and methodological diversity. Most studies were assessed as being at unclear risk of bias. Other reasons for downgrading evidence included inconsistency (for example, when point estimates varied widely between studies) and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). The variance in duration of symptoms prior to randomisation across the studies may impact the certainty in outcomes such as viral clearance. Certainty of evidence was low and very low for majority of outcomes and moderate for one outcome.

## Comparison: Ivermectin (multiple doses) vs placebo, standard care or placebo plus standard care in community setting

**Key results**

There remains a high degree of uncertainty over whether multiple doses of ivermectin is more effective than placebo, placebo plus standard care or standard care for management of COVID-19 in the community.

**What is the evidence informing this conclusion?**

Evidence comes from 7 randomised controlled trials that compared ivermectin with standard care, placebo or standard care plus placebo in 4769 people with COVID-19 managed in the community (Abbas 2022, Biber 2021, Buonfrate 2022, Chachar 2020, Lopez-Medina 2021, Reis 2022 and Vallejos 2021). Three new trials were added in this update (Reis 2022, Buonfrate 2022 and Abbas 2022). Studies were conducted in Argentina, Brazil, China, Colombia, Italy and Israel.

**Publication status**

One study was only available as a preprint (Biber 2021) posted to medRxiv on May 31 2021, and has therefore not been peer reviewed.

**Study characteristics**

The mean or median age in the studies ranges between 37 and 49 years and the proportion of women ranged between 16 and 58%. The severity of COVID-19 across the studies was mild to moderate. All studies included people with mild to moderate or asymptomatic COVID-19, generally not requiring supplemental oxygen. The majority of the data are from the TOGETHER trial (Reis 2022) which included 3515 people who had at least one risk factor for COVID-19 disease progression. The remaining studies were either low risk for COVID-19 disease progression or did not report this data.

Duration of symptoms prior to randomisation varied across the studies ranging between 1 and 7 days.

Standard care within the trials varied slightly across the studies but were not too dissimilar from UK standard care. Dose and duration of ivermectin varied across the studies. Some studies used 200 – 300 micrograms per kg or 12mg as the dosage whereas other studies used higher doses of 400-1200 micrograms per kg. The cumulative ivermectin dose ranged from 24mg to 378mg among trials. The duration of treatment ranged between 2 and 5 days

Due to the variability in dosage, subgroup analyses were conducted where the data allowed.

Children and pregnant women were excluded from the trials.

**What are the main results?**

Discontinuation of treatment due to adverse events

Discontinuation of treatment due to adverse events was significantly higher with 2-5 doses of ivermectin compared with control. The relative risk is 2.97 (CI 95% 1.10 — 8.02) based on data from 2 trials (n=899).

All-cause mortality

The evidence suggests that, compared with control groups in people with COVID-19 in the community, ivermectin administered for 2 to 5 days does not result in statistically significant differences in all-cause mortality. The relative risk is 1.46 (CI 95% 0.87 — 2.44) based on data from 4 trials (n=2159).

Hospitalisation

There was no statistically significant difference between 2-5 doses of ivermectin and control group in community setting for hospitalisation outcome.

Clinical recovery

No statistically significant findings were observed for clinical recovery between 2-5 doses of ivermectin and control group.

Viral clearance

Viral clearance did not statistically significant difference between 2-5 doses of ivermectin and control group.

Adverse events

There was no statistically significant difference between adverse events in people who received 2-5 doses of ivermectin compared to those who received control in community setting.

### Our confidence in the results

Studies are heterogenous with both clinical and methodological diversity. Most studies were assessed as being at unclear risk of bias. Other reasons for downgrading evidence included inconsistency (for example, when point estimates varied widely between studies) and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). The variance in duration of symptoms prior to randomisation across the studies may impact the certainty in outcomes such as viral clearance. Certainty of evidence was moderate, low or very low for all outcomes.

## Comparison: Ivermectin (single dose) vs placebo, standard care or placebo plus standard care in community setting

### Key results

There remains a high degree of uncertainty over whether single dose of ivermectin is more effective than placebo, placebo plus standard care or standard care for management of COVID-19 in the community.

### What is the evidence informing this conclusion?

Evidence comes from 2 randomised controlled trials that compared ivermectin with standard care, placebo or standard care plus placebo in 64 people with COVID-19 managed in the community (Podder 2020, Chaccour 2020). Studies were conducted in Bangladesh and Spain.

### Publication status

Both trials were published.

### Study characteristics

Podder 2020 included people with mild to moderate COVID-19 and Chaccour 2020 had people with non-severe COVID-19. Both trials included people with confirmed positive RT-PCR test for SARS-CoV-2. Placebo was used as comparator in Chaccour 2020, while symptomatic treatment including antipyretics, cough

suppressants, capsule doxycycline were administered to the comparator group in Podder 2020. Single dose of 400micrograms/kg ivermectin was used in intervention group by Chaccour 2020 and single dose of 200 micrograms/kg ivermectin by Podder 2020. The cumulative ivermectin dose was 12mg to 25mg in both trials.

Median age was 26 in both intervention and control group in Chaccour 2020. Mean age was 38.4 in ivermectin group and 39.9 in control group in Podder 2020. 28.15% were females in ivermectin group and 30.0% females in comparator group in Podder 2020, while Chaccour 2020 had 42% females in ivermectin and 58% in control group.

**What are the main results?**

Viral clearance at day 7-14

There was no statistically significant difference in viral clearance at day 7-14 between single dose of ivermectin and control group in community setting. It was based on data from 1 study (n=40).

**Adverse events**

No statistically significant difference was observed for adverse events in people who received single dose of ivermectin compared to standard of care or control in the community. This outcome was based on data from 1 study (n=24).

**Our confidence in the results**

Podder 2020 was assessed as high risk of bias due to lack of blinding and inappropriate reporting of outcomes. Chaccour 2020 was assessed as unclear risk of bias due to incomplete information on blinding.

Due to serious risk of bias and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect), both outcomes were marked as ‘low certainty’ of evidence.

See appendix H for forest plots and appendix I for full GRADE profiles.

## Evidence to decision

### Benefits and harms

### Hospital settings

The panel stated that mortality is important for decision making. They noted that the evidence does not show a statistically significant difference in mortality for people in hospital with COVID-19 having a single dose of ivermectin compared with people having control (standard care or placebo or standard care plus placebo). For 2 to 5 doses of ivermectin, the meta-analysis showed a statistically significant reduction in mortality. However, the panel had concerns about 2 studies judged to have high risk of bias because of randomisation issues and people with a negative or inconclusive PCR for SARS-CoV-2 result included in the trials. A sensitivity analysis removing 2 studies with high risk of bias showed no statistically significant difference for mortality with 2 to 5 doses of ivermectin compared with control. The panel discussed that some studies reported all-cause mortality, so it may be possible that deaths reported may not all be due to COVID-19. The panel considered the certainty of evidence for this outcome to be very low for both 2 to 5 doses of ivermectin and single dose ivermectin. They also agreed that there are issues with the applicability of the evidence in the hospital setting. This was because most people in the studies had less severe COVID-19 than people who would be hospitalised in the UK.

The panel noted that a statistically significant increase in adverse events was seen for people who had 2 to 5 doses of ivermectin compared with those who had control, with moderate certainty of evidence. However, there was no statistically significant difference in adverse events between single dose of ivermectin group and control group. Therefore, there is uncertainty around the safety of oral ivermectin used at the doses and frequencies in the multidose trials.

The panel noted that the evidence shows no statistically significant difference between ivermectin and control for the other outcomes of admission to intensive care, need for invasive mechanical ventilation, discharge from hospital, number of people needing oxygen, clinical improvement, clinical worsening, time to recovery, viral clearance (at days 1 to 6 and 7 to 14), duration to viral clearance and duration of symptoms.

**Community setting**

The panel discussed the evidence on ivermectin use for people with COVID-19 in the community. The evidence showed no statistically significant differences for ivermectin compared to control in: mortality; need for invasive mechanical ventilation; adverse events; serious adverse events, need for hospitalisation; number of people needing oxygen; clinical deterioration; clinical recovery; viral clearance (at days 1 to 6 and 7 to 14) both in 2 to 5 doses and single dose of ivermectin group. The panel noted that the certainty of evidence is moderate, low or very low for all outcomes.

The panel also noted that evidence suggests a statistically significant increase in stopping treatment because of adverse events with 2 to 5 doses of ivermectin but agreed that this evidence is of low certainty. Therefore, there is uncertainty around the safety of oral ivermectin used at the doses and frequencies in the multidose trials.

The panel saw no statistically significant findings on viral clearance and adverse events in people who had a single dose of ivermectin compared with control group. The certainty of evidence is low for both of these outcomes.

**Other panel considerations**

The panel discussed the potential for the occurrence of rare serious adverse events (such as myocardial infarction which was the most common serious adverse event reported in Lim 2022) with ivermectin. They considered that the available studies were too small to identify such events.

The panel noted that no studies were from the UK. They commented that some of the treatments (such as hydroxychloroquine, doxycycline, azithromycin and lopinavir–ritonavir) used in the control groups are either not used in the UK for COVID-19 or may not be effective against COVID-19. Detail on other treatments was lacking in some studies. The panel considered that this limits the applicability of the evidence to UK practice. Oral ivermectin may be used to treat strongyloidiasis. The panel discussed the possibility that some of the studies contributing to the evidence base may have been conducted in countries with higher prevalence of strongyloidiasis compared with others. Therefore, there is uncertainty around

whether results of studies of ivermectin for COVID-19 are generalisable between countries where there is high prevalence of strongyloidiasis and those countries where prevalence is low, with potential confounding effect. The panel also discussed that, because dosage varied widely across the included studies, it is uncertain what a safe dose of ivermectin would be for treating COVID-19.

The panel agreed that the uncertainty around the benefits and safety of ivermectin based on the current evidence means that it cannot be recommended for COVID-19 in people in hospital or community settings. They considered that this was the case for children, young people and adults. The panel were aware of ongoing trials investigating ivermectin, such as the PRINCIPLE trial. They considered that the available evidence for the effectiveness and safety of ivermectin could be improved by evidence from a well-designed randomised controlled trial.

**Certainty of evidence**

The panel agreed that the certainty of evidence on ivermectin for people with COVID-19 in hospital and in the community is moderate, low or very low for all outcomes. Reasons for downgrading evidence included: risk of bias (with most studies being at high or unclear risk of bias); inconsistency (for example, when point estimates varied widely between studies); indirectness (with, for example, standard care differing from that in the UK); and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). Some studies were only available as preprints so have not been peer reviewed.

**Values and preferences**

The panel were not aware of any systematically collected data on preferences and values about ivermectin for COVID-19. They discussed that people with COVID-19 may have different views on ivermectin use because of the quality of current evidence, uncertainty over its safety and the availability of recommended treatments for COVID-19 in the UK.

### Resources

The panel raised concerns about ivermectin being used to treat COVID-19 when there is limited evidence of benefit. They highlighted the importance of not diverting resources away from other evidence-based indications for ivermectin.

Cost effectiveness was not assessed as part of the evidence review.

### Equity

No evidence was found for ivermectin use in pregnancy. However, the BNF states that the manufacturer advises against using ivermectin in pregnancy. Limited evidence was identified in children or young people. However, because the overall recommendation is not to offer ivermectin, it is not expected to cause inequity among any groups. The panel considered the issue of equity and did not raise any additional concerns. However, the panel flagged the importance of not diverting ivermectin supply away from existing evidence-based indications in non-UK countries.

### Acceptability

The panel were not aware of any systematically collected evidence about acceptability. Ivermectin is not licensed in the UK for treating COVID-19. The low to very low certainty of current evidence may reduce acceptability.

### Feasibility

The panel were not aware of any systematically collected evidence about feasibility. However, the panel noted the current limited availability of ivermectin in the UK.

# Appendices

## Appendix A: PICO table

### PICO table

### PICO and eligibility criteria

What is the effectiveness and safety of ivermectin for acute symptoms and complications of COVID-19?

| Criteria | Notes |
|---|---|
| Population | Adults, young people and children with suspected or confirmed COVID-19 |
| Interventions | Ivermectin as monotherapy |
| Comparators | Standard care alone, standard care plus placebo, placebo or active comparator<br><br>*Note: Standard care comprises best supportive care and in certain circumstances the use of additional drugs (such as dexamethasone, remdesivir).* |
| Outcomes | • Mortality (n/N)<br>• Invasive mechanical ventilation (IMV) or intensive care admission (requirement and duration)<br>• Serious adverse events<br>• Adverse events<br>• Hospitalisation (requirement and duration)<br>• Discharge from hospital<br>• Supplemental oxygen, high-flow oxygen, continuous positive airway pressure or non-invasive ventilation (requirement and duration)<br>• Discontinuation due to adverse events<br>• Symptom resolution or clinical recovery (number and time until)<br>• Virological clearance (negative PCR)<br>• Clinical worsening / deterioration (number and time until)<br>• Sustained recovery (development of long-term effects of COVID) |

| | |
|---|---|
| | The definitions of mechanical ventilation, non-invasive ventilation and other forms of respiratory support such as high flow nasal oxygen (HFNO) therapy or continuous positive airway pressure or non-invasive bilevel ventilation may differ across the studies. In the context of UK practice the following definitions should be considered:<br>**Advanced respiratory support:** Invasive mechanical ventilation, bilevel positive airway pressure (BiPAP) via translaryngeal tube or tracheostomy, continuous positive airway pressure (CPAP) via translaryngeal tube, or extracorporeal respiratory support)<br>**Non-invasive ventilation:** includes HFNO, CPAP, CPAP via tracheostomy, and non-invasive bilevel ventilation.<br>Note: oxygen via (low flow) nasal cannulae or face mask does not fall within the categories above. |
| Settings | All settings |
| Subgroups | • Adults > 50 years<br>• Children <12 years of age<br>• Disease severity (moderate/severe/critical)<br>• Sex<br>• Ethnic background<br>• Pregnant women<br>• Comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity)<br>• Time from symptom onset<br>• Treatment with other therapeutics used for COVID-19<br>• Community vs hospital<br>• Confirmed versus negative for COVID<br>• Tested vs untested for COVID<br>• PCR confirmed versus clinically confirmed COVID<br>• Vaccination status<br>• Different variants |
| Study types | The search will look for: |

| | |
|---|---|
| | • Systematic review of randomised controlled trials (RCTs)<br>• RCTs<br>If no systematic reviews or RCT evidence is available progress to:<br>• non-randomised controlled trials<br>• systematic reviews of non-randomised controlled trials<br>• cohort studies<br>• before and after studies<br>• interrupted time series studies<br>Preprints will be considered as part of the evidence review. |
| Countries | Any |
| Timepoints | From 2020 onwards |
| Other exclusions | The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include:<br>• non-English language papers, studies that are only available as abstracts, and narrative reviews<br>• animal studies<br>• editorials, letters, news items, case reports and commentaries, conference abstracts and posters<br>• theses and dissertations |
| Equality issues | Sex, age, ethnicity, religion or beliefs, people with a learning disability and disabled people, gender reassignment, socioeconomic status, people who are pregnant or breastfeeding, people whose first language isn't English, people who are homeless, refugees, asylum seekers, migrant workers and people who are homeless. |

## Appendix B: Literature search strategy/Data source

### Search design and peer review

This search was developed in compliance with Appendix L of NICE's manual on developing guidelines.

A NICE information specialist conducted the literature searches for the evidence review. The searches were run on 14/09/2021 and updated on 21/05/2022. This search report is compliant with the requirements of PRISMA-S.

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist. The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

NICE's approach to retrieving preprints has evolved throughout the pandemic:

- Prior to 20th April 2020 MedRxiv and BioRxiv were searched directly.
- From 20th April 2020 an automated process was used to download the entire MedRxiv and BioRxiv COVID-19 and SARS-COV-2 collection into EPPI Reviewer 5 and update the results daily. Individual topic searches were conducted within EPPI Reviewer to get round the limitations of the native search functionality in MedRxiv and BioRxiv.
- From 19th August 2021, results from additional preprint servers were added to the EPPI Reviewer database on a weekly basis. The additional results were sourced from the aggregator sites Europe PMC and the NIH Office of Portfolio Analysis COVID-19 database. These sites index multiple preprint servers, including Arxiv, MedRxiv, BioRxiv, Research Square, SSRN and preprints.org. The NIH database is pre-sifted for COVID-19 related references. Europe PMC is broader, and so we initially used their stock strategy to narrow the results down to a subset that were related to COVID-19. References added to the aggregator sites from the 10th August 2021 were downloaded, but searches of these sources were not backdated further.

### Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

**Limits and restrictions**

English language limits were applied in adherence to standard NICE practice and the review protocol.
The search was limited from 2020 to date as defined in the review protocol.
**Search filters**

- Covid-19 filter

The development of NICE's main database search strategy for Covid-19 is covered in: Levay P and Finnegan A (2021) The NICE COVID-19 search strategy for Ovid MEDLINE and Embase: developing and maintaining a strategy to support rapid guidelines. MedRxiv preprint. https://doi.org/10.1101/2021.06.11.21258749

- RCT filters

The MEDLINE RCT filter was McMaster Therapy – Medline - "best balance of sensitivity and specificity" version. The standard NICE modifications were used: randomized.mp changed to randomi?ed.mp.
Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.
The Embase RCT filter was McMaster Therapy – Embase "best balance of sensitivity and specificity" version.
Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association*, 94(1), 41-47.

- RCT classifier

In EPPI R5, the RCT records identified by the search were assessed using the Cochrane's validated machine learning RCT classifier. The development of the classifier is covered in: Thomas J, McDonald S, Noel-Storr A, Shemilt I, Elliott J, Mavergames C, Marshall IJ. Machine learning reduced workload with minimal risk of missing studies: development and evaluation of a randomized controlled trial classifier for Cochrane Reviews. J Clin Epidemiol. 2021 May;133:140-151. doi: 10.1016/j.jclinepi.2020.11.003. Epub 2020 Nov 7. PMID: 33171275.

**Main search – Databases**

| Database | Date | Platform | Segment searched | No. of results |
|---|---|---|---|---|
| MEDLINE ALL | 14/09/2021 | Ovid | 1946 to September 13, 2021 | 60 |
| Embase | 14/09/2021 | Ovid | 1974 to 2021 September 13 | 86 |

| | | | | |
|---|---|---|---|---|
| Cochrane Library | 14/09/2021 | Wiley | Issue 9 of 12, September 2021 | 23 |
| Pre-prints – bioRxiv and medRxiv | 14/09/2021 | Pre-prints v3 | IS surveillance - pre-prints v3 | 48 |

**Search strategy history**

**Medline All Strategy**

1 Ivermectin/ (6814)
2 (Ivermectin* or Soolantra*).ti,ab. (6503)
3 1 or 2 (8944)
4 ("2020-001971-33" or "2020-001994-66" or "2020-002091-12").af. (0)
5 ("ChiCTR2000033627" or "CTRI/2020/04/024948" or "CTRI/2020/05/025068").af. (0)
6 ("CTRI/2020/05/025224" or "CTRI/2020/06/026232" or "IRCT20111224008507N3").af. (1)
7 ("IRCT20200408046987N1" or "IRCT20200422047168N2" or "ISRCTN40302986").af. (0)
8 ("NCT04343092" or "NCT04345419" or "NCT04351347" or "NCT04360356").af. (0)
9 ("CTRI/2020/04/024858" or "NCT04373824" or "NCT04374019").af. (0)
10 ("NCT04381884" or "NCT04382846" or "2020-001474-29" or "NCT04390022").af. (3)
11 ("NCT04391127" or "NCT04392427" or "NCT04392713" or "NCT04399746").af. (0)
12 ("NCT04403555" or "NCT04405843" or "NCT04407130" or "NCT04407507").af. (1)
13 ("NCT04422561" or "NCT04425707" or "NCT04429711" or "NCT04431466").af. (1)
14 ("NCT04434144" or "NCT04435587" or "NCT04438850" or "NCT04445311").af. (0)
15 ("NCT04446104" or "NCT04446429" or "NCT04447235").af. (1)
16 ("NCT04472585" or "NCT04482686").af. (1)
17 (NCT04646109 or NCT04681053 or NCT04920942 or NCT04510233 or NCT04712279 or NCT04530474 or NCT04739410 or NCT04937569 or NCT04894721 or NCT04668469 or NCT04529525 or NCT04729140 or NCT04723459 or NCT04886362 or NCT04944082 or NCT04959786 or NCT04834115 or NCT04784481 or NCT04703205 or NCT04768179 or NCT04602507 or NCT04746365 or NCT04832945 or NCT04551755 or NCT04527211 or NCT04716569 or NCT04701710 or NCT04673214 or NCT05040724 or NCT04891250 or NCT04635943 or NCT04836299 or NCT04727424 or NCT04510194 or NCT04747678 or NCT04779047 or NCT04384458 or NCT04425863 or NCT04885530 or NCT04951362 or NCT04703608 or NCT04632706 or NCT04714515 or NCT05041907 or NCT04460547 or NCT04681040).af. (5)
18 or/4-17 (13)

19 3 or 18 (8946)
20 randomized controlled trial.pt. (543280)
21 randomi?ed.mp. (958615)
22 placebo.mp. (228609)
23 or/20-22 (1020088)
24 19 and 23 (809)
25 SARS-CoV-2/ or COVID-19/ (105486)
26 (corona* adj1 (virus* or viral*)).ti,ab,kw,kf. (4081)
27 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab,kw,kf. (60920)
28 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab,kw,kf. (186696)
29 or/25-28 (191775)
30 limit 29 to yr="2020-Current" (178450)
31 (30 and english.lg.) not (letter or historical article or comment or editorial or news or case reports).pt. not (Animals/ not humans/) (130253)
32 24 and 31 (60)

**Embase Strategy**

1 closantel plus ivermectin/ or ivermectin/ (13683)
2 (Ivermectin* or Soolantra*).ti,ab. (8033)
3 1 or 2 (14435)
4 ("2020-001971-33" or "2020-001994-66" or "2020-002091-12").af. (0)
5 ("ChiCTR2000033627" or "CTRI/2020/04/024948" or "CTRI/2020/05/025068").af. (0)
6 ("CTRI/2020/05/025224" or "CTRI/2020/06/026232" or "IRCT20111224008507N3").af. (1)
7 ("IRCT20200408046987N1" or "IRCT20200422047168N2" or "ISRCTN40302986").af. (3)
8 ("NCT04343092" or "NCT04345419" or "NCT04351347" or "NCT04360356").af. (34)
9 ("CTRI/2020/04/024858" or "NCT04373824" or "NCT04374019").af. (21)
10 ("NCT04381884" or "NCT04382846" or "2020-001474-29" or "NCT04390022").af. (18)
11 ("NCT04391127" or "NCT04392427" or "NCT04392713" or "NCT04399746").af. (21)
12 ("NCT04403555" or "NCT04405843" or "NCT04407130" or "NCT04407507").af. (10)
13 ("NCT04422561" or "NCT04425707" or "NCT04429711" or "NCT04431466").af. (9)
14 ("NCT04434144" or "NCT04435587" or "NCT04438850" or "NCT04445311").af. (12)
15 ("NCT04446104" or "NCT04446429" or "NCT04447235").af. (17)
16 ("NCT04472585" or "NCT04482686").af. (4)
17 (NCT04646109 or NCT04681053 or NCT04920942 or NCT04510233 or NCT04712279 or NCT04530474 or NCT04739410 or NCT04937569 or

NCT04894721 or NCT04668469 or NCT04529525 or NCT04729140 or NCT04723459 or NCT04886362 or NCT04944082 or NCT04959786 or NCT04834115 or NCT04784481 or NCT04703205 or NCT04768179 or NCT04602507 or NCT04746365 or NCT04832945 or NCT04551755 or NCT04527211 or NCT04716569 or NCT04701710 or NCT04673214 or NCT05040724 or NCT04891250 or NCT04635943 or NCT04836299 or NCT04727424 or NCT04510194 or NCT04747678 or NCT04779047 or NCT04384458 or NCT04425863 or NCT04885530 or NCT04951362 or NCT04703608 or NCT04632706 or NCT04714515 or NCT05041907 or NCT04460547 or NCT04681040).af. (12)
18 or/4-17 (99)
19 3 or 18 (14482)
20 random:.tw. (1704088)
21 placebo:.mp. (480513)
22 double-blind:.tw. (223072)
23 or/20-22 (1967135)
24 19 and 23 (1211)
25 exp severe acute respiratory syndrome coronavirus 2/ or coronavirus disease 2019/ or experimental coronavirus disease 2019/ (152602)
26 (corona* adj1 (virus* or viral*)).ti,ab,kw. (3744)
27 (CoV not (Coefficien* or co-efficien* or covalent* or covington or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk" or CoVR or CoVS)).ti,ab,kw. (52977)
28 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab,kw. (186867)
29 or/25-28 (200494)
30 limit 29 to yr="2020-Current" (185359)
31 (30 and english.lg.) not (letter or editorial or conference).pt. not (nonhuman/ not human/) not "case report".sh. not medline*.db. (84905)
32 24 and 31 (86)

**Cochrane CENTRAL strategy**

#1 (Ivermectin* or Soolantra*):ti,ab 797

#2 MeSH descriptor: [Ivermectin] explode all trees 431

#3 #1 or #2 810

#4 ("2020-001971-33" or "2020-001994-66" or "2020-002091-12"):ti,ab,kw 0

#5 ("ChiCTR2000033627" or "CTRI/2020/04/024948" or "CTRI/2020/05/025068"):ti,ab,kw 0

#6 ("CTRI/2020/05/025224" or "CTRI/2020/06/026232" or "IRCT20111224008507N3"):ti,ab,kw 1

#7 ("IRCT20200408046987N1" or "IRCT20200422047168N2" or "ISRCTN40302986"):ti,ab,kw 0

#8 ("NCT04343092" or "NCT04345419" or "NCT04351347" or "NCT04360356"):ti,ab,kw 0

#9 ("NCT04381884" or "NCT04382846" or "2020-001474-29" or "NCT04390022"):ti,ab,kw 3

#10 ("NCT04391127" or "NCT04392427" or "NCT04392713" or "NCT04399746"):ti,ab,kw 0

#11 ("NCT04403555" or "NCT04405843" or "NCT04407130" or "NCT04407507"):ti,ab,kw 1

#12 ("NCT04422561" or "NCT04425707" or "NCT04429711" or "NCT04431466"):ti,ab,kw 2

#13 ("NCT04434144" or "NCT04435587" or "NCT04438850" or "NCT04445311"):ti,ab,kw 0

#14 ("NCT04446104" or "NCT04446429" or "NCT04447235"):ti,ab,kw 3

#15 ("NCT04472585" or "NCT04482686"):ti,ab,kw 0

#16 (NCT04646109 or NCT04681053 or NCT04920942 or NCT04510233 or NCT04712279 or NCT04530474 or NCT04739410 or NCT04937569 or NCT04894721 or NCT04668469 or NCT04529525 or NCT04729140 or NCT04723459 or NCT04886362 or NCT04944082 or NCT04959786 or NCT04834115 or NCT04784481 or NCT04703205 or NCT04768179 or NCT04602507 or NCT04746365 or NCT04832945 or NCT04551755 or NCT04527211 or NCT04716569 or NCT04701710 or NCT04673214 or NCT05040724 or NCT04891250 or NCT04635943 or NCT04836299 or NCT04727424 or NCT04510194 or NCT04747678 or NCT04779047 or NCT04384458 or NCT04425863 or NCT04885530 or NCT04951362 or NCT04703608 or NCT04632706 or NCT04714515 or NCT05041907 or NCT04460547 or NCT04681040):ti,ab,kw 4

#17 {or #4-#16} 14

#18 #3 or #17 with Publication Year from 2020 to 2021, in Trials 219

#19 MeSH descriptor: [SARS-CoV-2] this term only 427

#20 MeSH descriptor: [COVID-19] this term only 583

#21 (corona* near/1 (virus* or viral*)):ti,ab,kw 256

#22 (CoV NOT (Coefficien* or "co-efficient" or “co-efficiency” or “co-efficiencies” or covalent* or Covington* or covariant* or covarianc* or "cut-off value" or "cut-off values" or "cutoff value" or "cutoff values" or "cut-off volume" or "cut-off volumes" or "cutoff volume" or "cutoff volumes" or "combined optimisation value" or "combined optimisation values" or "combined optimization value" or "combined optimization values" or "central vessel trunk" or "central vessel trunks" or CoVR or CoVS)):ti,ab,kw 505

#23 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel" or Ncov* or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or SARSCoV2* or "SARS-CoV2" or "severe acute respiratory syndrome" or "severe acute respiratory syndromes" or covid19 or covid-19 or covid):ti,ab,kw 7472

#24 {or #19-#23} 7519

#25 (clinicaltrials or trialsearch):so 375575

#26 #24 not #25 2602

#27 #18 and #26 with Publication Year from 2021 to 2021, in Trials 23

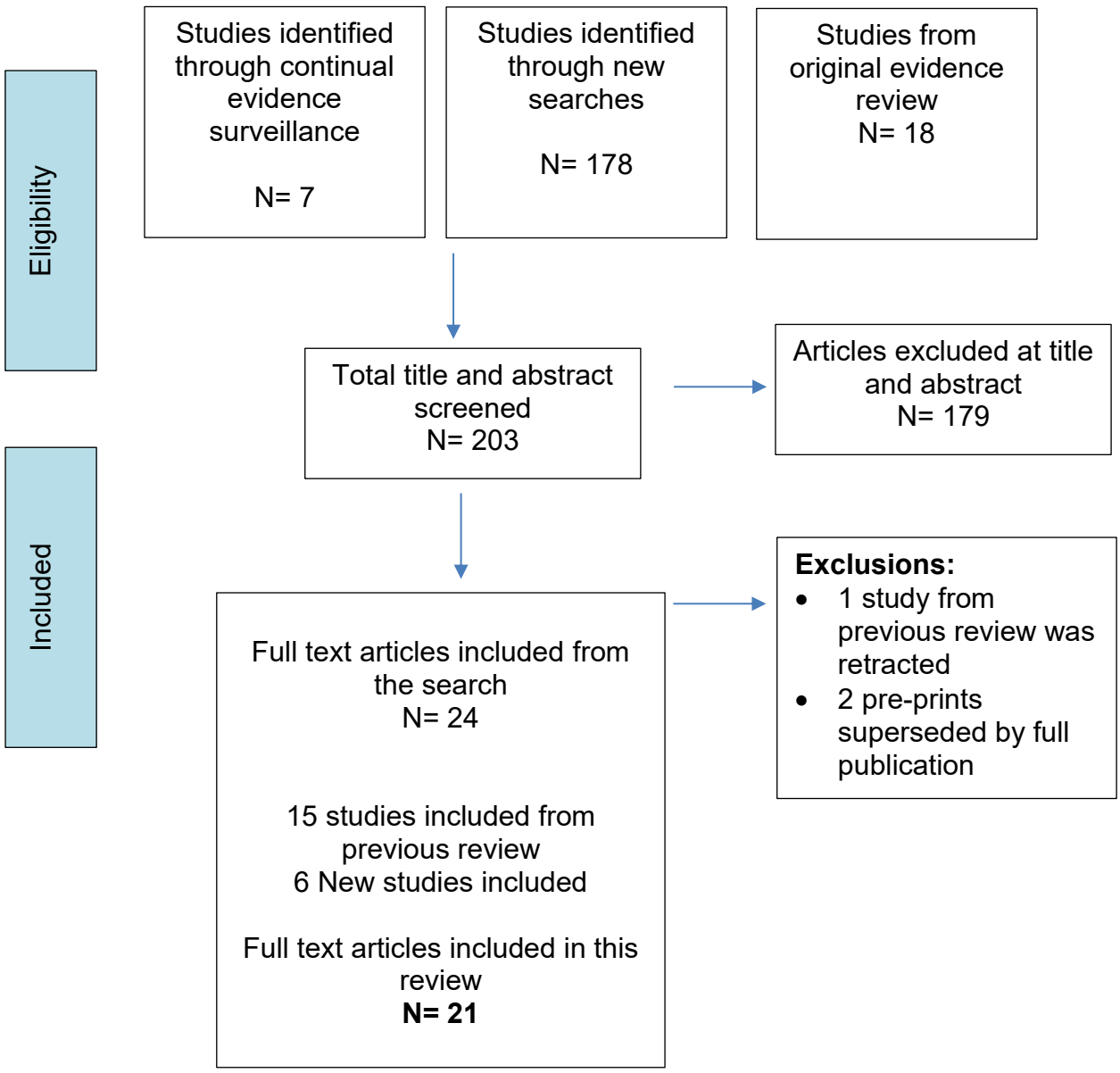
**Database name: Pre-print - medRxiv and bioRxiv/ Europe PMC/NIH Portfolio**

These were searched via EPPI reviewer v5 using filters Title and Abstract HAS ANY. The search terms were combined with OR: Ivermectin OR Soolantra

**Rerun search – Databases**

| Database | Date | Platform | Segment searched | No. of results |
|---|---|---|---|---|
| MEDLINE ALL | 21/04/2022 | Ovid | 1946 to April 19, 2022 | 38 |
| Embase | 21/04/2022 | Ovid | 1996 to 2022 April 20 | 140 |
| Cochrane Library | 21/04/2022 | Wiley | Issue 4 of 12, September 2022 | 35 |
| Pre-prints – bioRxiv and medRxiv | 21/04/2022 | Pre-prints v3 | IS surveillance - pre-prints v3 | 40 |

# Appendix C: PRISMA diagram



# Appendix D: Included studies

| Study | Status |
|---|---|
| Abbas K, U; Muhammad, S; Ding S, F (2022) The Effect of Ivermectin on Reducing Viral Symptoms in Patients with Mild COVID-19. Indian Journal of Pharmaceutical Sciences 84: 87-91 | New |
| Abd-Elsalam, Sherief, Noor, Rasha A, Badawi, Rehab et al. (2021) Clinical study evaluating the efficacy of ivermectin in COVID-19 treatment: A randomized controlled study. Journal of medical virology 93(10): 5833-5838 | |
| Ahmed, Sabeena, Karim, Mohammad Mahbubul, Ross, Allen G et al. (2021) A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 103: 214-216 | |
| Beltran, Gonzalez, Jose, Lenin, Gonzalez, Gamez et al. (2022) Efficacy and Safety of Ivermectin and Hydroxychloroquine in Patients with Severe COVID-19: A Randomized Controlled Trial. Infectious disease reports 14(2): 160-168 | New – Full text peer reviewed article available [Pre-print was included previously] |
| Biber, Asaf, Mandelboim, Michal, Harmelin, Geva et al. Favorable outcome on viral load and culture viability using Ivermectin in early treatment of non-hospitalized patients with mild COVID-19, A double-blind, randomized placebo-controlled trial. medrxiv preprint | |
| Bukhari Syed Karamat Hussain, Shah, Asghar, Asma, Perveen, Najma et al. Efficacy of Ivermectin in COVID-19 Patients with Mild to Moderate Disease. medrxiv preprint | |
| Buonfrate, D, Chesini, F, Martini, D et al. (2022) High-dose ivermectin for early treatment of COVID-19 (COVER study): a randomised, double-blind, multicentre, phase II, dose-finding, proof-of-concept clinical trial. International Journal of Antimicrobial Agents: 106516 | New - Full text peer reviewed article available [Pre-print was included previously] |
| Chaccour, Carlos, Casellas, Aina, Blanco-Di Matteo, Andres et al. (2021) The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial. EClinicalMedicine 32: 100720 | |
| Chachar, A.Z., Khan, K., Asif, M., Tanveer, K., Khaqan, A., & Basri R (2020) Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients. International journal of sciences 9: 31-35 | |
| Kishoria, N., Mathur, S., Parmar, V., Kaur, R., Agarwal, H., Parihar, B., & Verma S (2020) IVERMECTIN AS ADJUVANT TO HYDROXYCHOLOROQUINE IN PATIENTS RESISTANT TO STANDARD TREATMENT FOR SARS-CoV-2: RESULTS OF AN OPEN-LABEL RANDOMIZED CLINICAL STUDY. Paripex Indian Journal Of Research 9(8): 50-53 | |
| Krolewiecki, Alejandro, Lifschitz, Adrian, Moragas, Matias et al. (2021) Antiviral effect of high-dose ivermectin in adults with COVID-19: A proof-of-concept randomized trial. EClinicalMedicine 37: 100959 | |
| Lim Steven Chee, Loon, Hor Chee, Peng, Tay Kim, Heng et al. (2022) Efficacy of Ivermectin Treatment on Disease Progression Among Adults With Mild to Moderate COVID-19 and Comorbidities: The I-TECH Randomized Clinical Trial. JAMA internal medicine | New |

| Study | Status |
|---|---|
| Lopez-Medina, Eduardo, Lopez, Pio, Hurtado, Isabel C et al. (2021) Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial. JAMA 325(14): 1426-1435 | |
| Manomaipiboon, Anan, Pholtawornkulchai, Kitisak, Pupipatpab, Sujaree et al. (2022) Efficacy and safety of ivermectin in the treatment of mild-to-moderate COVID-19 infection: A randomized, double blind, placebo, controlled trial. | New |
| Mohan, Anant, Tiwari, Pawan, Suri, Tejas Menon et al. (2021) Single-dose oral ivermectin in mild and moderate COVID-19 (RIVET-COV): A single-centre randomized, placebo-controlled trial. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy | |
| Podder, C., Chowdhury, N., Sina, M.I., & Haque W (2021) Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study. IMC Journal of Medical Science 14(2): 11-18 | |
| Ravikirti, Roy, Ranjini, Pattadar, Chandrima et al. (2021) Evaluation of Ivermectin as a Potential Treatment for Mild to Moderate COVID-19: A Double-Blind Randomized Placebo Controlled Trial in Eastern India. Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques 24: 343-350 | |
| Reis, Gilmar, Silva Eduardo A S, M, Silva Daniela C, M et al. (2022) Effect of Early Treatment with Ivermectin among Patients with Covid-19. The New England journal of medicine | New |
| Shahbaznejad, Leila, Davoudi, Alireza, Eslami, Gohar et al. (2021) Effects of Ivermectin in Patients With COVID-19: A Multicenter, Double-blind, Randomized, Controlled Clinical Trial. Clinical therapeutics 43(6): 1007-1019 | |
| Shakhsi Niaee, Morteza, Cheraghi, Fatemeh, Namdar, Peyman et al. (2021) Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial. Asian Pacific Journal of Tropical Medicine 14(6): 266-273 | |
| Vallejos, Julio, Zoni, Rodrigo, Bangher, Maria et al. (2021) Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial. BMC infectious diseases 21(1): 635 | |

# Appendix E: Excluded studies at full text screening

| Study | Reason for exclusion |
|---|---|
| Aref, Zaki F, Bazeed, Shamardan Ezz Eldin S, Hassan, Mohammed H et al. (2021) Clinical, Biochemical and Molecular Evaluations of Ivermectin Mucoadhesive Nanosuspension Nasal Spray in Reducing Upper Respiratory Symptoms of Mild COVID-19. International journal of nanomedicine 16: 4063-4072 | - Study does not contain a relevant intervention<br>*Study uses a nasal spray and all other studies use oral medication, so not clear if relevant intervention. The standard of care used is not applicable to the UK setting.* |
| Babalola Olufemi, Emmanuel, Bode Christopher, Olusanjo, Ajayi Adesuyi, Adeyinka et al. Ivermectin shows clinical benefits in mild to moderate Covid19 disease: A randomised controlled double blind dose response study in Lagos. medrxiv preprint | - Comparator in study does not match that specified in protocol<br>*Excluded as study investigated active comparators without proven efficacy.* |
| Babalola, O E, Bode, C O, Ajayi, A A et al. (2021) Ivermectin shows clinical benefits in mild to moderate COVID19: A randomised controlled double-blind, dose-response study in Lagos. QJM : monthly journal of the Association of Physicians | - Comparator in study does not match that specified in protocol<br>*Excluded as study investigated active comparators without proven efficacy. Also, no relevant outcomes reported.* |
| Babalola, O E, Bode, C O, Ajayi, A A et al. (2022) Ivermectin shows clinical benefits in mild to moderate COVID19: a randomized controlled double-blind, dose-response study in Lagos. QJM : monthly journal of the Association of Physicians 114(11): 780-788 | - Comparator in study does not match that specified in protocol |
| Babalola, olufemi Emmanuel, Ndanusa, Yahaya, Adesuyi, Ajayi et al. A Randomized Controlled Trial of Ivermectin Monotherapy Versus Hydroxychloroquine, Ivermectin, and Azithromycin Combination Therapy in Covid-19 Patients in Nigeria. | - Comparator in study does not match that specified in protocol |
| Buonfrate, Dora, Chesini, Fabio, Martini, Davide et al. High Dose Ivermectin for the Early Treatment of COVID-19 (COVIER Study): A Randomised, Double-Blind, Multicentre, Phase II, Dose-Finding, Proof of Concept Clinical Trial. | - Pre-print now published |
| Chahla Rossana, Elena, Ruiz Luis, Medina, Mena, Teresa et al. (2022) Cluster Randomised Trials - Ivermectin Repurposing for Covid-19 Treatment of Outpatients with Mild Disease in Primary Health Care Centers. | - No eligible outcomes reported<br>*Ivermectin Regimen was not comparable to other studies either* |
| Chahla Rossana, Elena, Ruiz Luis, Medina, Mena, Teresa et al. IVERMECTIN REPROPOSING FOR COVID-19 TREATMENT OUTPATIENTS IN MILD STAGE IN PRIMARY HEALTH CARE CENTERS. medrxiv preprint | - Duplicate reference |
| Chahla Rossana, Elena, Ruiz Luis, Medina, Ortega Eugenia, Silvana et al. A RANDOMIZED TRIAL - INTENSIVE TREATMENT BASED IN IVERMECTIN AND IOTA-CARRAGEENAN AS PRE-EXPOSURE PROPHYLAXIS FOR COVID- 19 IN HEALTHCARE AGENTS. medrxiv preprint | - Irrelevant |
| Chahla, Rossana Elena, Ruiz, Luis Medina, Mena, Teresa et al. (2022) Cluster Randomised Trials - Ivermectin Repurposing for Covid-19 Treatment of Outpatients with Mild Disease in Primary Health Care Centers . | - Duplicate reference |

| Study | Reason for exclusion |
|---|---|
| Cruciani, M., Pati, I., Masiello, F. et al. (2021) Ivermectin for prophylaxis and treatment of covid-19: A systematic review and meta-analysis. Diagnostics 11(9): 1645 | - Systematic review used as source of primary studies |
| Deng, J., Zhou, F., Ali, S. et al. (2021) Efficacy and safety of ivermectin for the treatment of COVID-19: A systematic review and meta-analysis. QJM 114(10): 721-732 | - Systematic review used as source of primary studies |
| Galan, Luis Enrique Bermejo, Santos, Nayara Melo Dos, Asato, Mauro Shosuka et al. (2021) Phase 2 randomized study on chloroquine, hydroxychloroquine or ivermectin in hospitalized patients with severe manifestations of SARS-CoV-2 infection. Pathogens and global health 115(4): 235-242 | - Comparator in study does not match that specified in protocol<br>*Exclude on basis of no relevant active comparator of proven efficacy plus phase 2.* |
| Gonzalez Jose Lenin, Beltran-Gonzalez, Gamez Mario, Gonzalez-Gamez, Enciso Emmanuel-Antonio, Mendoza-Enciso et al. Efficacy and safety of Ivermectin and Hydroxychloroquine in patients with severe COVID-19. A randomized controlled trial. medrxiv preprint | - Pre-print now published |
| Hill, Andrew, Garratt, Anna, Levi, Jacob et al. (2021) Meta-analysis of Randomized Trials of Ivermectin to Treat SARS-CoV-2 Infection. Open forum infectious diseases 8(11): ofab358 | - Retracted study |
| Karale, Smruti, Bansal, Vikas, Makadia, Janaki et al. (2021) An Updated Systematic Review and Meta-Analysis of Mortality, Need for ICU admission, Use of Mechanical Ventilation, Adverse effects and other Clinical Outcomes of Ivermectin Treatment in COVID-19 Patients. | - Systematic review used as source of primary studies |
| Kirti, Ravi, Roy, Ranjini, Pattadar, Chandrima et al. Ivermectin as a potential treatment for mild to moderate COVID-19: A double blind randomized placebo-controlled trial. medrxiv preprint | - Duplicate reference<br>*This is a pre-print of the full publication, which we have included.* |
| Krolewiecki, Alejandro, Lifschitz, Adrian, Moragas, Matias et al. (2021) Corrigendum to Antiviral effect of high-dose ivermectin in adults with COVID-19: A proof-of-concept randomized trial [EClinicalMedicine 37 (2021) 100,959]". EClinicalMedicine 39: 101119 | - Duplicate reference<br>*This is a correction to an article we already included.* |
| Marcolino, Milena Soriano, Meira, Karina Cardoso, Guimar?es, Nathalia Sernizon et al. (2022) Systematic Review and Meta-analysis of Ivermectin for Treatment of COVID-19: Evidence Beyond the Hype. | - Systematic review used as source of primary studies |
| Marcolino, Milena Soriano, Meira, Karina Cardoso, Guimaraes, Nathalia Sernizon et al. (2022) Systematic Review and Meta-analysis of Ivermectin for Treatment of COVID-19: Evidence Beyond the Hype . | - Duplicate reference |
| Niaee MS; Gheibi N; Namdar PEA (2020) Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial. PREPRINT (Research Square) | - Duplicate reference |
| Okumus, Nurullah, Demirturk, Nese, Cetinkaya, Riza Aytac et al. (2021) Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients. BMC infectious diseases 21(1): 411 | - Not a relevant study design<br>*Concerns over randomisation methods and whether the standard care is relevant to the UK:In patients meeting the inclusion criteria, the distinction between study and control groups was made by a single-blind randomized method. Starting from the first patient included in the study,* |

| Study | Reason for exclusion |
|---|---|
| | *patients with odd numbers were grouped as the study group, and patients with even numbers as the control group.* |
| Padhy, B.M., Mohanty, R.R., Das, S. et al. (2020) Therapeutic potential of ivermectin as add-on treatment in COVID 19: A systematic review and meta-analysis. Journal of Pharmacy and Pharmaceutical Sciences 23: 462-469 | - Systematic review used as source of primary studies |
| Pott-Junior, Henrique, Paoliello, Monica Maria Bastos, Miguel, Alice de Queiroz Constantino et al. (2021) Use of ivermectin in the treatment of Covid-19: A pilot trial. Toxicology reports 8: 505-510 | - Retracted study |
| rajan, ravichandran, Surapaneni Krishna, Mohan, Sukumaran Suresh, Kumar et al. Use of Indomethacin for mild and moderate Covid -19 patients. A Randomized Control Trial. medrxiv preprint | - Comparator in study does not match that specified in protocol<br>*No relevant active comparator of proven efficacy.* |
| Reis, Gilmar, Dos Santos Moreira-Silva, Eduardo Augusto, Silva, Daniela Carla Medeiros et al. (2022) Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. The Lancet. Global health 10(1): e42-e51 | - Duplicate reference |
| Roman, Y.M., Burela, P.A., Pasupuleti, V. et al. (2022) Ivermectin for the Treatment of Coronavirus Disease 2019: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Clinical Infectious Diseases 74(6): 1022-1029 | - Systematic review used as source of primary studies |
| Samaha, Ali A, Mouawia, Hussein, Fawaz, Mirna et al. (2021) Effects of a Single Dose of Ivermectin on Viral and Clinical Outcomes in Asymptomatic SARS-CoV-2 Infected Subjects: A Pilot Clinical Trial in Lebanon. Viruses 13(6) | - Retracted study |
| Shoumann, Waheed M., Nafae, Ramadan M., Ragab, Moustafa I. et al. (2021) Use of ivermectin as a potential chemoprophylaxis for covid-19 in egypt: A randomised clinical trial. Journal of Clinical and Diagnostic Research 15(2): oc27-oc32 | *- Does not meet eligible population (of suspected or confirmed COVID-19) as defined in protocol. Study included asymptomatic household close contacts to confirmed RT-PCR COVID-19 index case. Contacts who developed symptoms or were diagnosed with COVID-19 before enrolment were excluded.* |

# Appendix F: Evidence tables

### Abbas K, 2022

| | |
|---|---|
| **Bibliographic Reference** | Abbas K, U; Muhammad, S; Ding S, F; The Effect of Ivermectin on Reducing Viral Symptoms in Patients with Mild COVID-19; Indian Journal of Pharmaceutical Sciences; 2022; vol. 84; 87-91 |

### Study details

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Study start date** | 01-May-2021 |
| **Study end date** | 31-Aug-2021 |
| **Aim of the study** | to investigate the effect of ivermectin on reducing viral symptoms in patients with mild COVID-19. |
| **Country/ Geographical location** | China |
| **Population description** | Patients aged 18-50 years with mild COVID-19 in community |
| **Inclusion criteria** | Inclusion criteria include patients with COVID-19 aged 18 to 50 year |
| **Exclusion criteria** | Exclusion criteria includes history of treatment with steroid drugs during the last week, concomitant use of anticoagulants, history of any allergies to the studied drugs, history of recent bleeding for any reason, patients with chronic diseases such as cardiovascular disease |
| **Intervention/test/approach** | Ivermectin 300 µg/ kg body weight per day for 5 days |
| **Comparator (where applicable)** | 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 provided by the manufacturer |
| **Methods for population selection/allocation** | Random selection<br>Patients were divided into two groups according to a random list generated, using random blocks of 100 volumes. In order to conceal (maintain the randomization process) doctor and data analyser were unaware of patient grouping |
| **Methods of data analysis** | Mann- Whitney and Wilcoxon test<br>T-test<br>Chi-square test |
| **Attrition/loss to follow-up** | Results are reported for 202 patients<br>103 in control group<br>99 in ivermectin group<br>lack of information on loss to follow-up |
| **Summary of findings** | Time of symptoms reduction in ivermectin group was less than placebo, but no statistically significant difference was observed (p=0.08)<br>A small number of patients scored two on the 8-point scale and had clinical deterioration. There was no significant |

| | |
|---|---|
| | difference between the two treatment groups in terms of deterioration score (p=0.09). |
| **Study limitations (Author)** | Author reported one of the limitations about drug dose used, which was considered in clinical trials due to United States (US) food laws and drug tolerance, and was several times lower than the effective cases. Another limitation reported by authors was that ivermectin plasma levels were not measured. |
| **Study limitations (Reviewer)** | relatively younger population to be considered for high risk of progression to severe disease<br>Incomplete information on loss to follow-up<br>discrepancies in total numbers in abstract and result section |
| **Other details** | patient's information was recorded by a structured telephone interview with a physician every 3 d. In both groups, the drug was given to the patients and the patient was instructed to take the drug twice a day. Patients were evaluated for response to treatment on d 4, d 7, d 12, d 18 and d 20 of treatment and compared with patients on the day of treatment (d 0) |

**Study arms**
**Ivermectin (N = 99)**
Ivermectin 300 µg/ kg body weight per day for 5 days

**Placebo (N = 103)**
Placebo: a mixture of 5 % dextrose in saline and 5 % dextrose in distilled water

**Characteristics**
**Arm-level characteristics**

| Characteristic | Ivermectin (N = 99) | Placebo (N = 103) |
|---|---|---|
| **Age**<br>Mean (SD) | 38.33 (6.84) | 37.33 (5.84) |
| **Male**<br>No of events | n = 47 ; % = 47.4 | n = 43 ; % = 42.3 |
| **Female**<br>No of events | n = 52 ; % = 52.6 | n = 60 ; % = 57.7 |

**Outcomes**
**Primary and Secondary Outcomes**

| Outcome | Ivermectin , , N = 99 | Placebo, , N = 103 |
|---|---|---|
| **Time of resolution of symptoms** (days)<br>Median (IQR) | 9 (8 to 12) | 13 (10 to 14) |
| **symptoms resolved**<br>Yes<br>No of events | n = 73 ; % = 73.6 | n = 61 ; % = 59.3 |
| **Deterioration of 2 or more points**<br>8 point score WHO<br>No of events | n = 4 ; % = 4.1 | n = 7 ; % = 6.7 |

| Outcome | Ivermectin , , N = 99 | Placebo, , N = 103 |
|---|---|---|
| **Death %**<br>Apgar Score<br>No of events | n = 1 ; % = 1.01 | n = 1 ; % = 0.99 |

### Abd-Elsalam, 2021

| | |
|---|---|
| **Bibliographic Reference** | Abd-Elsalam, Sherief; Noor, Rasha A; Badawi, Rehab; Khalaf, Mai; Esmail, Eslam S; Soliman, Shaimaa; Abd El Ghafar, Mohamed S; Elbahnasawy, Mohamed; Moustafa, Ehab F; Hassany, Sahar M; Medhat, Mohammed A; Ramadan, Haidi Karam-Allah; Eldeen, Maii A S; Alboraie, Mohamed; Cordie, Ahmed; Esmat, Gamal; Clinical study evaluating the efficacy of ivermectin in COVID-19 treatment: A randomized controlled study.; Journal of medical virology; 2021; vol. 93 (no. 10); 5833-5838 |

### Study details

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Trial registration (if reported)** | NCT04403555 |
| **Study start date** | Mar-2020 |
| **Study end date** | Oct-2020 |
| **Aim of the study** | To evaluate the efficacy of ivermectin for the treatment of hospitalised mild-moderate COVID-19 patients |
| **Country/ Geographical location** | Egypt |
| **Study setting** | Hospitalised patients |
| **Population description** | This study included data from 164 patients with 84 assigned to each treatment arm.<br>The mean age for participants in Group 1 was 42.38 years (16.02 SD) and in group 2 39.38 ( 16.92 SD).<br>Males made up 45% of group 1and 54.9% of group 2.<br>Patients with mild to moderate COVID-19 in hospital setting |
| **Inclusion criteria** | Adults aged between 20 years - 65 years old<br>Patients with mild to moderate COVID-19 disease (RT-PCR confirmed) |
| **Exclusion criteria** | Patients who had an allergy or contraindication to drugs used in study<br>Pregnant and lactating mothers<br>Patients with cardiac problems |
| **Intervention/test/approach** | Single-dose of oral ivermectin (12mg) everyday for 3 days alongside standard care |
| **Comparator (where applicable)** | Standard care alone for 14 days |
| **Methods for population selection/allocation** | Patients were randomised using a computer number generator and equal allocation ratio (1:1). Sequentially numbered, opaque, sealed envelopes were used to ensure |

| | |
|---|---|
| | concealment. Three members of the study team recruited, enrolled, and assigned participants to a computer-generated randomisation sequence, held by an independent observer. During randomisation, the proportional allocation of each clinical stratum was equalised in both groups. The included patients were first stratified according to their age (18–25, 26–40, 40–55, and >55), then by their gender (inside each stratum into males and females) and then their associated morbidities (absent and present). |
| **Methods of data analysis** | The primary analysis was done based on an intention-to-treat basis including all randomly assigned individuals. The study included all the eligible patients who agreed to participate. The calculated post hoc sample power was 0.80 based the following inputs: two-tailed sample power, 0.44 effect size, 0.05 α error probability, and 82 as the sample size in each group (the outputs were: 3.02 as noncentrality parameter $\delta$, 1.97 as critical $t$, 162 as $df$). The normality of the variables was tested by the Shapiro–Wilks test. Data were analyzed by Statistical Package for Social Sciences (SPSS) V. 23 and were expressed in number (No), percentage (%) mean ($\overline{x}$), and standard deviation ($SD$). Student's $t$-test was used for normally distributed continuous variables and Mann–Whitney's test for not normally distributed variables. A $\chi 2$ test (with $Z$ test to compare column proportions) was used to study the association between categorical variables, and whenever any of the expected cells were less than five, Fisher's Exact test was used. Binary logistic regression was used to ascertain the effect of the potential l risk factors on the patients' mortality. The regression model was a simple one including one variable at each time. The included risk factors were age, gender, smoking, alanine aminotransferase (ALT), albumin, creatinine, ferritin, C-reactive protein (CRP), need for mechanical ventilation, diabetes mellitus, and ivermectin treatment. All the variables were continuous except for gender, smoking, need for mechanical ventilation, presence of diabetes, and treatment with ivermectin (each was of two categories only). Two-sided $p$ value of less than 0.05 was considered statistically significant. |
| **Attrition/loss to follow-up** | Not reported |
| **Source of funding** | Not reported |
| **Study limitations (Author)** | Small ivermectin dose, small sample size and lack of blinding and lack of a placebo group. |
| **Study limitations (Reviewer)** | The study did not include a placebo group and included a small sample size |
| **Other details** | NA |

**Study arms**
**Ivermectin (N = 82)**

**Control (N = 82)**

### Characteristics
### Arm-level characteristics

| Characteristic | Ivermectin (N = 82) | Control (N = 82) |
|---|---|---|
| **Age**<br>Mean (SD) | 42.38 (16.02) | 39.38 (16.92) |
| **Male**<br>No of events | n = 37 ; % = 45.1 | n = 45 ; % = 54.9 |
| **Female**<br>No of events | n = 45 ; % = 54.9 | n = 37 ; % = 45.1 |
| **Comorbidities**<br>No of events | n = 36 ; % = 43.9 | n = 45 ; % = 54.9 |
| **Hypertension**<br>No of events | n = 18 ; % = 21.9 | n = 14 ; % = 17.1 |
| **Diabetes**<br>No of events | n = 17 ; % = 20.7 | n = 10 ; % = 12.2 |

### Outcomes
### Clinical course

| Outcome | Ivermectin, , N = 82 | Control, , N = 82 |
|---|---|---|
| **Mortality**<br>No of events | n = 3 ; % = 3.7 | n = 4 ; % = 4.9 |
| **Length of hospital stay** (days)<br>Mean (SD) | 8.82 (4.94) | 10.97 (5.28) |
| **Need for mechanical ventilation**<br>No of events | n = 3 ; % = 3.7 | n = 3 ; % = 3.7 |

### Adverse events

| Outcome | Ivermectin, , N = 82 | Control, , N = 82 |
|---|---|---|
| **Mild side effects**<br>No of events | n = 3 ; % = 3.7 | n = 0 ; % = 0 |

## Ahmed, 2021

| | |
|---|---|
| **Bibliographic Reference** | Ahmed, Sabeena; Karim, Mohammad Mahbubul; Ross, Allen G; Hossain, Mohammad Sharif; Clemens, John D; Sumiya, Mariya Kibtiya; Phru, Ching Swe; Rahman, Mustafizur; Zaman, Khalequ; Somani, Jyoti; Yasmin, Rubina; Hasnat, Mohammad Abul; Kabir, Ahmedul; Aziz, Asma Binte; Khan, Wasif Ali; A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness.; International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases; 2021; vol. 103; 214-216 |

### Study details

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Trial registration (if reported)** | Not reported |

| | |
|---|---|
| **COVID-19 prevalence at the time of the study** | Unclear |
| **Aim of the study** | To determine the rapidity of viral clearance and safety of ivermectin among adults with COVID-19 diagnosis. |
| **Country/ Geographical location** | Bangladesh |
| **Study setting** | Hospital |
| **Population description** | Adults aged 18–65 years hospitalised for COVID-19, confirmed by positive RT-PCR |
| **Inclusion criteria** | Age 18-65 years<br>Admitted to the hospital within last 7 days<br>Presence of a fever, cough and or sore throat<br>Diagnosed positive for SARS-CoV-2 by RT-PCR |
| **Exclusion criteria** | Allergy to ivermectin or doxycycline<br>If there was a potential for a drug-drug interaction with ivermectin or doxycycline<br>Chronic illnesses<br>Received ivermectin and/or doxycycline in the last 7 days<br>Pregnant or lactating<br>Participated in another clinical trial within the last month |
| **Intervention/test/approach** | Oral ivermectin alone (12mg once daily) for 5 days<br>Ivermectin combined with doxycycline (12mg ivermectin single dose and 200mg doxycycline on day 1 followed by 100mg every 12 hours for 4 more days) |
| **Comparator (where applicable)** | Placebo/control |
| **Methods for population selection/allocation** | Not reported |
| **Methods of data analysis** | Data were entered into SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA) |
| **Attrition/loss to follow-up** | Not reported |
| **Summary of findings** | Virological clearance was earlier in the 5-day ivermectin treatment arm when compared to the placebo group, but this was not the case for ivermectin+doxycycline arm. There were no severe adverse drug events recorded in the study |
| **Source of funding** | Beximco Pharmaceutical Limited, Bangladesh |
| **Study limitations (Author)** | Sample size for the study was small |
| **Study limitations (Reviewer)** | Sample size of the study was small. Details on methodology, randomisation and allocation concealment, and data analysis were not clear. No information on baseline characteristics for participants was provided. Overall, the study reported minimal detail on methodology and analysis of results so the lack of raw data from the authors makes it difficult to develop appropriate analysis plan. |
| **Other details** | The study was published as a short publication |

**Study arms**

**Ivermectin (N = 22)**

**Placebo (N = 23)**

### Characteristics
### Study-level characteristics

| Characteristic | Study (N = 69) |
|---|---|
| **Age**<br>Mean (SD) | 42 (*empty data*) |
| **Gender**<br>Female %<br>No of events | % = 54 |

### Outcomes
### Outcomes

| Outcome | Ivermectin, , N = 22 | Placebo, , N = 23 |
|---|---|---|
| **Duration of Hospitalisation** (days)<br>Mean (95% CI) | 9.6 (7.7 to 11.7) | 9.7 (8.1 to 11) |
| **Duration to virological clearance**<br>Mean (95% CI) | 9.7 (7.8 to 11.8) | 12.7 (11.3 to 14.2) |
| **Adverse events**<br>No of events | n = 0 ; % = 0 | n = 0 ; % = 0 |
| **Number of patients requiring oxygen**<br>No of events | n = 0 ; % = 0 | n = 0 ; % = 0 |

## Beltran, 2022

| | |
|---|---|
| **Bibliographic Reference** | Beltran, Gonzalez; Jose, Lenin; Gonzalez, Gamez; Mario; Mendoza Enciso Emanuel, Antonio; Esparza, Maldonado; Ramiro, Josue; Hernandez, Palacios; Daniel; Duenas, Campos; Samuel; Robles Itzel, Ovalle; Macias, Guzman; Mariana, Jocelyn; Garcia, Diaz; Andrea, Lucia; Gutierrez, Pena; Cesar, Mauricio; Martinez, Medina; Lucila; Monroy, Colin; Victor, Antonio; Arreola Guerra Jose, Manuel; Efficacy and Safety of Ivermectin and Hydroxychloroquine in Patients with Severe COVID-19: A Randomized Controlled Trial.; Infectious disease reports; 2022; vol. 14 (no. 2); 160-168 |

### Study details

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Trial registration (if reported)** | NCT04391127 |
| **Study end date** | 15-Aug-2020 |
| **Aim of the study** | The aim of the study is to evaluate the efficacy and safety of hydroxychloroquine and ivermectin in hospitalised patients with moderate pneumonia secondary to COVID-19. |

| | |
|---|---|
| **Country/ Geographical location** | Mexico |
| **Study setting** | Hospital Centenario Miguel Hidalgo |
| **Population description** | Hospitalised patients with pneumonia secondary to SARS-CoV-2 infection and met following criteria for hospitalisation<br><br>• severity of clinical presentation (determined with the CURB-65 scoring system),<br>• need for supplemental oxygen,<br>• comorbidities, and laboratory markers suggesting a poor prognosis (High D-Dimer, Ferritin, Troponin, Creatinine)<br>• Patients with QT interval of ≥500ms [randomised to receive ivermectin or placebo, while patients with <500ms were randomised to ivermectin, hydroxychloroquine or placebo] |
| **Inclusion criteria** | The patients included in the study had to fulfil the operational definition of a suspected or confirmed COVID-19 case as well as the pneumonia American Thoracic Society criteria. The following patients were considered:<br><br>(1) positive RT-PCR for SARS-CoV-2 by nasal and oropharyngeal swabbing,<br><br>(2) pneumonia, diagnosed by an X-ray or high-resolution chest computed tomography (CT) scan, with a pattern suggesting involvement due to coronavirus, and<br><br>(3) recently established hypoxemic respiratory failure or acute clinical deterioration of pre-existing lung or heart disease |
| **Exclusion criteria** | Patients were excluded:<br><br>1. if they required high oxygen volumes (face mask > 10 L/ min),<br>2. if they had predictors of a poor response to high-flow oxygen nasal prong therapy, or<br>3. if they required mechanical ventilation<br><br>In the absence of these exclusion criteria, patients were included regardless of other risk factors for poor prognosis. |
| **Intervention/test/approach** | The dose of ivermectin was 12 mg in patients weighing less than 80 kg and 18 mg in those above 80 kg |
| **Comparator (where applicable)** | Calcium citrate was chosen as a placebo and was administered as 2 tablets every 12 h on the first day, followed by one tablet every 12 h for the following 4 days |

| | |
|---|---|
| | All patients received pharmacological thromboprophylaxis with low molecular weight heparin or unfractionated heparin<br><br>Since last week of June 2020, patients requiring oxygen therapy also received dexamethasone, 6mg IV every 24h for 10 days or until discharge |
| **Methods for population selection/allocation** | Allocation: randomised to one of the three groups: Group 1—hydroxychloroquine, 400 mg every 12 h on the first day and, subsequently, 200 mg every 12 h for 4 days (data not used in this) ; Group 2—ivermectin, 12 mg or 18 mg, according to patient weight; and Group 3—placebo<br><br>Randomisation methods not reported |
| **Methods of data analysis** | Outcomes of death and respiratory deterioration - Survival analysis with Kaplan-Meier curves<br><br>Between group comparison - Log rank test |
| **Attrition/loss to follow-up** | 108 recruited in total<br><br>• 2 were removed due to transfer to another hospital (not clear which arm) |
| **Source of funding** | Centenario Hospital Miguel Hidalgo |
| **Study limitations (Author)** | • limited number of patients per group and low statistical power shown in important outcomes such as death (25%); also, among the pre-established outcomes<br>• Authors were unable to determine whether the SARS-CoV-2 PCR tests became negative, due to the lack of reactants and the minimal usefulness of proving its negativity from a clinical-practical viewpoint. |
| **Other details** | |

**Study arms**
**Ivermectin (N = 36)**
12 mg in patients with weight<80 kg 18mg in patients with weight>80kg

**Placebo (N = 37)**
Calcium citrate

**Characteristics**
**Arm-level characteristics**

| Characteristic | Ivermectin (N = 36) | Placebo (N = 37) |
|---|---|---|
| **Age** (years)<br>Mean (SD)<br>Mean (SD) | 56 (16.5) | 53.8 (16.9) |
| **Males** (n (%))<br>No of events | n = 21 ; % = 58.3 | n = 23 ; % = 62.1 |

| Characteristic | Ivermectin (N = 36) | Placebo (N = 37) |
|---|---|---|
| **Diabetes mellitus** (n (%))<br>No of events | n = 9 ; % = 25 | n = 16 ; % = 43.2 |
| **SAH** (n (%))<br>Systemic Arterial Hypertension<br>No of events | n = 12 ; % = 33.3 | n = 14 ; % = 37.8 |
| **CKD** (n (%))<br>Chronic Kidney Disease<br>No of events | n = 2 ; % = 5.5 | n = 1 ; % = 2.7 |
| **COPD** (n (%))<br>Chronic Obstructive Pulmonary Disease<br>No of events | n = 2 ; % = 5.5 | n = 4 ; % = 10.8 |
| **Weight** (kg)<br>Mean (SD) | 80 (19.7) | 82 (18.2) |
| **BMI** (Mean (SD))<br>Mean (SD) | 29.2 (7) | 29.4 (6.6) |
| **Days symptom onset** (days)<br>Median (IQR) | 6 (4 to 10) | 7 (5 to 10) |
| **Days of +RT-PCR** (days)<br>Median (IQR) | 1 (0 to 2) | 1 (1 to 2) |

**Outcomes**
**Outcomes**

| Outcome | Ivermectin, , N = 36 | Placebo, , N = 37 |
|---|---|---|
| **Duration of Hospitalisation** (days)<br>Median (IQR) | 6 (4 to 11) | 5 (4 to 7) |
| **Hospital Discharge** (n (%))<br>Hospital discharge was considered when the patient fulfilled the following criteria: absence of neurologic complications, no fever, hemodynamic stability over at least the previous 72 h, minimal oxygen requirements (nasal prongs at 1–2 L per minute), and the availability of a well-established social support network.<br>No of events | n = 32 ; % = 88.8 | n = 34 ; % = 91.8 |
| **Discharge without respiratory deterioration or death** (n (%))<br>No of events | n = 27 ; % = 75 | n = 27 ; % = 72.9 |
| **Respiratory deterioration or death** (n (%))<br>No of events | n = 8 ; % = 22.2 | n = 9 ; % = 24.3 |
| **Death** (n (%))<br>No of events | n = 5 ; % = 13.8 | n = 6 ; % = 16.2 |

## Biber et al.

| | |
|---|---|
| **Bibliographic Reference** | Biber, Asaf; Mandelboim, Michal; Harmelin, Geva; Lev, Dana; Ram, Li; Shaham, Amit; Nemet, Ital; Kliker, Limor; Erster, Oran; Schwartz, Eli; |

Favorable outcome on viral load and culture viability using Ivermectin in early treatment of non-hospitalized patients with mild COVID-19, A double-blind, randomized placebo-controlled trial.; medrxiv preprint

## Study details

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Trial registration (if reported)** | NCT044297411 |
| **Study start date** | 15-May-2020 |
| **Study end date** | Jan-2021 |
| **COVID-19 prevalence at the time of the study** | Unclear |
| **Aim of the study** | To assess whether ivermectin can shorten the viral shedding phase in patients with early COVID-19 |
| **Country/ Geographical location** | Israel |
| **Study setting** | Non-hospitalised |
| **Population description** | A total of 116 patients underwent randomisation but only 89 were eligible for analysis. The median age of patients was 35 years (range 20-71 years). 22.4% of participants were 50 years or older and 7.8% were 60 years or older. The majority of patients were males (78.4%) and 13.5% of patients had comorbidities associated with risk for severe disease. |
| **Inclusion criteria** | Patients aged 18 years or older<br>Laboratory confirmed diagnosis of COVID-19 |
| **Exclusion criteria** | Pregnancy<br>Weighed less than 40kg<br>With known allergy to drug<br>Unable to take oral medication<br>Participating in another trial for treatment of COVID-19<br>Patients with RT-PCR results with cycle threshold value >35 |
| **Intervention/test/approach** | Oral ivermectin according to body weight (12mg for people weighing between 40-69kg), patients weighing greater than or equal to 70 kg received 15mg daily; all for 3 days |
| **Comparator (where applicable)** | Placebo |
| **Methods for population selection/allocation** | Randomisation was completed using a computer-generated program and the clinical research coordinator blinded the rest of the study team. Participants were randomised in a 1:1 ratio |
| **Methods of data analysis** | Based on published data from the Ministry of Health at the time of study initiation, it was expected that expected less than 10% of patients at day six show a negative RT-PCR test. With the interventional drug we expected a reduction of at least 25% in the proportion of positive cases. Hence, considering a potential decrease from 90% to 67·5% (25% decrease), with a power (1-β) of 80% at a significance level of 5% (α= 0·05), a minimal sample size of 96 participants in total, was required to detect a statistically significant |

| | |
|---|---|
| | difference. Therefore, 48 patients were needed in each study arm. To account for a loss to follow-up of 10% after 14 day, we aimed to recruit a total of 105 participants. Statistical analysis was done by the Biostatistics and Biomathematics Unit, Gertner Institute, Sheba Medical Center, Tel-Hashomer, Israel. Continuous variables are presented as mean ± standard deviation or as median and interquartile range. Categorical variables are presented as N (%). Differences between ivermectin and placebo groups were assessed using a Chi square test and t-test, for categorical and continuous data respectively. Where cross-tabulation frequencies were less than 5, the Fisher exact test was used. A multivariate logistic regression model was used to determine the impact of ivermectin while controlling for age, sex, weight, and being symptomatic or not on reduction of viral load on day 6 as reflected by Cycle threshold (Ct) level>30. Results include adjusted odds ratios (OR), and 95% confidence intervals (CI). Kaplan Meier curves were drawn, and survival analysis conducted with log-rank test using for time to negative RT-PCR (Ct level>30) result. Boxplots were produced in R version 4·0·2. For figure readability, viral load values were log-transformed. For all analyses, significance was set at p < 0·05. All data analyses were performed with the SAS 9·4 software (Cary, NC, USA). |
| **Attrition/loss to follow-up** | 3 participants were lost to follow up in each treatment arm |
| **Summary of findings** | |
| **Study limitations (Author)** | The study had a small sample size and was only designed to look for differences in viral load and not clinical deterioration or prevention of hospitalisation. Secondly, drug therapy was not observed by the investigators physically. As the study was conducted in mild-moderate non-hospitalised patients the results cannot be applied to a more severe or immune-suppressed population. |
| **Study limitations (Reviewer)** | The study had a small population size and did not account for important confounding factors such as previous or existing therapy for COVID-19. |
| **Other details** | None |

### Study arms
**Ivermectin (N = 47)**

**Placebo (N = 42)**

### Characteristics
**Arm-level characteristics**

| Characteristic | Ivermectin (N = 47) | Placebo (N = 42) |
|---|---|---|
| **Age**<br>Median (IQR) | 35 (28 to 47) | 36 (32 to 50) |
| **Male**<br>No of events | n = 36 | n = 33 ; % = 78.6 |

| Characteristic | Ivermectin (N = 47) | Placebo (N = 42) |
|---|---|---|
| **Weight (median; IQR)**<br>Median (IQR) | 80 (70 to 90) | 75 (67 to 85) |

### Outcomes
### Ivermectin vs placebo

| Outcome | Ivermectin, , N = 47 | Placebo, , N = 42 |
|---|---|---|
| **Viral clearance within 7-12 days**<br>No of events | n = 40 ; % = 85 | n = 29 ; % = 69.1 |
| **Number of patients requiring oxygen**<br>No of events | n = 0 ; % = 0 | n = 1 ; % = 2.4 |
| **Hospitalisation**<br>No of events | n = 1 ; % = 2.1 | n = 3 ; % = 7.1 |
| **Adverse events**<br>No of events | n = 2 ; % = 3.5 | n = 3 ; % = 5.1 |

## Bukhari (preprint)

| | |
|---|---|
| **Bibliographic Reference** | Bukhari Syed Karamat Hussain, Shah; Asghar, Asma; Perveen, Najma; Hayat, Arshad; Mangat Sermad, Ahmad; Butt Kamil, Rehman; Abdullah, Mohammad; Fatima, Tehreem; Mustafa, Ahmad; Cheema, Talal; Merrill, Anna; Perlman, Stanley; Knudson, Mike; Kalyani, Suraj; Raut, Prathamesh; Bapte, Madhura; Mehta, Anshul; Reddy M, Sateesh; Bhayani, Krushnadas; Laxmi S, S; Vishnu P, D; Srivastava, Shipra; Khandelwal, Shubham; More, Sailee; Shinde, Rohit; Pawar, Mohit; Harshe, Amol; Kadam, Sagar; Mahajan, Uma; Joshi, Gaurav; Mane, Dilip; Efficacy of Ivermectin in COVID-19 Patients with Mild to Moderate Disease; medrxiv preprint |

### Study details

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Trial registration (if reported)** | NCT04392713 |
| **Study start date** | 15-Mar-2020 |
| **Study end date** | 15-Jun-2020 |
| **Aim of the study** | To evaluate the efficacy of ivermectin as an addition to standard of care treatment in COVID-19 patients with mild to moderate disease |
| **Country/ Geographical location** | Pakistan |
| **Population description** | Adults aged 15-65 with confirmed RT-PCR COVID-19 and mild to moderate disease severity |
| **Inclusion criteria** | Adults aged 15-65<br>Confirmed COVID-19 by RT-PCR<br>Mild to moderate disease |

| | |
|---|---|
| | Patients who were eligible to consent for the trial and comply with study procedures |
| **Exclusion criteria** | Pregnant women<br>Patients with severe symptoms<br>Patients with uncontrolled comorbidities and immunocompromised<br>Patients with a history of ivermectin allergy<br>Patients taking CYP 3A4 inhibitors or inducers<br>Patients with oxygen requirements greater than or equal to 50% |
| **Intervention/test/approach** | Single-dose ivermectin (12mg) alongside standard care |
| **Comparator (where applicable)** | Standard of care treatment (includes vitamin C once daily, vitamin D once weekly and paracetamol) |
| **Methods for population selection/allocation** | Unblinded, open label study were participants were randomised in a 1:1 ratio via a lottery method |
| **Methods of data analysis** | The data was entered and analysed using SPSSv25 for relevant statistical tests of significance at a 95% confidence interval and p-values ≤ 0.05 were considered significant. No further information on statistical methods. |
| **Attrition/loss to follow-up** | 5 participants in control arm were lost to follow up<br>9 participants in intervention arm were lost to followup |
| **Summary of findings** | Early viral clearance was observed in people treated with ivermectin with minimal side effects. |
| **Source of funding** | None |
| **Study limitations (Author)** | The duration and severity of individual symptoms and time of resolution of these symptoms were not studied. Most of the patients were lost to follow up after the trial period concluded and very few could be traced back to assess for any potential adverse reaction that may have occurred due to treatment with ivermectin, hence prolonged safety of drug could not be established. However, no side effects were noted during the trial period and ivermectin was well tolerated. The majority of results were from males and so may not be generalisable. |
| **Study limitations (Reviewer)** | The study included a small population, with limited information on baseline characteristics. There was also no provision of a detailed analysis plan or development of models to mitigate confounding or other biases. Lastly, this was an unblinded trial and so there are some concerns with performance bias. |
| **Other details** | SARS-CoV-2 RT-PCR was repeated at 72 hours, on day 7, and day 14 post-admission. Complete blood count, renal and liver function tests were done at recruitment day, 72 hours, at day 7, and at day 14, to monitor for derangements in any lab parameters. Adverse reactions (i.e., pruritus, fever, rash, myalgia, headache), ocular symptoms, gastrointestinal symptoms, neurological symptoms, joint problems were monitored daily.<br>Patients were discharged after 14 days with a single negative PCR result or when they had 2 negative PCR results. All patients were then followed up with a telephonic interview on the 28th day and questions pertaining to general health and |

| | |
|---|---|
| | the possible development of any side effects to ivermectin were inquired. |

**Study arms**
**Ivermectin (N = 41)**

**Standard care (N = 45)**

**Characteristics**
**Arm-level characteristics**

| Characteristic | Ivermectin (N = 41) | Standard care (N = 45) |
|---|---|---|
| **Age**<br>Mean (SD) | 38.98 (12.61) | 42.24 (12) |
| **Male**<br>No of events | n = 36 ; % = 80 | n = 37 ; % = 90.2 |
| **Female**<br>No of events | n = 9 ; % = 20 | n = 4 ; % = 9.8 |
| **Diabetes**<br>No of events | n = 4 ; % = 8.9 | n = 6 ; % = 14.6 |
| **Hypertension**<br>No of events | n = 7 ; % = 15.6 | n = 5 ; % = 12.2 |
| **Ischaemic heart disease**<br>No of events | n = 2 ; % = 4.4 | n = 3 ; % = 7.3 |

**Outcomes**
**Outcomes**

| Outcome | Ivermectin, , N = 41 | Standard care, , N = 45 |
|---|---|---|
| **Virological clearance within 7-12 days**<br>No of events | n = 37 ; % = 90.2 | n = 20 ; % = 44.4 |
| **Adverse events**<br>No of events | n = 0 ; % = 0 | n = 0 ; % = 0 |

**Buonfrate, 2022**

| | |
|---|---|
| **Bibliographic Reference** | Buonfrate, D; Chesini, F; Martini, D; Roncaglioni M, C; Ojeda Fernandez, M.L; Alvisi M, F; De Simone, I; Rulli, E; Nobili, A; Casalini, G; Antinori, S; Gobbi, M; Campoli, C; Deiana, M; Pomari, E; Lunardi, G; Tessari, R; Bisoffi, Z; High-dose ivermectin for early treatment of COVID-19 (COVER study): a randomised, double-blind, multicentre, phase II, dose-finding, proof-of-concept clinical trial; International Journal of Antimicrobial Agents; 2022; 106516 |

**Study details**

| | |
|---|---|
| **Trial registration (if reported)** | Randomised double-blind Phase II trial (NCT04438850) |
| **Study start date** | 31-Jul-2020 |

| | |
|---|---|
| **Study end date** | 26-May-2021 |
| **Aim of the study** | The aim of this study was to assess the efficacy and safety of high doses of ivermectin (namely doses of 600 micrograms/kg and 1200 micrograms/kg for 5 consecutive days) for the treatment of SARS-CoV-2 infection. |
| **Country/ Geographical location** | Multicentre study (4 sites)<br><br>Country: Italy |
| **Study setting** | Community setting: Non-hospitalised participants who did not require hospitalisation or oxygen supplementation |
| **Population description** | Adults≥18 years with confirmed SARS-CoV-2 infection by PCR |
| **Inclusion criteria** | Participants were adult (≥18 years) subjects newly diagnosed with SARS-CoV-2 infection by RT-PCR, not requiring hospitalisation or oxygen supplementation with COVID-19 severity score <3) and provided informed consent |
| **Exclusion criteria** | The main exclusion criteria were:<br><br>• pregnant or lactating women<br>• central nervous system disease<br>• patients on dialysis<br>• any severe medical condition with a prognosis of <6 months<br>• treatment with either warfarin, antiviral, chloroquine phosphate or hydroxychloroquine |
| **Intervention/test/approach** | Single dose of Ivermectin 600 micrograms/kg or 1200 micrograms/kg for five days |
| **Comparator (where applicable)** | Placebo |
| **Methods for population selection/allocation** | Sampling method: Consecutive diagnosis in four sites<br><br>Allocation: randomised by a centralised computer system in 1:1:1 ratio to three arms (using permuted block procedure) |
| **Methods of data analysis** | Safety outcomes: Serious adverse events or serious adverse drug reactions were reported as frequency and percentage<br><br>Efficacy outcomes: Decline in viral load from baseline was reported as continuous outcomes and compared via T-test and Wilcoxon test<br><br>Secondary outcomes : Adverse events, proportions of patients with virological clearance were compared between placebo and intervention groups using Chi-square or Fishcer's exact test |

| | |
|---|---|
| | Time to clinical resolution was analysed with Cox regression models and Kaplan-Meier method |
| **Attrition/loss to follow-up** | Primary Efficacy analysis: 4 withdrew consent and 2 had a missing sample of viral load [3 in placebo arm (n=29), 1 in ivermectin 600 micrograms/kg (n=28) and 2 in ivermectin 1200 micrograms/kg group (n=30)]<br><br>Per protocol analysis: Excluded because did not receive 5 days of treatment<br><br>Placebo (n=30), ivermectin 600 micrograms/kg (n=26), ivermectin 1200 micrograms/kg(n=19) |
| **Summary of findings** | The safety analysis included 89 participants and the change in viral load was calculated in 87 participants. No SADRs/SAEs were registered. Mean (S.D.) log10 viral load reduction was 2.9 (1.6) in arm C ivermectin 1200 micrograms/kg, 2.5 (2.2) in arm B ivermectin 600 micrograms/kg and 2.0 (2.1) in arm A placebo, with no significant differences (P = 0.099 and 0.122 for C vs. A and B vs. A, respectively). High-dose ivermectin was safe but did not show efficacy to reduce viral load. |
| **Source of funding** | The sponsor was IRCCS Sacro Cuore Don Calabria Hospital, which received funds for this trial from the Italian Ministry of Health in the framework of 'Ricerca corrente'. Tablets of 9 mg ivermectin and placebo were donated by Insud Pharma (Madrid, Spain). |
| **Study limitations (Author)** | • it failed to reach the planned sample size. However, the conditional power (CP) analysis showed that even reaching the target sample size, the hypothesised effect would hardly be demonstrated (arm B vs. arm A, CP = 0.001; arm C vs. arm A, CP = 0.27).<br>• Another limitation was the extreme difficulty in recruiting participants. Approximately 90% of subjects screened were not eligible to be included for various reasons, including a high proportion of refusal to give their consent.<br>• Moreover, 79 (84.9%) of the 93 study participants were recruited by the co-ordinating site. |

**Study arms**
**Placebo (N = 32)**
Arm A

**Ivermectin 600micrograms/kg (N = 29)**
Arm B (lower dose)

**Ivermectin 1200micrograms/kg (N = 32)**
Arm C (Higher dose)

**Characteristics**
**Study-level characteristics**

| Characteristic | Study (N = 93) |
|---|---|
| **Age** (Years (median, IQR))<br>Median (IQR)<br>Median (IQR) | 47 (31 to 58) |
| **Gender** (n (%))<br>Female sex<br>No of events | n = 39 ; % = 41.9 |
| **European**<br>n (%)<br>No of events | n = 90 ; % = 96.8 |
| **Extra-European - Nation of origin**<br>n (%)<br>No of events | n = 3 ; % = 3.2 |
| **Home - Nation of origin**<br>n (%)<br>No of events | n = 74 ; % = 79.6 |
| **Hospital emergency room**<br>n (%)<br>No of events | n = 11 ; % = 11.8 |
| **Hospital outpatient ambulatory care**<br>n (%)<br>No of events | n = 6 ; % = 6.5 |
| **Other**<br>n (%)<br>No of events | n = 2 ; % = 2.2 |
| **Comorbidities** (n (%))<br>No of events | n = 31 ; % = 33.3 |
| **Respiratory**<br>No of events | n = 6 ; % = 19.4 |
| **Cardiovascular**<br>No of events | n = 22 ; % = 71 |
| **Diabetes**<br>No of events | n = 3 ; % = 9.7 |
| **1, no limitation of activities**<br>No of events | n = 78 ; % = 83.9 |
| **2, limitation of activities**<br>No of events | n = 15 ; % = 16.1 |
| **SARS CoV-2 vaccine** (n (%))<br>No of events | n = 2 ; % = 2.2 |

### Arm-level characteristics

| Characteristic | Placebo (N = 32) | Ivermectin 600micrograms/kg (N = 29) | Ivermectin 1200micrograms/kg (N = 32) |
|---|---|---|---|
| **Age** (Years (median))<br>Median (IQR)<br>Median (IQR) | 50 (26 to 57) | 47 (31 to 62) | 44.5 (31 to 55.5) |

| Characteristic | Placebo (N = 32) | Ivermectin 600micrograms/kg (N = 29) | Ivermectin 1200micrograms/kg (N = 32) |
|---|---|---|---|
| **Female sex** (n (%))<br>No of events | n = 17 ; % = 53.1 | n = 14 ; % = 48.3 | n = 8 ; % = 25 |
| **Weight** (kg)<br>median (IQR)<br>Median (IQR) | 69 (62.5 to 74) | 72 (61 to 84) | 79 (70.5 to 85) |
| **Height** (cm)<br>median (IQR)<br>Median (IQR) | 170 (164.5 to 178) | 170 (167 to 175) | 173 (170 to 180) |
| **European**<br>No of events | n = 29 ; % = 90.6 | n = 29 ; % = 100 | n = 32 ; % = 100 |
| **Extra-European**<br>No of events | n = 3 ; % = 9.4 | n = 0 ; % = 0 | n = 0 ; % = 0 |
| **Home**<br>No of events | n = 27 ; % = 84.4 | n = 24 ; % = 82.8 | n = 23 ; % = 71.9 |
| **Hospital emergency room**<br>No of events | n = 3 ; % = 9.4 | n = 2 ; % = 6.9 | n = 6 ; % = 18.8 |
| **Hospital outpatient ambulatory care**<br>No of events | n = 1 ; % = 3.1 | n = 2 ; % = 6.9 | n = 3 ; % = 9.4 |
| **Other**<br>No of events | n = 1 ; % = 3.1 | n = 1 ; % = 3.4 | n = 0 ; % = 0 |
| **Comorbidities** (n (%))<br>No of events | n = 8 ; % = 25 | n = 11 ; % = 37.9 | n = 12 ; % = 37.5 |
| **Respiratory**<br>No of events | n = 0 ; % = 0 | n = 4 ; % = 36.4 | n = 2 ; % = 16.7 |
| **Cardiovascular**<br>No of events | n = 7 ; % = 87.5 | n = 7 ; % = 63.6 | n = 8 ; % = 66.7 |
| **Diabetes**<br>No of events | n = 2 | n = 0 ; % = 0 | n = 1 ; % = 8.3 |
| **1, no limitation of activities**<br>No of events | n = 27 ; % = 84.4 | n = 24 ; % = 82.8 | n = 27 ; % = 84.4 |
| **2, limitation of activities**<br>No of events | n = 5 ; % = 15.6 | n = 5 ; % = 17.2 | n = 5 ; % = 15.6 |
| **SARS CoV-2 vaccine** (n (%))<br>No of events | n = 1 ; % = 3.1 | n = 1 ; % = 3.4 | n = 0 ; % = 0 |

## Outcomes
### Primary and Secondary Outcomes

| Outcome | Placebo, , N = 29 | Ivermectin 600micrograms/kg , , N = 28 | Ivermectin 1200micrograms/kg , , N = 30 |
|---|---|---|---|
| **No. of SAEs/SADRs** (n (%))<br>Serious adverse events or serious drug reactions<br>No of events | n = 0 | n = 1 ; % = 3.57 | n = 3 ; % = 10 |
| **Time to clinical resolution TCR** (days)<br>80 participants<br>Median (IQR) | 14 (13 to 30) | 29 (13.5 to 32) | 14 (7 to 37) |
| **Reduction in Viral Load at day 7** (log 10)<br>Change from baseline in SARS-CoV-2 viral load to day 7<br>Mean (SD) | 2 (2.1) | 2.5 (2.2) | 2.9 (1.6) |
| **Virological Clearance within 14 days** (n (%))<br>Proportion of patients with virological clearance<br>No of events | n = 16 ; % = 59.3 | n = 16 ; % = 69.6 | n = 15 ; % = 57.7 |
| **Virological clearance within 30 days** (n (%))<br>Proportion of patients within 30 days<br>No of events | n = 18 ; % = 94.7 | n = 18 ; % = 94.7 | n = 17 ; % = 89.5 |
| **Hospitalisation rate** (n (%))<br>No of events | n = 0 ; % = 0 | n = 1 ; % = 3.4 | n = 3 ; % = 10 |
| **Adverse events**<br>No of events | n = 46 ; % = 20.1 | n = 69 ; % = 30.1 | n = 114 ; % = 49.8 |

## Chaccour, 2021

| | |
|---|---|
| **Bibliographic Reference** | Chaccour, Carlos; Casellas, Aina; Blanco-Di Matteo, Andres; Pineda, Inigo; Fernandez-Montero, Alejandro; Ruiz-Castillo, Paula; Richardson, Mary-Ann; Rodriguez-Mateos, Mariano; Jordan-Iborra, Carlota; Brew, Joe; Carmona-Torre, Francisco; Giraldez, Miriam; Laso, Ester; Gabaldon-Figueira, Juan C; Dobano, Carlota; Moncunill, Gemma; Yuste, Jose R; Del Pozo, Jose L; Rabinovich, N Regina; Schoning, Verena; Hammann, Felix; Reina, Gabriel; Sadaba, Belen; Fernandez-Alonso, Mirian; The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial.; EClinicalMedicine; 2021; vol. 32; 100720 |

**Study details**

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Trial registration (if reported)** | NCT04390022 |
| **Study start date** | 31-Jul-2020 |
| **Study end date** | 11-Sep-2020 |
| **COVID-19 prevalence at the time of the study** | Lower prevalence (e.g when services were resuming) |
| **Aim of the study** | To determine the efficacy of a single dose of ivermectin, administered to low risk, non-severe COVID-19 patients in the first 72 hours after symptom onset |
| **Country/ Geographical location** | Spain |
| **Study setting** | Non-hospitalised |
| **Population description** | The study included 24 patients in its primary analysis. The median age for patients was 26 years [range 18-54], and 50% of participants were male. All patients presented with at least one symptom of COVID-19 disease and most had mild to moderate disease progression. |
| **Inclusion criteria** | • Patients with symptoms compatible with COVID-19 with an onset of no more than 72 hours |
| **Exclusion criteria** | • Patients with positive IgG against SARS-CoV-2<br>• Patients with comorbidities considered risk factors for severe disease<br>• Patients with COVID-19 pneumonia at baseline |
| **Intervention/test/approach** | Ivermectin 400mcg/kg single oral dose |
| **Comparator (where applicable)** | Placebo |
| **Methods for population selection/allocation** | The randomisation sequence was computer-generated by a trial statistician using blocks of four to ensure balance. Patients were randomised in a 1:1 ratio and allocation was made by the attending investigator using opaque envelopes. The treatment was administered under direct supervision by a non-participating nurse in order for the clinical trial team to remain blinded. |
| **Methods of data analysis** | Descriptive analyses used frequency and percentage (based on the non-missing sample size) for qualitative variables and median, interquartile range and n (non-missing sample size) for quantitative variables. For the primary objective, the proportion of participants with positive PCR at day seven post-treatment was calculated. Proportions were compared between study arms using Fisher's exact test and presented as a relative risk ratio (RR) with their corresponding 95% confidence interval (CI). In the analysis of the symptoms reported by patients (symptom diary), missing data was |

| | |
|---|---|
| | carried over from the last data available. Significance was set at 0.05. The analysis was carried out using Stata (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).<br><br>Boxplots and bar plots were produced for the description of quantitative and qualitative variables, respectively. For figure readability, viral load values were log-transformed. Graphs were produced in R version 4.0.2 (R Core Team, R: A Language and Environment for Statistical Computing, Vienna, Austria: R Foundation for Statistical Computing, 2020) with the package ggplot2 (H. Wickham, ggplot2: Elegant Graphics for Data Analysis, Springer-Verlag New York, 2016.). Viral load data were synchronized prior to analysis by accounting for days since onset of any symptoms and, since the day of infection was not known, an average incubation time of 5 days was assumed. Peak viral load (Cmax) and time to peak viral load (Tmax) were determined directly from the profiles. Area under the viral load curve was calculated using the trapezoidal rule from assumed time of infection to last sample (AUCobs). Duration of time above a cycle threshold (Ct) of 35 was derived directly from profiles or linearly extrapolated profiles if the last recorded Ct value was not below the threshold. |
| **Attrition/loss to follow-up** | None |
| **Summary of findings** | There was no difference in the proportion of PCR positives in patients who were treated with Ivermectin versus those treated with placebo. Furthermore, there was a marked reduction of self-reported anosmia/hyposmia, a reduction of cough and lower viral loads and IgG titers. |
| **Source of funding** | Idipharma SL<br><br>ISGlobal<br><br>University of Navarra<br><br>Unitaid (BOHEMIA grant to ISGlobal)<br><br>Spanish Ministry of Science and Innovation<br><br>Generalitat de Catalunya (CERCA program) |
| **Study limitations (Author)** | The study was designed to explore a potential signal for the use of ivermectin in COVID-19 and therefore has a small size. The study only included patients with non-severe disease and no risk factors and whom treatment was provided for in the first 48 hours of fever or cough. The quantification of viral load is limited by heterogeneity in the samples. |
| **Study limitations (Reviewer)** | The study included a small sample size and so no further extrapolation on the efficacy and mechanism of action of ivermectin can be made. Furthermore, study outcomes were not adjusted for variations in COVID-19 pandemic phases. |
| **Other details** | NA |

**Study arms**
**Ivermectin 400mcg/kg (N = 12)**

**Placebo (N = 12)**

**Characteristics**
**Arm-level characteristics**

| Characteristic | Ivermectin 400mcg/kg (N = 12) | Placebo (N = 12) |
|---|---|---|
| **Age**<br>Median (IQR) | 26 (19 to 36) | 26 (21 to 44) |
| **Female**<br>No of events | n = 5 ; % = 42 | n = 7 ; % = 58 |
| **Male**<br>No of events | n = 7 ; % = 58 | n = 5 ; % = 42 |

**Outcomes**
**Ivermectin vs Placebo**

| Outcome | Ivermectin 400mcg/kg, , N = 12 | Placebo, , N = 12 |
|---|---|---|
| **Adverse events**<br>No of events | n = 5 ; % = 41.2 | n = 5 ; % = 41.2 |
| **Serious adverse events**<br>No of events | n = 0 ; % = 0 | n = 0 ; % = 0 |
| **Viral clearance 1-7 days**<br>No of events | n = 0 ; % = 0 | n = 0 ; % = 0 |

## Chachar, 2020

| | |
|---|---|
| **Bibliographic Reference** | Chachar, A.Z., Khan, K., Asif, M., Tanveer, K., Khaqan, A., & Basri R; Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients; International journal of sciences; 2020; vol. 9; 31-35 |

**Study details**

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Trial registration (if reported)** | |
| **Study start date** | 01-May-2020 |
| **Study end date** | 30-Jun-2020 |
| **Aim of the study** | To assess the efficacy of Ivermectin in mild cases of COVID-19 patients on the basis of predefined assessment criteria |
| **Country/ Geographical location** | Pakistan |
| **Study setting** | Outpatient |

| | |
|---|---|
| **Population description** | Patients were labelled to have mild disease due to acute respiratory syndrome coronavirus 2 (SARSCoV-2; previously named as 2019-nCoV) proven via RT-real time COVID-19 polymerase chain reaction<br><br>(PCR) test. |
| **Inclusion criteria** | • All patients diagnosed with COVID-19 infection with positive reverse transcriptase RT-PCR test, who were willing to participate in this study<br>• Patients having age of 18-75 years<br>• Patients of both genders male and female<br>• Patients who had mild symptoms of Coronavirus disease and RT- PCR positive for SARSCov-2<br>• Ability to take oral medication and were willing to adhere to the drug intake regimen |
| **Exclusion criteria** | • Known severe allergic reactions to Ivermectin<br>• Pregnancy or breastfeeding<br>• Severe symptoms likely attributed to Cytokine Release Storm<br>• Malignant diseases<br>• Chronic kidney disease<br>• Cirrhosis liver with Child class B or C |
| **Intervention/test/approach** | Patients were prescribed Ivermectin 12mg stat and then 12 mg after 12 hours and 12mg after 24 hours |
| **Comparator (where applicable)** | Only symptomatic treatment |
| **Methods for population selection/allocation** | Patients were allocated randomly to the groups by computer generated number. Sampling technique was convenient sampling as per the inclusion and exclusion criteria. |
| **Methods of data analysis** | Frequency and percentages were calculated for the qualitative variables like gender, comorbidity, symptoms, response to treatment. Quantitative variables of the study like age were expressed as<br><br>Mean ± SD |
| **Attrition/loss to follow-up** | No loss to follow up |
| **Summary of findings** | |
| **Source of funding** | Not reported |
| **Study limitations (Author)** | None reported |
| **Study limitations (Reviewer)** | • Control group participants' were older than the case group statistically but there is no difference between the average ages of both groups<br>• Predominantly male population and younger population |

**Study arms**

**Ivermectin (N = 25)**

**Control (N = 25)**

### Characteristics
### Arm-level characteristics

| Characteristic | Ivermectin (N = 25) | Control (N = 25) |
|---|---|---|
| **Age**<br>Mean (SD) | 43.08 (14.8) | 41.84 (14.8) |
| **Male**<br>No of events | n = 17 ; % = 34 | n = 14 ; % = 28 |
| **Female**<br>No of events | n = 8 ; % = 16 | n = 11 ; % = 22 |

### Outcomes
### Recovery

| Outcome | Ivermectin, , N = 25 | Control , , N = 25 |
|---|---|---|
| **Aysymptomatic at day 7**<br>No of events | n = 16 ; % = 64 | n = 15 ; % = 60 |

**Kishoria, 2020**

| | |
|---|---|
| **Bibliographic Reference** | Kishoria, N., Mathur, S., Parmar, V., Kaur, R., Agarwal, H., Parihar, B., & Verma S; IVERMECTIN AS ADJUVANT TO HYDROXYCHOLOROQUINE IN PATIENTS RESISTANT TO STANDARD TREATMENT FOR SARS-CoV-2: RESULTS OF AN OPEN-LABEL RANDOMIZED CLINICAL STUDY; Paripex Indian Journal Of Research; 2020; vol. 9 (no. 8); 50-53 |

### Study details

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Trial registration (if reported)** | Not reported |
| **COVID-19 prevalence at the time of the study** | Unclear |
| **Aim of the study** | To assess the efficacy of ivermectin as adjuvant drug in patients resistant to standard treatment for SARS-CoV-2 and to compare the effects ivermectin therapy to standard treatment |
| **Country/ Geographical location** | India |
| **Study setting** | Hospital |
| **Population description** | 32 participants were included in this study. The mean age of participants is 39.5 group in the treatment group and 37 years in the control group. The majority of participants were male (71.5%). |

| | |
|---|---|
| **Inclusion criteria** | • Patients aged 18 years or older<br>• Tested positive for SARS-CoV-2 (RT-PCR) after completion of standard care treatment<br>• Mild/asymptomatic<br>• No comorbidities affecting the patients prognosis (high risk patients)<br>• Documented acceptance to participate |
| **Exclusion criteria** | • Patients with an allergy or hypersensitivity to ivermectin and or its inactive ingredients<br>• Respiratory distress or requiring intensive care<br>• Used immunosuppressants (including corticosteroids) in the last 300 days<br>• Known HIV infection with CD4 count <300 cell/L<br>• Pregnancy or lactating patients<br>• Medical conditions such as mal-absorption syndromes affecting proper ivermectin absorption<br>• Autoimmune disease and or decompensated chronic diseases<br>• Uncontrolled, intercurrent diseases including renal impairment, hepatic impairment, symptomatic congestive heart failure, unstable chest angina or heart arrhythmia<br>• Treated in any other study in the previous 30 days<br>• Concomitant administration of enzyme inducers (carbamazepine)<br>• Those receiving CYP3A4 substrates (statins) |
| **Intervention/test/approach** | Oral hydroxychloroquine (400mg) twice a day plus ivermectin 12mg single dose (one day only); course of treatment was 5 days but ivermectin was received first day only |
| **Comparator (where applicable)** | Hydroxychloroquine 400mg twice a day for 5 days |
| **Methods for population selection/allocation** | Patients were randomised in a 1:1 ratio for each trial arm. Randomisation was generated by a computerised system. |
| **Methods of data analysis** | Not reported |
| **Attrition/loss to follow-up** | Not reported |
| **Summary of findings** | The use of ivermectin alongside hydroxychloroquine was not associated with any benefit in comparison with hydroxychloroquine alone. There were minimal adverse reactions to the drug indicating that it was safely tolerated |
| **Source of funding** | Not reported |
| **Study limitations (Author)** | Study included a small sample size and due to changes in guidelines asymptomatic patients could not be followed up within a hospital setting ad had to be discharged home |
| **Study limitations (Reviewer)** | This study was open-label, with small population size. The data analysis plan was not reported so it was not clear how data was transformed. Important reporting on confounders |

| | |
|---|---|
| | such as participants baseline characteristics was not reported and no information on how it was accounted for in analysis. |
| **Other details** | NA |

**Study arms**
**Ivermectin (N = 19)**

**Control (N = 13)**

**Characteristics**
**Arm-level characteristics**

| Characteristic | Ivermectin (N = 19) | Control (N = 13) |
|---|---|---|
| **Age**<br>Mean (t value) | 39.5 (-0.59) | 37 (-0.78) |
| **Male**<br>No of events | n = 14 ; % = 73.7 | n = 9 ; % = 69.3 |
| **Female**<br>No of events | n = 5 ; % = 26.3 | n = 4 ; % = 30.7 |

**Outcomes**
**Efficacy of ivermectin**

| Outcome | Ivermectin, , N = 19 | Control, , N = 13 |
|---|---|---|
| **Positive**<br>No of events | n = 11 ; % = 57.8 | n = 7 ; % = 53.8 |
| **Negative**<br>No of events | n = 8 ; % = 42.2 | n = 6 ; % = 46.2 |
| **Positive**<br>No of events | n = 1 ; % = 20 | n = 0 ; % = 0 |
| **Negative**<br>No of events | n = 4 ; % = 80 | n = 6 ; % = 100 |
| **Discharged from hospital**<br>No of events | n = 8 ; % = 42.2 | n = 6 ; % = 46.2 |
| **Not discharged**<br>No of events | n = 11 ; % = 57.8 | n = 7 ; % = 53.8 |
| **Viral clearance 1-7 days**<br>No of events | n = 8 ; % = 42 | n = 6 ; % = 46.2 |

**Krolewiecki, 2021**

| | |
|---|---|
| **Bibliographic Reference** | Krolewiecki, Alejandro; Lifschitz, Adrian; Moragas, Matias; Travacio, Marina; Valentini, Ricardo; Alonso, Daniel F; Solari, Ruben; Tinelli, Marcelo A; Cimino, Ruben O; Alvarez, Luis; Fleitas, Pedro E; Ceballos, Laura; Golemba, Marcelo; Fernandez, Florencia; Fernandez de Oliveira, Diego; Astudillo, German; Baeck, Ines; Farina, Javier; Cardama, Georgina A; Mangano, Andrea; Spitzer, Eduardo; Gold, Silvia; Lanusse, Carlos; |

Antiviral effect of high-dose ivermectin in adults with COVID-19: A proof-of-concept randomized trial.; EClinicalMedicine; 2021; vol. 37; 100959

## Study details

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Trial registration (if reported)** | NCT04381884 |
| **Study start date** | 18-May-2020 |
| **Study end date** | 09-Sep-2020 |
| **COVID-19 prevalence at the time of the study** | Unclear |
| **Aim of the study** | To evaluate the antiviral activity and safety profile of high dose ivermectin in COVID-19 patients |
| **Country/ Geographical location** | Argentina |
| **Study setting** | Hospital |
| **Population description** | The study included 45 participants with a mean age of 40.2 years. The majority of participants were male (58.5%) and the majority of people were hospitalised within 3.5 days of symptom onset on average. Baseline characteristics between groups were balanced. |
| **Inclusion criteria** | • COVID-19 symptom onset within 5 days at recruitment<br>• Absence of use of drugs with potential activity against SARS-CoV-2 (hydroxychloroquine, lopinavir, remdesivir and azithromycin)<br>• Patients of child bearing age were eligible if agreed to take effective contraceptive measures during the study period and for at least 30 days after the last study drug administration |
| **Exclusion criteria** | • Use of immunomodulators within 30 days of recruitment<br>• Pregnancy<br>• Breastfeeding<br>• Poorly controlled comorbidities |
| **Intervention/test/approach** | Oral ivermectin for 5 consecutive days at a dose of 600ug/kg/day |
| **Comparator (where applicable)** | Placebo |
| **Methods for population selection/allocation** | A blocked randomization with random block sizes (of 3 or 6 allocations) and stratified by center was used. Participants were randomised in a 2:1 ratio. The randomisation list was developed prior to study initiation and by means of a centralised eCRF/IWRS web system (Jazz Clinical, Buenos Aires, Argentina). For reproducibility, a random seed of 1701214029 was used. Once the availability of the informed |

| | |
|---|---|
| | consent and the verification of all eligibility criteria had been confirmed, the assignment was communicated to the investigators on the computer screen and by email. The patients and center personnel were not blinded to the allocated group. The outcome assessors (personnel in charge of viral load determinations) were blinded to the allocated group upon receiving the samples labelled with the randomisation number and the visit number. |
| **Methods of data analysis** | Sample size calculation was determined on current recommendations for pilot trials, indicating that either at least 10 cases per group should be included or based on the sample size calculation for the full-scale clinical trial and include at least 9% of that size for a confidence interval of 80%. Based on these grounds and aiming for a sample size with the ability to detect a low effect size (0·3) of the intervention in the difference between baseline and day-5 viral load values compared to untreated controls given the absence of preliminary or historical data; sample size for a full-scale trial for two study groups with a significance level of 5% and 80% power, a 2:1 randomization and inflated for 10% lost-to-follow-up was calculated in 342 participants and a pilot trial would be at least 31. In view of the presumed effect of ivermectin on the replication of SARS-CoV-2 and the limited available information of viral dynamics at the time of study design (April 2020), the sample size of the pilot trial according to standardised size effects was calculated for a 2:1 randomisation to be 45 patients, including 30 participants in the IVM arm and 15 controls without consideration to the center-based stratification.<br><br>Baseline characteristics of the two groups (control and ivermectin) were compared with Student`s *T*- test and Chi square. Difference in viral load between baseline and day-5 in the two groups as well as the comparison between the viral decay rate of both groups was compared by the non-parametric Mann–Whitney test. The clinical evolution at day-7 was evaluated by Fisher's Exact Test. Finally, the relationship between IVM plasma concentrations with viral load reduction and viral decay rate were measured by Spearman rank test. When difference across three groups by Kruskal-Wallis was significant, pairwise comparisons with Dunn`s multiple comparisons test were used. Two randomly occurring single missed values of viral load in two different participants were assumed as “missing completely at random” type of values and estimated by regression analysis using the interpolation of all the existing data from that particular curve. In all cases, *p*-values <0·05 were considered statistically significant. All analyses were performed with GraphPad Prism version 5·00 for Windows (La Jolla California USA). |
| **Attrition/loss to follow-up** | 3 patients in ivermectin group and 1 patient in placebo group. |
| **Summary of findings** | There was no difference in viral load reduction between groups but a significant difference was found in patients with |

| | |
|---|---|
| | higher median plasma ivermectin levels. thus indicating that high dose ivermectin was well tolerated. |
| **Source of funding** | Agencia Nacional de Promocion de la Investigacion, el Desarrollo Tecnologico y la Innovacion |
| **Study limitations (Author)** | The sample size of the study was small however it was only used to detect the antiviral activity of ivermectin against SARS-CoV-2. The analysis of the primary outcome was based on days since study entry rather than since symptom onset and may have introduced variability in viral load values. Furthermore, no adjustments regarding infection stage or comorbidities were made in the analysis. . |
| **Study limitations (Reviewer)** | The study was unblinded to participants and included a small sample size. The analysis did not account for or adjust for variation in infection stages or COVID-19 pandemic phases. |
| **Other details** | NA |

**Study arms**
**Ivermectin 600ug/kg/day (N = 30)**

**Placebo (N = 15)**

**Characteristics**
**Arm-level characteristics**

| Characteristic | Ivermectin 600ug/kg/day (N = 30) | Placebo (N = 15) |
|---|---|---|
| **Age**<br>Mean (SD) | 42.3 (*empty data*) | 38.1 (11.7) |
| **Female**<br>No of events | n = 15 ; % = 50 | n = 5 ; % = 33 |
| **Male**<br>No of events | n = 15 ; % = 50 | n = 10 ; % = 67 |
| **Weight (kg)**<br>Mean (SD) | 75.3 (15) | 79.7 (14.4) |
| **Hypertension**<br>No of events | n = 3 ; % = 10 | n = 3 ; % = 20 |
| **Diabetes**<br>No of events | n = 6 ; % = 20 | n = 1 ; % = 7 |
| **Chronic lung disease/asthma**<br>No of events | n = 4 ; % = 13 | n = 1 ; % = 7 |

**Outcomes**
**Ivermecin vs Placebo**

| Outcome | Ivermectin 600ug/kg/day, , N = 30 | Placebo, , N = 15 |
|---|---|---|
| **Adverse events**<br>No of events | n = 13 ; % = 43 | n = 5 ; % = 33 |
| **Serious adverse events**<br>No of events | n = 1 ; % = 3 | n = 0 ; % = 0 |

| Outcome | Ivermectin 600ug/kg/day, , N = 30 | Placebo, , N = 15 |
|---|---|---|
| **Invasive mechanical ventilation** No of events | n = 1 ; % = 5 | n = 0 ; % = 0 |

### Lim, 2022

| | |
|---|---|
| **Bibliographic Reference** | Lim Steven Chee, Loon; Hor Chee, Peng; Tay Kim, Heng; Mat, Jelani; Anilawati; Tan Wen, Hao; Ker Hong, Bee; Chow Ting, Soo; Zaid, Masliza; Cheah Wee, Kooi; Lim Han, Hua; Khalid Khairil, Erwan; Cheng Joo, Thye; Mohd, Unit; Hazfadzila; An, Noralfazita; Nasruddin Azraai, Bahari; Low Lee, Lee; Khoo Song Weng, Ryan; Loh Jia, Hui; Zaidan Nor, Zaila; Ab, Wahab; Suhaila; Song Li, Herng; Koh Hui, Moon; King Teck, Long; Lai Nai, Ming; Chidambaram Suresh, Kumar; Peariasamy Kalaiarasu, M; I-TECH, Study; Group; Efficacy of Ivermectin Treatment on Disease Progression Among Adults With Mild to Moderate COVID-19 and Comorbidities: The I-TECH Randomized Clinical Trial.; JAMA internal medicine; 2022 |

#### Study details

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Trial registration (if reported)** | NCT04920942 |
| **Study start date** | 31-May-2021 |
| **Study end date** | 25-Oct-2021 |
| **Aim of the study** | To determine the efficacy of ivermectin for preventing progression to severe disease among high-risk patients with COVID-19 in Malaysia |
| **Country/ Geographical location** | Malaysia (20 hospitals) |
| **Study setting** | 20 public hospitals and a COVID-19 quarantine center |
| **Population description** | Patients with mild to moderate COVID-19 disease at risk of disease progression and are referred for hospitalisation or COVD-19 quarantine centre to allow monitoring for 10 or more days in case of timely intervention for deterioration |
| **Inclusion criteria** | RT-PCR confirmed COVID-19<br>50 years or older<br>with at least 1 comorbidity<br>with mild to moderate illness (Malaysian COVID-19 clinical severity stage 2 or 3; WHO clinical progression scale 2-4)<br>within 7 days from symptom onset |
| **Exclusion criteria** | asymptomatic<br>required supplemental oxygen<br>had pulse oximetry oxygen saturation level less than 95% at rest<br>severe hepatic impairment<br>acute medical or surgical emergency,<br>concomitant viral infection, |

| | |
|---|---|
| | pregnancy or breastfeeding,<br>warfarin therapy,<br>history of taking ivermectin or any antiviral drugs with reported activity against COVID-19 (favipiravir, hydroxychloroquine, lopinavir, and remdesivir) within 7 days before enrolment. |
| **Intervention/test/approach** | Ivermectin 0.4 mg/kg body weight daily for 5 days plus standard of care |
| **Comparator (where applicable)** | Standard of care for patients with mild to moderate disease consisted of symptomatic therapy and monitoring for signs of early deterioration based on clinical findings, laboratory test results, and chest imaging. |
| **Methods for population selection/allocation** | Randomisation 1:1 ratio<br>The randomization was based on an investigator-blinded randomization list uploaded to REDCap, which allocated the patients via a central, computer-generated randomization scheme across all study sites during enrolment. The randomization list was generated independently using random permuted block sizes 2 to 6. The randomization was not stratified by site. |
| **Methods of data analysis** | Fisher exact test<br>t-test or Mann-Whitney U test<br>Relative risks<br>Mixed analysis of variance |
| **Attrition/loss to follow-up** | 500 patients were randomised<br>Four patients were excluded after randomization. One patient in the control arm was diagnosed with dengue coinfection; in the intervention arm, 2 failed to meet inclusion criteria owing to symptom duration greater than 7 days and negative COVID-19 RT-PCR test result, while 1 had acute coronary syndrome before ivermectin initiation. In addition, 6 patients in the intervention arm withdrew consent before taking a dose of ivermectin.<br>The modified intention-to-treat population for the primary analysis included 490 patients (98% of those enrolled), with 241 in the intervention group and 249 in the control group. |
| **Summary of findings** | In high risk patients with COVID-19, a 5-day course of oral ivermectin during the first week of illness did not reduce the risk of developing severe disease compared with standard of care alone<br>The study findings do not support the use of ivermectin for patients with COVID-19 |
| **Study limitations (Author)** | The study has following limitations. First, the open-label trial design might contribute to the underreporting of adverse events in the control group while overestimating the drug effects of ivermectin. Second, our study was not designed to assess the effects of ivermectin on mortality from COVID-19. Finally, the generalizability of our findings may be limited by the older study population, although younger and healthier individuals with low risk of severe disease are less likely to benefit from specific COVID-19 treatments |

**Study arms**
**Ivermectin (N = 241)**
0.4 mg/kg body weight daily for 5 days plus standard of care

**Standard of care (N = 249)**

**Characteristics**
**Arm-level characteristics**

| Characteristic | Ivermectin (N = 241) | Standard of care (N = 249) |
|---|---|---|
| **Age**<br>Mean (SD) | 63 (8.9) | 62 (8.4) |
| **Female**<br>No of events | n = 130 ; % = 53.9 | n = 137 ; % = 55 |
| **Male**<br>No of events | n = 111 ; % = 46.1 | n = 112 ; % = 45 |
| **Chinese**<br>No of events | n = 37 ; % = 15.4 | n = 32 ; % = 12.9 |
| **Indian**<br>No of events | n = 38 ; % = 15.8 | n = 30 ; % = 12 |
| **Malay**<br>No of events | n = 153 ; % = 63.5 | n = 172 ; % = 69.1 |
| **Other**<br>No of events | n = 13 ; % = 5.4 | n = 15 ; % = 6 |
| **Weight** (kg)<br>Mean (SD) | 68 (14.5) | 68.7 (14.6) |
| **BMI** (kg/m²)<br>Mean (SD) | 26.8 (5.2) | 26.9 (5.4) |
| **Not vaccinated**<br>No of events | n = 75 ; % = 31.1 | n = 84 ; % = 33.7 |
| **1 dose of vaccine**<br>No of events | n = 42 ; % = 17.4 | n = 35 ; % = 14.1 |
| **2 doses of vaccine**<br>No of events | n = 124 ; % = 51.5 | n = 130 ; % = 52.2 |
| **Mild**<br>No of events | n = 83 ; % = 34.4 | n = 84 ; % = 33.7 |
| **Moderate**<br>No of events | n = 158 ; % = 65.6 | n = 165 ; % = 66.3 |
| **Days of symptoms at enrolment** (days)<br>Mean (SD) | 5.1 (1.3) | 5.1 (1.3) |
| **Hypertension**<br>No of events | n = 178 ; % = 73.9 | n = 191 ; % = 76.7 |
| **Diabetes mellitus**<br>No of events | n = 131 ; % = 54.4 | n = 131 ; % = 52.6 |
| **Dyslipidemia**<br>No of events | n = 102 ; % = 42.3 | n = 82 ; % = 32.9 |

| Characteristic | Ivermectin (N = 241) | Standard of care (N = 249) |
|---|---|---|
| **Obesity**<br>No of events | n = 56 ; % = 23.2 | n = 61 ; % = 24.5 |
| **Presence of any COVID-19 related lung changes**<br>Chest Radiography<br>No of events | n = 158 ; % = 65.6 | n = 165 ; % = 66.3 |

## Outcomes

### Outcomes in primary analysis population

| Outcome | Ivermectin, , N = 241 | Standard of care, , N = 249 |
|---|---|---|
| **Progression to severe disease**<br>WHO scale 5-9<br>No of events | n = 52 ; % = 21.6 | n = 43 ; % = 17.3 |
| **Time of progression to severe disease** (days)<br>mean (SD)<br>Mean (SD) | 3.2 (2.4) | 2.9 (1.8) |
| **Patients who had mechanical ventilation** (n (%))<br>No of events | n = 4 ; % = 1.7 | n = 10 ; % = 4 |
| **Patients admitted to ICU** (n (%))<br>No of events | n = 6 ; % = 2.5 | n = 8 ; % = 3.2 |
| **All-cause in-hospital mortality** (n (%))<br>Among total 13 deaths, 9 were related to severe COVID-19<br>No of events | n = 3 ; % = 1.2 | n = 10 ; % = 4 |
| **Length of stay** (days)<br>mean (SD)<br>Mean (SD) | 7.7 (4.4) | 7.3 (4.3) |
| **Complete symptom resolution** (n (%))<br>No of events | n = 122 ; % = 51.3 | n = 131 ; % = 53 |
| **Complete symptom resolution** (n (%))<br>Sample size | n = 238 ; % = NA | n = 247 ; % = NA |
| **Normal chest radiography** (n (%))<br>No of events | n = 61 ; % = 25.6 | n = 61 ; % = 24.9 |
| **Normal chest radiography** (n (%))<br>Sample size | n = 238 ; % = NA | n = 245 ; % = NA |
| **1 or more than 1 Adverse events or Serious adverse events**<br>No of events | n = 33 ; % = 13.7 | n = 11 ; % = 4.4 |
| **Total serious adverse events**<br>No of events | n = 4 ; % = 1.65 | n = 1 ; % = 0.4 |

Primary analyses were performed based on the modified intention-to-treat principle, randomised patients in the intervention group who received at least 1 ivermectin

dose and all patients in the control group were followed and evaluated for efficacy and safety

### Lopez-Medina, 2021

| | |
|---|---|
| **Bibliographic Reference** | Lopez-Medina, Eduardo; Lopez, Pio; Hurtado, Isabel C; Davalos, Diana M; Ramirez, Oscar; Martinez, Ernesto; Diazgranados, Jesus A; Onate, Jose M; Chavarriaga, Hector; Herrera, Socrates; Parra, Beatriz; Libreros, Gerardo; Jaramillo, Roberto; Avendano, Ana C; Toro, Dilian F; Torres, Miyerlandi; Lesmes, Maria C; Rios, Carlos A; Caicedo, Isabella; Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial.; JAMA; 2021; vol. 325 (no. 14); 1426-1435 |

#### Study details

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Trial registration (if reported)** | NCT04405843 |
| **Study start date** | 15-Jul-2020 |
| **Study end date** | 21-Dec-2020 |
| **COVID-19 prevalence at the time of the study** | Unclear |
| **Aim of the study** | To determine whether ivermectin is an efficacious treatment for mild COVID-19 |
| **Country/ Geographical location** | Colombia |
| **Study setting** | At home or hospitalised (not receiving high flow nasal oxygen or mechanical ventilation) |
| **Population description** | The study included 498 patients in the primary analysis. The median age for participants was 37 years. The majority of participants were male (58%), with varying pre-existing co-morbidities such as hypertension (13.3%), diabetes (5.6%) and thyroid disease (3.75%). |
| **Inclusion criteria** | • Adults and non-pregnant or breastfeeding women were eligible<br>• Patients whose symptoms began within the previous 7 days<br>• Patients with mild disease |
| **Exclusion criteria** | • Patients who were asymptomatic<br>• Patients with severe pneumonia<br>• Patients who received ivermectin within the previous 5 days<br>• Patients with hepatic dysfunction or liver function test results more than 1.5 times the normal level |

| | |
|---|---|
| **Intervention/test/approach** | Oral ivermectin in solution with a dose of 300ug/kg once per day for 5 days |
| **Comparator (where applicable)** | Placebo |
| **Methods for population selection/allocation** | Eligible patients were randomly assigned in a 1:1 ratio to receive either oral ivermectin or placebo in solution for 5 days. Patients were randomised in permuted blocks of 4 in a randomisation sequence prepared by the unblinded pharmacist in Microsoft Excel version 19.0 who provided masked ivermectin or placebo to a field nurse for home or hospital patient visits. Allocation assignment was concealed from investigators and patients. |
| **Methods of data analysis** | The primary outcome was originally defined as the time from randomisation until worsening by 2 points on the 8-category ordinal scale. According to the literature, approximately 18% of patients were expected to have such an outcome. However, before the interim analysis, it became apparent that the pooled event rate of worsening by 2 points was substantially lower than the initial 18% expectation, requiring an unattainable sample size. Therefore, on August 31, 2020, the principal investigator proposed to the data and safety monitoring board to modify the primary endpoint to time from randomisation to complete resolution of symptoms within the 21-day follow-up period. This was approved on September 2, 2020. The original sample size of 400 based on the log-rank test for the new primary endpoint was kept, using ivermectin to placebo assignment ratio of 1:1. This would allow the detection of 290 events of interest (symptom resolution), assuming that 75% of patients would have the outcome of interest at 21 days, with a 2% dropout rate. This would provide an 80% power under a 2-sided type I error of 5% if the hazard ratio (HR) comparing ivermectin vs placebo is 1.4, corresponding to a 3-day faster resolution of symptoms in patients receiving ivermectin, assuming that time to resolution of symptoms is 12 days with placebo. With an HR of 1.4, 75% and 85% of patients in the placebo and ivermectin groups, respectively, would experience the outcome of interest at 21 days.<br><br>On October 20, 2020, the lead pharmacist observed that a labelling error had occurred between September 29 and October 15, 2020, resulting in all patients receiving ivermectin and none receiving a placebo during this time frame. The study blind was not unmasked due to this error. The data and safety monitoring board recommended excluding these patients from the primary analysis but retaining them for sensitivity analysis. The protocol was amended to replace these patients to retain the originally calculated study power. The primary analysis population included patients who were analysed according to their randomisation group, but excluded patients recruited between September 29 and October 15, 2020, as well as patients who were randomised but later found to be in violation of selection criteria. Patients were |

| | |
|---|---|
| | analysed according to the treatment they received in the as-treated population (sensitivity analysis).<br><br>The primary endpoint of time from randomisation to complete resolution of symptoms with ivermectin vs placebo was assessed by a Kaplan-Meier plot and compared with a log-rank test. The HRs and 95% CIs for the cumulative incidence of symptom resolution in both treatment groups were estimated using the Cox proportional hazards model. The proportional hazards assumption was tested graphically using a log-log plot and the test of the nonzero slope. There was no evidence to reject the proportionality assumption.<br><br>The time to complete resolution of symptoms was assessed after all patients reached day 21. Data for patients who died or lacked symptom resolution before day 21 were right-censored at death or day 21, respectively. Evaluation of the effect of the treatment in each study visit using the 8-point ordinal scale was estimated using the proportional odds ratio (OR) with its respective 95% CI with an ordinal logistic regression. The proportional odds assumption was met according to the Brant test. The 8-point ordinal scale was inverted in its score, where 0 corresponded to death and 7 to a patient without symptoms.<br><br>For sensitivity analysis, primary and secondary endpoints were compared in the as-treated population.<br><br>Clustered standard errors were estimated to adjust for the correlation between multiple patients from the same household. Statistical significance was set at $P < .05$, and all tests were 2-tailed. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary endpoints should be interpreted as exploratory. Statistical analyses were done with Stata version 16.0 (StataCorp). Bootstrapping 95% CIs for differences of medians were calculated with R statistical package version 3.6.3 (The R Foundation). |
| **Attrition/loss to follow-up** | Not reported |
| **Source of funding** | Centro de Estudios en Infectologia Pediatrica grant |
| **Study limitations (Author)** | The study was not conducted according to the original design and the primary outcome was changed 6 weeks into the trial. The study may have been underpowered to detect smaller changes in the primary endpoint. The study did not include virological assessments and the placebo used in the first 65 patients differed in taste and smell from ivermectin. As the trial required patient self-reporting, this may have introduced subjectivity. |
| **Study limitations (Reviewer)** | The trial design and post hoc analyses were changed from the original protocol due to the low rate of events in the original outcome. Secondly, the trial population was relatively young and so the results cannot be extrapolated to other populations. |

| | |
|---|---|
| **Other details** | NA |

**Study arms**
**Ivermectin (N = 200)**

**Placebo (N = 198)**

**Characteristics**
**Arm-level characteristics**

| Characteristic | Ivermectin (N = 200) | Placebo (N = 198) |
|---|---|---|
| **Age**<br>Median (IQR) | 37 (29 to 47.7) | 37 (28.7 to 49.2) |
| **Male**<br>No of events | n = 78 ; % = 39 | n = 89 ; % = 44.9 |
| **Female**<br>No of events | n = 122 ; % = 61 | n = 109 ; % = 55 |
| **Mixed Race**<br>No of events | n = 178 ; % = 89 | n = 179 ; % = 90.4 |
| **Black or African American**<br>No of events | n = 16 ; % = 8 | n = 16 ; % = 8.1 |
| **Colombian Native**<br>No of events | n = 6 ; % = 3 | n = 3 ; % = 1.5 |
| **Obesity (BMI 30 kg/m2 or above)**<br>No of events | n = 37 ; % = 18.5 | n = 38 ; % = 19.4 |
| **Hypertension**<br>No of events | n = 28 ; % = 14 | n = 25 ; % = 12.6 |
| **Diabetes**<br>No of events | n = 10 ; % = 5 | n = 12 ; % = 6.1 |
| **Thyroid disease**<br>No of events | n = 7 ; % = 3.5 | n = 8 ; % = 4 |
| **Respiratory disease**<br>No of events | n = 6 ; % = 3 | n = 6 ; % = 3 |
| **Cardiovascular disease**<br>No of events | n = 4 ; % = 2 | n = 3 ; % = 1.5 |
| **Any coexisting condition**<br>No of events | n = 44 ; % = 22 | n = 38 ; % = 19.2 |

**Outcomes**
**Ivermectin vs Placebo**

| Outcome | Ivermectin, , N = 200 | Placebo , , N = 198 |
|---|---|---|
| **Time to resolution of symptoms**<br>Median (IQR) | 10 (9 to 13) | 12 (9 to 13) |
| **Death**<br>No of events | n = 0 ; % = 0 | n = 1 ; % = 0.5 |
| **Deterioration by 2 or more points**<br>No of events | n = 4 ; % = 2 | *empty data* |

| Outcome | Ivermectin, , N = 200 | Placebo , , N = 198 |
|---|---|---|
| **Adverse events**<br>No of events | n = 154 ; % = 77 | n = 161 ; % = 81.3 |
| **Serious adverse events**<br>No of events | n = 2 ; % = 1 | n = 2 ; % = 1 |

### Manomaipiboon, 2022

| | |
|---|---|
| **Bibliographic Reference** | Manomaipiboon, Anan; Pholtawornkulchai, Kitisak; Pupipatpab, Sujaree; Suraamornkul, Swangjit; Maneerit, Jakravoot; Ruksakul, Wiroj; Phumisantiphong, Uraporn; Trakarnvanich, Thananda; Efficacy and safety of ivermectin in the treatment of mild-to-moderate COVID-19 infection: A randomized, double blind, placebo, controlled trial; 2022 |

### Study details

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Trial registration (if reported)** | not reported |
| **Study start date** | 01-Sep-2021 |
| **Study end date** | 30-Nov-2021 |
| **Aim of the study** | To establish the efficacy of ivermectin for COVID-19 patients with mild-to-moderate disease, compare to usual care alone. |
| **Country/ Geographical location** | Thailand |
| **Study setting** | Community<br><br>Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, |
| **Population description** | Adult men and women aged 18–80 years, and mild-to-moderate symptoms as defined by WHO severity score for COVID-19.<br><br>RT-PCR confirmed positive<br><br>Mild disease was defined as cough, runny nose, anosmia, fever, and diarrhea without dyspnea or tachypnea. Moderate disease was defined as pneumonia with oxygen saturation >90%. |
| **Inclusion criteria** | Adult men and women aged 18–80 years, non-pregnant or breast-feeding women, and mild-to-moderate symptoms as defined by WHO severity score for COVID-19. |
| **Exclusion criteria** | Excluded if:<br><br>• allergic to ivermectin; |

| | |
|---|---|
| | • had the potential for a drug-drug interaction with ivermectin, such as tamoxifen or warfarin;<br>• were previously treated with ivermectin in the last 7 days;<br>• had received any herbal medicine;<br>• had severe chronic illness (severe congestive heart failure, chronic kidney disease stage 4–5, chronic liver disease, terminal cancer);<br>• had concurrent bacterial infection;<br>• were unwilling to participate in the trial<br>• patients with severe symptoms, likely due to cytokine release syndrome, uncontrolled co-morbidities, and immunocompromised status |
| **Intervention/test/approach** | 12 mg per day of ivermectin for 5 days plus standard care |
| **Comparator (where applicable)** | standard care included favipiravir or andrographolide, corticosteroids, cetrizine and paracetamol |
| **Methods for population selection/allocation** | Permuted block of four randomised sequence<br><br>1:1 ratio |
| **Methods of data analysis** | t-test<br><br>Mann-Whitney U<br><br>Pearson chi-square test<br><br>Kaplan–Meier plot and a log rank test<br><br>Cox proportional hazards model |
| **Attrition/loss to follow-up** | One patient each from the ivermectin and comparator group withdrew their consent during the study due to drug addiction and psychiatric problems. After that, 72 patients were equally randomised to ivermectin or SOC<br><br>No loss to follow up reported. |
| **Summary of findings** | At day 7 and 14, a negative RT-PCR result was not significantly different between the two groups. The other secondary outcomes were reported to be comparable. However, the time to resolution of many symptoms were shorter in the ivermectin group, albeit not significantly. No adverse events were reported. |
| **Source of funding** | Navamindradhiraj University Grant no: 171/64 |
| **Study limitations (Author)** | • Small sample size due to the fact that the incidence of COVID-19 at the time of the study was rapidly decreasing in the country.<br>• Second, the duration of follow-up was short, i.e., up to 28 days only. A longer follow-up time might reveal long-term benefits of ivermectin.<br>• Third, authors reported that included patients mild-to-moderate COVID-19, wherein the disease might |

| | |
|---|---|
| | subside spontaneaously without any proven benefit of any medications.<br>• The author stated that the ivermectin dosage has varied from study-to-study, and we still do not know the exact appropriate dose of ivermectin. |
| **Other details** | |

**Study arms**
**Ivermectin (N = 36)**
12 mg per day of ivermectin for 5 days plus standard care

**Control (N = 36)**
Standard care included favipiravir or andrographolide, corticosteroids, cetrizine and paracetamol.

**Characteristics**
**Arm-level characteristics**

| Characteristic | Ivermectin (N = 36) | Control (N = 36) |
|---|---|---|
| **Male**<br>No of events | n = 14 ; % = 38.9 | n = 13 ; % = 36.1 |
| **Female**<br>No of events | n = 22 ; % = 61.1 | n = 23 ; % = 63.9 |
| **Age**<br>Mean (SD) | 49.42 (14.29) | 47.72 (15.45) |
| **Diabetes %**<br>No of events | n = 11 ; % = 30.6 | n = 6 ; % = 16.7 |
| **Hypertension %**<br>No of events | n = 16 ; % = 44.4 | n = 13 ; % = 36.1 |
| **Dyslipidemia %**<br>No of events | n = 16 ; % = 44.4 | n = 9 ; % = 25 |
| **COVID-19 Vaccine dose 1**<br>No of events | n = 18 ; % = 50 | n = 16 ; % = 44.4 |
| **COVID-19 Vaccine dose 2**<br>No of events | n = 5 ; % = 13.9 | n = 8 ; % = 22.2 |

**Outcomes**
**Primary and Secondary Outcomes**

| Outcome | Ivermectin, , N = 36 | Control, , N = 36 |
|---|---|---|
| **RT-PCR Negative day 7**<br>No of events | n = 7 ; % = 17.3 | n = 6 ; % = 14.3 |
| **RT-PCR Negative Day 14**<br>No of events | n = 17 ; % = 47.2 | n = 16 ; % = 44.4 |
| **Mortality at day 28**<br>No of events | n = 0 ; % = 0 | n = 0 ; % = 0 |
| **Adverse events day 14** | n = 0 ; % = 0 | n = 0 ; % = 0 |

| Outcome | Ivermectin, , N = 36 | Control, , N = 36 |
|---|---|---|
| No of events | | |
| **Adverse Events Day 28**<br>No of events | n = 0 ; % = 0 | n = 0 ; % = 0 |

## Mohan, 2021

| | |
|---|---|
| **Bibliographic Reference** | Mohan, Anant; Tiwari, Pawan; Suri, Tejas Menon; Mittal, Saurabh; Patel, Ankit; Jain, Avinash; Velpandian, Thirumurthy; Das, Ujjalkumar Subhash; Boppana, Tarun Krishna; Pandey, Ravindra Mohan; Shelke, Sushil Suresh; Singh, Angel Rajan; Bhatnagar, Sushma; Masih, Shet; Mahajan, Shelly; Dwivedi, Tanima; Sahoo, Biswajeet; Pandit, Anuja; Bhopale, Shweta; Vig, Saurabh; Gupta, Ritu; Madan, Karan; Hadda, Vijay; Gupta, Nishkarsh; Garg, Rakesh; Meena, Ved Prakash; Guleria, Randeep; Single-dose oral ivermectin in mild and moderate COVID-19 (RIVET-COV): A single-centre randomized, placebo-controlled trial.; Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy; 2021 |

### Study details

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Trial registration (if reported)** | CTRI/2020/06/ 026001 |
| **Study start date** | Jul-2020 |
| **Study end date** | Sep-2020 |
| **Aim of the study** | To determine the efficacy and safety of a novel elixir formulation of ivermectin aimed to maximize oral bioavailability of ivermectin in COVID-19. |
| **Country/ Geographical location** | India |
| **Study setting** | Hospital - COVID-19 facility at the National Cancer Institute, All India Institute of Medical Sciences, New Delhi. |
| **Population description** | Adults aged 18 and over admitted with non-severe COVID-19 (room air saturation (SpO2) >90%, and with no hypotension or requirement of mechanical ventilation) |
| **Inclusion criteria** | Consecutive patients aged above 18 years admitted at the trial site were considered eligible for inclusion if they were diagnosed with non-severe COVID-19, i.e., room air saturation (SpO2) >90%, and with no hypotension or requirement of mechanical ventilation. Diagnosis of COVID-19 was based on a positive result on either SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) or a rapid antigen test. |
| **Exclusion criteria** | Patients were excluded if they did not give informed consent. Other exclusion criteria included: pregnancy or lactation, known hypersensitivity to ivermectin, chronic kidney disease with creatinine clearance <30 mL/min, elevated transaminase |

| | |
|---|---|
| | levels (>5X upper limit of normal), myocardial infarction or heart failure within 90 days prior to enrolment, prolonged corrected QT interval (>450 ms), any other severe comorbidity as per investigator's assessment, or enrolment in another clinical trial. |
| **Intervention/test/approach** | Single dose of Ivermectin 12 mg or 24 mg elixir |
| **Comparator (where applicable)** | Placebo |
| **Methods for population selection/allocation** | • Randomised in a 1:1:1 ratio<br>• A variable block randomization stratified based on disease severity (mild or moderate illness) was done using a centralized telephone-based system and the patients, investigators, caregivers, and statisticians were blinded to the allocation |
| **Methods of data analysis** | • All randomised patients who received study medication were included in the intention to treat analysis<br>• Patients with a positive nasopharyngeal/ oropharyngeal SARS-CoV-2 RT-PCR on the day of enrolment were included in the modified intention-to-treat analysis.<br>• The primary outcomes (viral load decline and conversion to negative RT-PCR at day 5) were assessed in the mITT population.<br>• Clinical outcomes were assessed in the mITT population, whereas the adverse effects were evaluated in the ITT population.<br>• Inter-group comparisons of categorical outcome variables were performed using Fisher's exact test. Inter-group comparisons of continuous outcome variables were performed using analysis of variance (ANOVA) or Kruskal-Wallis test. |
| **Attrition/loss to follow-up** | • 5/157 withdrew consent (1 in24mg arm, 3 in 12mg arm and 1 in placebo arm)<br>• 27 had negative RT-PCR at baseline and excluded from mITT analysis (11/51 in 24 mg arm, 9/49 in 12mg arm and 7/52 in placebo arm) |
| **Summary of findings** | |
| **Source of funding** | The trial was supported by the Science and Engineering Research Board, Department of Science and Technology, Government of India [grant number CVD/2020/001105]. The funder had no role in study design, data collection, data analysis or writing of the report. The corresponding author had full access to the study data and had the final responsibility for the decision to submit for publication. |
| **Study limitations (Author)** | • Single centre with small sample size<br>• Majority of the population was male and relatively young with few comorbidities |

| | |
|---|---|
| | • The elixir formulation of ivermectin used in the study is not commercially available (at the time of publication)<br>• Patients were recruited irrespective of duration of illness beforehand |

**Study arms**
**Ivermectin 12 mg (N = 40)**

**Ivermectin 24mg (N = 40)**

**Placebo (N = 45)**

**Characteristics**
**Arm-level characteristics**

| Characteristic | Ivermectin 12 mg (N = 40) | Ivermectin 24mg (N = 40) | Placebo (N = 45) |
|---|---|---|---|
| **Age**<br>Mean (SD) | 36.3 (10.54) | 34.3 (10.45) | 35.3 (10.52) |
| **Male**<br>No of events | n = 35 ; % = 87.5 | n = 37 ; % = 92.5 | n = 39 ; % = 86.7 |
| **Female**<br>No of events | n = 5 ; % = 12.5 | n = 3 ; % = 7.5 | n = 6 ; % = 13.3 |
| **Mild COVID Severity**<br>No of events | n = 27 ; % = 67.5 | n = 24 ; % = 60 | n = 29 ; % = 64.4 |
| **Moderate COVID Severity**<br>No of events | n = 13 ; % = 32.5 | n = 16 ; % = 40 | n = 16 ; % = 35.6 |

**Outcomes**
**Outcomes**

| Outcome | Ivermectin 12 mg, , N = 40 | Ivermectin 24mg, , N = 40 | Placebo , , N = 45 |
|---|---|---|---|
| **Mortality**<br>Data extracted from supplementary info<br>No of events | n = 0 ; % = 0 | n = 0 ; % = 0 | n = 0 ; % = 0 |
| **Invasive mechanical ventilation**<br>Data extracted from supplementary info<br>No of events | n = 0 ; % = 0 | n = 0 ; % = 0 | n = 0 ; % = 0 |
| **Adverse events**<br>No of events | n = 8 ; % = 49 | n = 6 ; % = 51 | n = 6 ; % = 52 |
| **Negative PCR day 3**<br>No of events | n = 7 ; % = 17.5 | n = 3 ; % = 7.5 | n = 7 ; % = 15.6 |
| **Negative PCR day 3**<br>Sample size | n = 40 | n = 40 | n = 45 |

| Outcome | Ivermectin 12 mg, , N = 40 | Ivermectin 24mg, , N = 40 | Placebo , , N = 45 |
|---|---|---|---|
| **Negative PCR day 5** No of events | n = 14 ; % = 35 | n = 19 ; % = 47.5 | n = 14 ; % = 31.1 |
| **Negative PCR day 5** Sample size | n = 40 | n = 40 | n = 45 |
| **Negative PCR day 7** No of events | n = 13 ; % = 36.1 | n = 16 ; % = 44.4 | n = 16 ; % = 38.1 |
| **Negative PCR day 7** Sample size | n = 36 | n = 36 | n = 42 |
| **Serious adverse events** Data extracted from supplementary info No of events | n = 0 ; % = 0 | n = 0 ; % = 0 | n = 0 ; % = 0 |

## Podder, 2021

| | |
|---|---|
| **Bibliographic Reference** | Podder, C., Chowdhury, N., Sina, M.I., & Haque W; Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study; IMC Journal of Medical Science; 2021; vol. 14 (no. 2); 11-18 |

### Study details

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Trial registration (if reported)** | |
| **Study start date** | May-2020 |
| **Study end date** | Jul-2020 |
| **Aim of the study** | This study was designed to evaluate the benefit of, if any, adding ivermectin to usual care, compared to usual care alone in the treatment of COVID-19 cases at a semi-rural settings. |
| **Country/ Geographical location** | Bangladesh |
| **Study setting** | Outpatient department |
| **Population description** | Adults with RT=PCR positive mild to moderate COVID-19 |
| **Inclusion criteria** | Mild to moderate diseases were defined according to WHO COVID-19 disease severity classification.<br><br>Symptomatic patients without evidence of viral pneumonia or hypoxia (SpO2 >93% on room air) were considered as a mild disease and patients with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO2≥ 90% on room air were considered as a moderate disease |

| | |
|---|---|
| **Exclusion criteria** | Patients with known pre-existing hypersensitivity to Ivermectin, pregnant and lactating mothers, and patients taking other antimicrobials or hydroxychloroquine were excluded from the study. |
| **Intervention/test/approach** | Single dose of ivermectin 200 micrograms/kg on the day 1 of randomisation. |
| **Comparator (where applicable)** | Upon enrolment, all COVID-19 cases received symptomatic treatment which included antipyretics, cough suppressants, and capsule doxycycline (100 mg every 12 hours for seven days) to treat possible community-acquired pneumonia as part of the local working protocol and this treatment schedule was termed as 'usual care' |
| **Methods for population selection/allocation** | Randomisation was done using an odd even methodology applied to registration numbers, in a consecutive fashion of 1:1 ratio |
| **Methods of data analysis** | Intention to treat analysis<br><br>The unpaired t-test was used to compare the means between control and intervention arms. Crosstab and chi square tests were used to compare demographic parameters between control and intervention arms. P-value of less than 0.05 was taken as significant. |
| **Attrition/loss to follow-up** | Initially, 82 patients were recruited; of these, 62 patients who presented within seven days of onset of symptoms were finally selected for analysis. Twenty patients were excluded as 18 had symptoms for more than seven days at the time of enrolment and two other patients had insufficient data |
| **Summary of findings** | |
| **Source of funding** | The study was self-financed |
| **Study limitations (Author)** | • Unable to perform biochemical and haematological investigations due tot he primary health care setting in a semi-rural area so were unable to determine the effect of ivermectin on those parameters |
| **Study limitations (Reviewer)** | • Open label trial with a subjective outcome (symptom resolution)<br>• Small sample size<br>• Majority male and a younger population<br>• Odd-even randomisation method may not be robust although characteristics appear balanced, albeit restricted to presenting symptoms<br>• " Some parameters are excluded from the analysis due to inadequate data" Could mean that for some symptom sets, insufficient data, so excluded for entire symptom set (and possibly from overall Recovery outcomes). |

**Study arms**
**Ivermectin (N = 32)**

**Control (N = 30)**

### Characteristics
### Arm-level characteristics

| Characteristic | Ivermectin (N = 32) | Control (N = 30) |
|---|---|---|
| **Age**<br>Mean (SD) | 39.97 (13.24) | 38.41 (11.02) |
| **Male**<br>No of events | n = 23 ; % = 71.9 | n = 21 ; % = 70 |
| **Female**<br>No of events | n = 9 ; % = 28.1 | n = 9 ; % = 30 |

### Outcomes
### Recovery

| Outcome | Ivermectin, , N = 32 | Control, , N = 30 |
|---|---|---|
| **Time to resolution of symptoms from date of enrolment** (days)<br>Mean (SD) | 5.31 (2.48) | 6.33 (4.23) |
| **Time to resolution of symptoms from date of illness onset** (days)<br>Mean (SD) | 10.09 (3.24) | 11.5 (5.32) |
| **Viral clearance on 10th day**<br>No of events | n = 18 ; % = 90 | n = 19 ; % = 95 |
| **Viral clearance on 10th day**<br>Sample size | n = 20 | n = 20 |

## Ravikirti, 2021

| | |
|---|---|
| **Bibliographic Reference** | Ravikirti; Roy, Ranjini; Pattadar, Chandrima; Raj, Rishav; Agarwal, Neeraj; Biswas, Bijit; Manjhi, Pramod Kumar; Rai, Deependra Kumar; Shyama; Kumar, Anjani; Sarfaraz, Asim; Evaluation of Ivermectin as a Potential Treatment for Mild to Moderate COVID-19: A Double-Blind Randomized Placebo Controlled Trial in Eastern India.; Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques; 2021; vol. 24; 343-350 |

### Study details

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Trial registration (if reported)** | CTRI/2020/08/027225) |
| **Study start date** | Aug-2020 |
| **Study end date** | Oct-2020 |

| | |
|---|---|
| **Aim of the study** | To elicit efficacy of two consecutive day 12mg ivermectin enteral regimen among mild to moderate COVID-19 patients admitted in a COVID dedicated healthcare facility of eastern India |
| **Country/ Geographical location** | India |
| **Study setting** | Hospital |
| **Population description** | Adults with confirmed mild to moderate COVID 19 |
| **Inclusion criteria** | All adult patients (aged ≥18 years) admitted with a diagnosis of COVID-19 (on the basis of a positive reverse transcriptase polymerase chain reaction (RTPCR)or rapid antigen test report) at our hospital with mild or moderate disease on admission as defined by the Ministry of Health and Family Welfare (MOHFW), Government of India (GOI)<br><br>Definitions of mild, moderate ,and severe COVID-19 used during enrolment of the study participants were as following :Mild: No evidence of breathlessness or hypoxia (normal saturation);<br>Moderate: Breathlessness and/or hypoxia (saturation 90-94% on room air), respiratory rate of 24 or more and no features of severe disease; Severe: Any of the following-severe respiratory distress, oxygen saturation < 90% on room air, respiratory rate > 30,<br>shock or evidence of a life-threatening organ dysfunction |
| **Exclusion criteria** | Known allergy or adverse drug reaction with ivermectin; unwillingness or inability to provide consent to participate in the study; prior use of ivermectin during the course of current illness; pregnancy and lactation. |
| **Intervention/test/approach** | Ivermectin 12mg, 2 consecutive days |
| **Comparator (where applicable)** | Placebo<br><br>All patients received usual care and treatment by their respective treating teams abiding by the standard treatment guidelines laid out by the institute |
| **Methods for population selection/allocation** | Patients were randomly allocated to either treatment group A or group Bin a 1:1 ratio. Block randomisation was done with variable random block sizes of 4, 6 and 8. A random allocation list of 120 patients was generated using the sealed envelope(an online block randomisation list generating software) and kept with a third person (not a part of the investigation team) prior to the commencement of the trial. Once an eligible study participant has provided consent for the trial, the investigation team doctor used to contact the concerned third person having the random allocation list over telephone to know the treatment group (A/B) for that |

| | |
|---|---|
| | particular patient. One of these two groups was the intervention group, and the other was the placebo group. However, up until the analysis of the data, this information was confined to the pharmacist dispensing the tablets. After confirmation of the treatment group, the investigation team doctor used to indent2 tablets designated for that particular group. Both these treatment groups received 2 tablets similar in size, shape, colour, odour, and packaging on subsequent days. |
| **Methods of data analysis** | To compare baseline characteristics of both the trial arms bivariate analysis was performed using the independent samples Student's t-test for continuous variables and chi square test for categorical variables. To compare various outcome measures of the study across interventional and non-interventional arms rate ratio (RR) was used. The minimum acceptable confidence level used for this trial was $\alpha=0.95$ and any observed difference with $p<0.05$ was considered as statistically significant. |
| **Attrition/loss to follow-up** | One patient in either arm was administered unblinded ivermectin tablet by the treating team on day 2, hence excluded. Additionally, one patient in the intervention arm could not be tracked from day 2. So, all these were considered as lost to follow-up. |
| **Summary of findings** | |
| **Source of funding** | Not reported |
| **Study limitations (Author)** | There was an absence of a conclusive 6th day RT-PCR report in 32.1% of the cases (41.8% in intervention arm and 22.8% in placebo arm)<br><br>As serial RT-PCR tests could not be considered due to feasibility, the median time to viral clearance in the two groups could not be ascertained |
| **Study limitations (Reviewer)** | • Those with no or inconclusive PCR reports were included in the analysis<br>• Predominantly male population |
| **Other details** | Other treatments given:<br><br>• Hydroxychloroquine - 112 (100%)<br>• Steroid -12 (100%)<br>• Enoxaparin - 108 (96.4% )<br>• Antibiotics -112 (100%)<br>• Remdesivir - 23 (20.5%)<br>• Convalescent Plasma -15 (13.4%)<br>• Tocilizumab - 7 (6.3%<br>• Other Drugs - 74 (66.1%) |

**Study arms**
**Ivermectin (N = 55)**

**Placebo (N = 57)**

**Characteristics**
**Arm-level characteristics**

| Characteristic | Ivermectin (N = 55) | Placebo (N = 57) |
|---|---|---|
| **Age**<br>Mean (SD) | 50.7 (12.7) | 54.2 (16.3) |
| **Male**<br>No of events | n = 40 ; % = 72.7 | n = 41 ; % = 71.9 |
| **Female**<br>No of events | n = 15 ; % = 27.3 | n = 16 ; % = 28.1 |
| **Hypertension**<br>No of events | n = 21 ; % = 38.2 | n = 18 ; % = 31.6 |
| **Diabetes**<br>No of events | n = 21 ; % = 38.2 | n = 19 ; % = 33.3 |
| **Ischaemic heart disease**<br>No of events | n = 2 ; % = 3.6 | n = 8 ; % = 14 |
| **Heart failure**<br>No of events | n = 1 ; % = 1.8 | n = 1 ; % = 1.8 |
| **COPD**<br>No of events | n = 1 ; % = 1.8 | n = 0 ; % = 0 |
| **Asthma**<br>No of events | n = 1 ; % = 1.8 | n = 0 ; % = 0 |
| **Cancer**<br>No of events | n = 2 ; % = 3.6 | n = 4 ; % = 7 |
| **Other comorbidities**<br>No of events | n = 7 ; % = 12.7 | n = 11 ; % = 19.3 |
| **CKD**<br>No of events | n = 1 ; % = 1.8 | n = 2 ; % = 3.5 |

**Outcomes**
**Primary outcome**

| Outcome | Ivermectin, , N = 55 | Placebo , , N = 57 |
|---|---|---|
| **Negative RT-PCR on day 6**<br>No of events | n = 13 ; % = 23.6 | n = 18 ; % = 31.6 |

**Secondary outcome**

| Outcome | Ivermectin, , N = 55 | Placebo , , N = 57 |
|---|---|---|
| **Symptom free on day 6**<br>No of events | n = 46 ; % = 83.6 | n = 51 ; % = 89.5 |
| **Discharged by day 10**<br>No of events | n = 44 ; % = 80 | n = 42 ; % = 73.7 |
| **Admission to ICU**<br>No of events | n = 5 ; % = 9.7 | n = 6 ; % = 10.5 |

| Outcome | Ivermectin, , N = 55 | Placebo , , N = 57 |
|---|---|---|
| **Invasive ventilation**<br>No of events | n = 1 ; % = 1.8 | n = 5 ; % = 8.8 |
| **In-hospital mortality**<br>No of events | n = 0 ; % = 0 | n = 4 ; % = 7 |
| **Discharged**<br>No of events | n = 55 ; % = 100 | n = 53 ; % = 93 |

### Reis, 2022

| | |
|---|---|
| **Bibliographic Reference** | Reis, Gilmar; Silva Eduardo A S, M; Silva Daniela C, M; Thabane, Lehana; Milagres Aline, C; Ferreira Thiago, S; Dos, Santos; Castilho V, Q; Campos Vitoria H, S; Nogueira Ana M, R; de Almeida Ana P F, G; Callegari Eduardo, D; Neto Adhemar D, F; Savassi Leonardo C, M; Simplicio Maria I, C; Ribeiro Luciene, B; Oliveira, Rosemary; Harari, Ofir; Forrest Jamie, I; Ruton, Hinda; Sprague, Sheila; McKay, Paula; Guo Christina, M; Rowland-Yeo, Karen; Guyatt Gordon, H; Boulware David, R; Rayner Craig, R; Mills Edward, J; TOGETHER, Investigators; Effect of Early Treatment with Ivermectin among Patients with Covid-19.; The New England journal of medicine; 2022 |

### Study details

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Trial registration (if reported)** | NCT04727424 |
| **Study start date** | 23-Mar-2021 |
| **Study end date** | 06-Aug-2021 |
| **Aim of the study** | To evaluate the efficacy of ivermectin for the prevention of progression of Covid-19 resulting in hospitalization among outpatients with SARS-CoV-2 infection |
| **Country/ Geographical location** | Brazil (12 sites) |
| **Study setting** | Community |
| **Population description** | Adult outpatients at high risk of hospitalisation |
| **Inclusion criteria** | Inclusion criteria<br><br>1. age of 18 years or older<br>2. presentation to an outpatient care setting with an acute clinical condition consistent with Covid-19 within 7 days after symptom onset; and<br>3. at least one high-risk criterion for progression of Covid-19, including<br><br>• an age older than 50 years,<br>• diabetes mellitus,<br>• hypertension leading to the use of medication, |

| | |
|---|---|
| | • cardiovascular disease,<br>• lung disease, smoking,<br>• obesity,<br>• organ transplantation,<br>• chronic kidney disease (stage IV) or receipt of dialysis,<br>• immunosuppressive therapy (receipt of ≥10 mg of prednisone or equivalent daily),<br>• a diagnosis of cancer within the previous 6 months, or receipt of chemotherapy for cancer.<br><br>Patients who had been vaccinated against SARS CoV-2 were eligible for participation in the trial. |
| **Exclusion criteria** | Following patients were excluded<br><br>• Patients with acute respiratory condition<br>• Severe terminal illness<br>• Use of medications such as antiretroviral agents<br>• Pregnant or breast feeding<br>• Inability to given inform consent or follow protocol |
| **Intervention/test/approach** | ivermectin 400 µg per kilogram for 3 days |
| **Comparator (where applicable)** | Placebo since the day of randomisation, once per day |
| **Methods for population selection/allocation** | Block stratified randomisation for each site and age (≤50 years or >50 years) |
| **Attrition/loss to follow-up** | 3515 underwent randomisation<br><br>1. 679 received ivermectin for 3 days<br>2. 679 received placebo<br><br>• 679 in each group were included in intention to treat analysis<br>• 674 in ivermectin and 675 in placebo group were included in modified intention to treat analysis<br>• 624 in ivermectin and 288 in placebo were included in per-protocol analysis |
| **Summary of findings** | Overall, 100 patients (14.7%) in the ivermectin group had a primary-outcome event, as compared with 111 (16.3%) in the placebo group (relative risk, 0.90; 95% Bayesian credible interval, 0.70 to 1.16).<br><br>There were no significant effects of ivermectin use on secondary outcomes or adverse events. |
| **Source of funding** | FastGrants and the Rainwater Charitable Foundation |
| **Study limitations (Author)** | not reported in the paper |

**Study arms**
**Ivermectin 400 µg/kg (N = 679)**

**Placebo (N = 679)**

**Characteristics**
**Study-level characteristics**

| Characteristic | Study (N = 1358) |
|---|---|
| **Age**<br>Median (IQR) | 49 (38 to 57) |
| **Gender**<br>Female sex<br>No of events | n = 791 ; % = 58.2 |
| **Race - Mixed**<br>No of events | n = 1293 ; % = 95.2 |
| **Race - white**<br>No of events | n = 12 ; % = 0.9 |
| **Race - Black**<br>No of events | n = 12 ; % = 0.9 |
| **Race - Other**<br>No of events | n = 1 ; % = 0.1 |
| **Race - Unknown**<br>No of events | n = 40 ; % = 2.9 |
| **Age ≤50 year**<br>No of events | n = 731 ; % = 53.8 |
| **Age greater than 50 years**<br>No of events | n = 627 ; % = 46.2 |
| **BMI less than 30**<br>No of events | n = 683 ; % = 50.3 |
| **BMI greater than or equal to 30**<br>No of events | n = 675 ; % = 49.7 |
| **Time since onset of symptoms 0-3 days**<br>No of events | n = 597 ; % = 44 |
| **Time since onset of symptoms 4-7 days**<br>No of events | n = 761 ; % = 56 |

**Arm-level characteristics**

| Characteristic | Ivermectin 400 µg/kg (N = 679) | Placebo (N = 679) |
|---|---|---|
| **Age**<br>Median (IQR) | 49 (39 to 57) | 49 (37 to 56) |
| **≤50 year**<br>No of events | n = 359 ; % = 52.9 | n = 372 ; % = 54.8 |
| **greater than 50 years**<br>>50 year<br>No of events | n = 320 ; % = 47.1 | n = 307 ; % = 45.2 |
| **Female sex**<br>No of events | n = 383 ; % = 56.4 | n = 408 ; % = 60.1 |
| **Mixed Race** | n = 648 ; % = 95.4 | n = 645 ; % = 95 |

| Characteristic | Ivermectin 400 µg/kg (N = 679) | Placebo (N = 679) |
|---|---|---|
| No of events | | |
| **Race, % white**<br>No of events | n = 6 ; % = 0.9 | n = 6 ; % = 0.9 |
| **Race - Black**<br>No of events | n = 7 ; % = 1 | n = 5 ; % = 0.7 |
| **Race - Other**<br>No of events | n = 1 ; % = 0.1 | n = 0 ; % = 0 |
| **Race - Unknown**<br>No of events | n = 17 ; % = 2.5 | n = 23 ; % = 3.4 |
| **BMI less than 30**<br>less than 30<br>No of events | n = 347 ; % = 51.1 | n = 336 ; % = 49.5 |
| **BMI equal to or greater than 30**<br>greater than or equal to 30<br>No of events | n = 332 ; % = 48.9 | n = 343 ; % = 50.5 |
| **Time since symptom onset 0-3 days**<br>No of events | n = 302 ; % = 44.5 | n = 295 ; % = 43.4 |
| **Time since symptom onset 4-7 days**<br>No of events | n = 377 ; % = 55.5 | n = 384 ; % = 56.6 |

## Outcomes

### Primary outcomes

| Outcome | Ivermectin 400 µg/kg, , N = 679 | Placebo, , N = 679 |
|---|---|---|
| **Hospitalisation for COVID-19** (n (%))<br>No of events | n = 78 ; % = 11.5 | n = 93 ; % = 13.7 |
| **Emergency room visit for greater than 6 hours** (n (%))<br>No of events | n = 36 ; % = 5.3 | n = 31 ; % = 4.6 |
| **Primary outcome event (intention-to-treat analysis)**<br>composite of hospitalisation due to progression of COVID-19 or emergency dept visit of >6 hours due to clinical worsening of COVID-19<br>No of events | n = 100 ; % = 14.7 | n = 111 ; % = 16.3 |

### Primary Outcome Event (Modified intention-to-treat)

| Outcome | Ivermectin 400 µg/kg, , N = 674 | Placebo, , N = 675 |
|---|---|---|
| **Primary outcome event**<br>Hospitalisation or visit to emergency dept<br>No of events | n = 95 ; % = 14.1 | n = 107 ; % = 15.9 |

Primary outcome event is defined as composite of hospitalisation due to progression of COVID-19 or an emergency dept visit due to clinical worsening of COVID-19

### Primary outcome event (per-protocol population)

| Outcome | Ivermectin 400 µg/kg, , N = 624 | Placebo, , N = 288 |
|---|---|---|
| **Primary outcome event**<br>Hospitalisation or visit to emergency dept due to COVID-19<br>No of events | n = 82 ; % = 13.1 | n = 40 ; % = 13.9 |

The primary composite outcome was hospitalisation due to Covid-19 within 28 days after randomisation or an emergency department visit due to clinical worsening of Covid-19 (defined as the participant remaining under observation for >6 hours) within 28 days after randomization.

**Secondary Outcomes**

| Outcome | Ivermectin 400 µg/kg, , N = 679 | Placebo, , N = 679 |
|---|---|---|
| **Viral Clearance Day 3** (n (%))<br>No of events | n = 11 ; % = 7.4 | n = 17 ; % = 10 |
| **Viral Clearance Day 3** (n (%))<br>Sample size | n = 148 | n = 170 |
| **Viral Clearance Day 7** (n (%))<br>No of events | n = 36 ; % = 25.4 | n = 42 ; % = 25.5 |
| **Viral Clearance Day 7** (n (%))<br>Sample size | n = 142 | n = 165 |
| **Hospitalisation for any cause**<br>No of events | n = 79 ; % = 11.6 | n = 95 ; % = 14 |
| **Median no of days of hospitalisation** (Median (IQR))<br>Median (IQR) | 6 (4 to 10) | 6 (3 to 11) |
| **Median no of days to clinical recovery**<br>Clinical recovery was assessed via WHO clinical progression scale<br>Median (IQR) | 14 (11 to 14) | 14 (11 to 14) |
| **Death %**<br>No of events | n = 21 ; % = 3.1 | n = 24 ; % = 3.5 |
| **Mechanical ventilation** (n (%))<br>No of events | n = 19 ; % = 2.8 | n = 25 ; % = 3.7 |
| **Median no of days with mechanical ventilation**<br>Median (IQR) | 6 (3 to 16) | 7 (2 to 12) |
| **100% adherence to assigned regimen** (n (%))<br>No of events | n = 624 ; % = 91.9 | n = 547 ; % = 80.6 |
| **Adverse events Grade 1**<br>No of events | n = 16 ; % = 2.4 | n = 12 ; % = 1.8 |
| **Adverse events Grade 2**<br>No of events | n = 49 ; % = 7.2 | n = 76 ; % = 11.2 |
| **Adverse events Grade 3**<br>No of events | n = 41 ; % = 6 | n = 50 ; % = 7.4 |
| **Adverse events Grade 4**<br>No of events | n = 17 ; % = 2.5 | n = 18 ; % = 2.7 |

| Outcome | Ivermectin 400 µg/kg, , N = 679 | Placebo, , N = 679 |
|---|---|---|
| **Adverse events Grade 5**<br>No of events | n = 21 ; % = 3.1 | n = 24 ; % = 3.5 |

**Subgroup Analyses of Ivermectin compared to Placebo for primary composite outcome**

| Outcome | Ivermectin 400 µg/kg, , N = | Placebo, , N = |
|---|---|---|
| **Age less than or equal to 50**<br>No of events | n = 38 | n = 39 |
| **Age less than or equal to 50**<br>Sample size | n = 335 | n = 347 |
| **Age greater than 50**<br>>50<br>No of events | n = 53 | n = 66 |
| **Age greater than 50**<br>>50<br>Sample size | n = 295 | n = 283 |
| **BMI less than 30**<br><30<br>No of events | n = 38 | n = 48 |
| **BMI less than 30**<br><30<br>Sample size | n = 345 | n = 333 |
| **BMI equal to or greater than 30**<br>≥30<br>No of events | n = 60 | n = 63 |
| **BMI equal to or greater than 30**<br>≥30<br>Sample size | n = 330 | n = 339 |
| **CVD No**<br>No of events | n = 53 | n = 58 |
| **CVD No**<br>Sample size | n = 397 | n = 407 |
| **CVD Yes**<br>No of events | n = 47 | n = 53 |
| **CVD Yes**<br>Sample size | n = 282 | n = 272 |
| **Lung disease No**<br>No of events | n = 96 | n = 106 |
| **Lung disease No**<br>Sample size | n = 665 | n = 664 |
| **Lung disease Yes**<br>No of events | n = 4 | n = 5 |
| **Lung disease Yes**<br>Sample size | n = 14 | n = 14 |
| **Female** | n = 47 | n = 59 |

| Outcome | Ivermectin 400 µg/kg, , N = | Placebo, , N = |
|---|---|---|
| No of events | | |
| **Female**<br>Sample size | n = 383 | n = 408 |
| **Male**<br>No of events | n = 53 | n = 52 |
| **Male**<br>Sample size | n = 296 | n = 271 |
| **Time since onset of symptoms 0-3 days**<br>No of events | n = 41 | n = 35 |
| **Time since onset of symptoms 0-3 days**<br>Sample size | n = 282 | n = 276 |
| **Time since onset of symptoms 4-7 days**<br>No of events | n = 43 | n = 43 |
| **Time since onset of symptoms 4-7 days**<br>Sample size | n = 242 | n = 241 |

The primary composite outcome was hospitalisation due to Covid-19 within 28 days after randomisation or an emergency department visit due to clinical worsening of Covid-19 (defined as the participant remaining under observation for >6 hours) within 28 days after randomisation

### Shahbaznejad, 2021

| | |
|---|---|
| **Bibliographic Reference** | Shahbaznejad, Leila; Davoudi, Alireza; Eslami, Gohar; Markowitz, John S; Navaeifar, Mohammad Reza; Hosseinzadeh, Fatemeh; Movahedi, Faeze Sadat; Rezai, Mohammad Sadegh; Effects of Ivermectin in Patients With COVID-19: A Multicenter, Double-blind, Randomized, Controlled Clinical Trial.; Clinical therapeutics; 2021; vol. 43 (no. 6); 1007-1019 |

### Study details

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Trial registration (if reported)** | IRCT20111224008507N3 |
| **Study start date** | May-2020 |
| **Study end date** | Jul-2020 |
| **Aim of the study** | This study reports the effects of ivermectin on outcomes in hospitalised patients with COVID-19 in a double-blind randomized clinical trial |
| **Country/ Geographical location** | Iran |
| **Study setting** | Hospital |
| **Population description** | Adults and children (aged over 5 years, weight over 15kg) with suspected or confirmed COVID-19 |

| | |
|---|---|
| **Inclusion criteria** | The diagnostic criteria for COVID-19 included any of the following: (1) positive result on COVID-19 reverse-transcription polymerase chain reaction; (2) clinical symptoms of COVID-19, with a history of contact with a patient with COVID-19; and/or (3) abnormalities on chest computed tomography (CT) compatible with COVID19 (ground-glass opacity, halo sign, reversed halo sign, and patchy infiltration) |
| **Exclusion criteria** | The exclusion criteria were as follows: a history of chronic liver and/or renal disease; receipt of treatment with warfarin, an angiotensin-converting enzyme inhibitor, or a angiotensin II receptor antagonist; and acquired immunodeficiency. Pregnant or breast-feeding women were also excluded from the study. |
| **Intervention/test/approach** | A single oral dose (0.2mg/kg) of ivermectin utilizing 3-mg oral tablets, or a multiple thereof, on the first day of admission, at the following weight-based doses: 15 to 24 kg, 3 mg; 25 to 30 kg, 6 mg; 36 to 50 kg, 9 mg; 51 to 80 kg, 12 mg; and >80 kg, 0.2 mg/kg.<br><br>All of the participants received appropriate antibiotics and/or supplemental oxygen as indicated. |
| **Comparator (where applicable)** | Supportive medical treatment for COVID-19 according to the national protocols of Iran at the time of this study (hydroxychloroquine and/or lopinavir/ritonavir)<br><br>All of the participants received appropriate antibiotics and/or supplemental oxygen as indicated. |
| **Methods for population selection/allocation** | The patients were randomly divided into 2 groups (ivermectin and control) by a simple randomisation method using a table of random numbers<br><br>Neither the participants nor the evaluators were aware of the randomisation process or group allocation.<br><br>After patients were admitted to the hospital and provided written informed consent, a package containing oral medications was given to the patients in both groups. |
| **Methods of data analysis** | For comparison of differences between intervention and control group, t test and $\chi 2$ tests were used. The Kaplan-Meier Breslow method was used for estimating the duration of hospitalization and symptoms in both groups. A P value of $<0.05$ was considered as statistically significant. |
| **Attrition/loss to follow-up** | 4 patients withdrew in the control group |
| **Source of funding** | Not reported |
| **Study limitations (Author)** | • Small sample size |

| | |
|---|---|
| | • Effects of ivermectin on mortality could not be evaluated<br>• Only 25/69 (36%) patients received a PCR test of which 9 (36%) were negative for COVID-19 an remained in the analysis |
| **Study limitations (Reviewer)** | Unclear if randomisation methods were adequate.<br><br>Unclear allocation concealment |

**Study arms**
**Ivermectin (N = 35)**

**Control (N = 34)**

**Characteristics**
**Arm-level characteristics**

| Characteristic | Ivermectin (N = 35) | Control (N = 34) |
|---|---|---|
| **< 18 years**<br>No of events | n = 4 ; % = 11.4 | n = 5 ; % = 14.7 |
| **< 18 years**<br>No of events | n = 31 ; % = 88.6 | n = 29 ; % = 85.3 |
| **Male**<br>No of events | n = 18 ; % = 51.4 | n = 15 ; % = 52.9 |
| **Female**<br>No of events | n = 17 ; % = 48.6 | n = 16 ; % = 47.1 |

**Outcomes**
**Outcomes**

| Outcome | Ivermectin, , N = 35 | Control, , N = 34 |
|---|---|---|
| **Invasive mechanical ventilation**<br>No of events | n = 2 ; % = 0.6 | n = 1 ; % = 0.3 |
| **Length of hospital stay** (days)<br>Mean (SD) | 7.1 (0.5) | 8.4 (0.6) |
| **Needed supplemental oxygen**<br>No of events | n = 10 ; % = 28.6 | n = 9 ; % = 26.5 |
| **Duration of symptoms** (days)<br>Mean (SD) | 4.2 (0.3) | 5.2 (0.3) |
| **Adverse events**<br>No of events | n = 0 ; % = 0 | n = 0 ; % = 0 |

**Shakhsi Niaee, 2021**

| | |
|---|---|
| **Bibliographic Reference** | Shakhsi Niaee, Morteza; Cheraghi, Fatemeh; Namdar, Peyman; Allami, Abbas; Karampour, Amin; Zolghadr, Leila; Javadi, Amir; Varnaseri, Mehran; Karamyan, Masoumeh; Yadyad, Mohammad; Jamshidian, Ramin; Bijani, Behzad; Naderi, Yazdan; Gheibi, Nematollah; Amini, |

Fatemeh; Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial; Asian Pacific Journal of Tropical Medicine; 2021; vol. 14 (no. 6); 266-273

## Study details

| | |
|---|---|
| **Study design** | Randomised controlled trial (RCT) |
| **Trial registration (if reported)** | Iranian Registry of Clinical Trials website (registration ID: IRCT20200408046987N1) |
| **Study start date** | 01-Jun-2020 |
| **Study end date** | 15-Jul-2020 |
| **Aim of the study** | to investigate appropriate dose of ivermectin and its possible treatment efficacy on COVID-19 patients. |
| **Country/ Geographical location** | Qazvin and Khuzestan, Iran |
| **Study setting** | five hospitals (Velayat, Bu Ali, Taleghani, Razi, and Sina), in two provinces |
| **Population description** | hospitalised adults (age>18 years) with COVID-19 |
| **Inclusion criteria** | Eligible patients with COVID-19 who met the following criteria were admitted:<br><br>(1) age>18 years;<br><br>(2) signed the informed consent;<br><br>(3) clinical symptoms of suggestive of COVID-19 pneumonia: cough (with or without sputum), fever, pleuritic chest pain or dyspnea;<br><br>(4) mild to severe COVID-19 disease confirmed by chest computed tomography (CT) scan findings compatible with COVID-19 or positive RT-PCR |
| **Exclusion criteria** | Exclusion criteria included<br><br>• children (have lower rates of severe COVID-19),<br>• presence of severe immunosuppression (e.g., use of immune-suppressants and HIV positive),<br>• pregnant women (risk to fetus/infant)<br>• a known allergic reaction to the intervention drugs,<br>• chronic kidney disease,<br>• malignancy,<br>• severe COVID-19 patients<br>• indications that the patients were unable and/or unlikely to comprehend and/or follow the protocol. |
| **Intervention/test/approach** | Six arms:<br><br>1. single dose ivermectin (200 micrograms/kg)<br>2. three low interval doses of ivermectin (200, 200, 200 micrograms/kg) |

| | |
|---|---|
| | 3. single dose ivermectin (400 micrograms/kg)<br>4. three high interval doses of ivermectin (400, 200, 200 micrograms/kg). |
| **Comparator (where applicable)** | All patients were treated according to “Iranian Guideline of Hospitalised COVID-19 Patients’ Management (Version 5)”. This comprised oral hydroxychloroquine 200 mg twice per day as standard regimen and a heparin prophylaxis in combination with supplemental oxygen. Tablet of ivermectin (14 mg) and placebo were formulated in Alborz Darou pharmaceutical Co., Qazvin, Iran.<br><br>Two Arms:<br><br>1. hydroxychloroquine 200 mg twice per day<br>2. placebo plus hydroxychloroquine 200 mg twice per day |
| **Methods for population selection/allocation** | The transposed block randomisation sequence, including stratification, was prepared by a statistician not involved in the trial using Random Allocation Software. |
| **Methods of data analysis** | • Kruskal-Wallis *H* test,<br>• t-tests or Mann-Whitney U-tests<br>• Pearson Chi-squared test<br><br>Analyses were performed based on non-missing data |
| **Attrition/loss to follow-up** | n=30 allocated to each arms<br><br>Following number of patients discontinued due to death<br><br>• n=5 in standard care group - hydroxychloroquine 200mg twice per day<br>• n=6 in standard care group - hydroxychloroquine 200mg twice per day plus placebo,<br>• n=0 in arm 1, single dose ivermectin (200 micrograms/kg)<br>• n=3 in arm 2, three low interval doses of ivermectin (200, 200, 200 micrograms/kg)<br>• n=0 in arm 3, single dose ivermectin (400 micrograms/kg)<br>• n=1 in arm 4, three high interval doses of ivermectin (400, 200, 200 micrograms/kg). |
| **Summary of findings** | |

| | |
|---|---|
| **Study limitations (Author)** | The sample size was not large and the study was limited to the selected hospitals.<br><br>Some participants' disease was confirmed by a chest Image and not by RT-PCR |
| **Study limitations (Reviewer)** | Standard care is hydroxychloroquine, which is not used as standard in the UK. This raises concerns about generalisability of findings in the UK population |

**Study arms**
**Standard care (N = 30)**
Hydroxychloroquine 200 mg twice per day

**Placebo (N = 30)**
placebo plus hydroxychloroquine 200 mg twice per day

**Arm 1 (N = 30)**
Single dose of ivermectin 200 micrograms/kg

**Arm 2 (N = 30)**
three doses of ivermectin 200 micrograms/kg

**Arm 3 (N = 30)**
single dose ivermectin 400 microgram/kg

**Arm 4 (N = 30)**
three doses of ivermectin 400ug/kg, 200ug/kg, 200ug/kg

**Characteristics**
**Arm-level characteristics**

| Characteristic | Standard care (N = 30) | Placebo (N = 30) | Arm 1 (N = 30) | Arm 2 (N = 30) | Arm 3 (N = 30) | Arm 4 (N = 30) |
|---|---|---|---|---|---|---|
| **Sex - male**<br>No of events | n = 16 ; % = 53.3 | n = 14 ; % = 46.7 | n = 12 ; % = 40 | n = 19 ; % = 63.3 | n = 16 ; % = 53.3 | n = 13 ; % = 43.3 |
| **Sex - female**<br>No of events | n = 14 ; % = 46.7 | n = 16 ; % = 53.3 | n = 18 ; % = 60 | n = 11 ; % = 36.7 | n = 14 ; % = 46.7 | n = 17 ; % = 56.7 |
| **Age**<br>Median (IQR) | 55 (45 to 70) | 58 (45 to 68) | 61 (42 to 68) | 53 (42 to 65) | 54 (47 to 60) | 54 (46 to 65) |
| **BMI**<br>Median (IQR) | 26 (24.4 to 27.6) | 25.6 (23.9 to 26.9) | 26.1 (24.8 to 28) | 26.4 (25.5 to 27.2) | 27.7 (25.7 to 32.6) | 25.1 (23.9 to 26.2) |
| **PCR Positive**<br>No of events | n = 18 ; % = 60 | n = 14 ; % = 46.7 | n = 23 ; % = 76.7 | n = 23 ; % = 76.7 | n = 29 ; % = 96.7 | n = 21 ; % = 70 |

**Outcomes**
**Relevant outcomes**

| Outcome | Standard care, , N = 30 | Placebo, , N = 30 | Arm 1, , N = 30 | Arm 2, , N = 30 | Arm 3, , N = 30 | Arm 4, , N = 30 |
|---|---|---|---|---|---|---|
| **Duration of hospital stay** (days) Median (IQR) | 7 (7 to 9) | 8 (6 to 11) | 6 (5 to 7) | 8 (6 to 9) | 5 (4 to 7) | 7 (6 to 10) |
| **Mortality** No of events | n = 5 ; % = 16.7 | n = 6 ; % = 20 | n = 0 ; % = 0 | n = 3 ; % = 10 | n = 0 ; % = 0 | n = 1 ; % = 3.3 |

## Vallejos, 2021

| | |
|---|---|
| **Bibliographic Reference** | Vallejos, Julio; Zoni, Rodrigo; Bangher, Maria; Villamandos, Silvina; Bobadilla, Angelina; Plano, Fabian; Campias, Claudia; Chaparro Campias, Evangelina; Medina, Maria Fernanda; Achinelli, Fernando; Guglielmone, Hector Andres; Ojeda, Jorge; Farizano Salazar, Diego; Andino, Gerardo; Kawerin, Pablo; Dellamea, Silvana; Aquino, Antonia Cristina; Flores, Victor; Martemucci, Carolina N; Martinez, Silvina Maria; Segovia, Juan Emanuel; Reynoso, Paola Itati; Sosa, Noelia Carolina; Robledo, Mariana Elizabeth; Guarrochena, Joaquina Maria; Vernengo, Maria Mercedes; Ruiz Diaz, Natalia; Meza, Elba; Aguirre, Maria Gabriela; Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial.; BMC infectious diseases; 2021; vol. 21 (no. 1); 635 |

### Study details

| | |
|---|---|
| **Trial registration (if reported)** | ClinicalTrials.gov (NCT04529525) |
| **Study start date** | 19-Aug-2020 |
| **Study end date** | 22-Feb-2021 |
| **Country/ Geographical location** | Corrientes, Argentina |
| **Study setting** | Community, Argentina |
| **Population description** | Individuals over 18 years of age residing in the province of Corrientes at the time of diagnosis with confirmed COVID-19 diagnosis by RT-PCR for SARS-CoV2 detection in the last 48 h. |
| **Inclusion criteria** | • aged 18 years of age<br>• residing in the province of Corrientes<br>• diagnosis with confirmed COVID-19 diagnosis by RT-PCR for SARS-CoV2 detection in the last 48 h<br>• If they are women of childbearing age, must be using a contraceptive method of proven efficacy and safety.<br>• weight at the time of inclusion equal to or greater than 48 kg. |

| | |
|---|---|
| **Exclusion criteria** | Participants were excluded if they<br><br>• required current home oxygen use<br>• required hospitalisation for COVID-19 at the time of diagnosis<br>• had a history of hospitalisation for COVID-19<br>• pregnant or breastfeeding women<br>• known allergy to ivermectin or the components of ivermectin or placebo tablets<br>• presence of mal-absorptive syndrome<br>• presence of any other concomitant acute infectious disease<br>• known history of severe liver disease, and recent or expected need for dialysis<br>• Concomitant use of hydroxychloroquine or chloroquine or antiviral drugs due to a viral pathology other than COVID-19 at the time of admission<br>• the use of ivermectin up to 7 days before randomisation |
| **Intervention/test/approach** | ivermectin plus standard of care<br><br>• Those weighing up to 80 kg received 2 tablets of 6 mg (mg) each at inclusion and another 2 tablets of 6 mg each 24 h after the first dose (total 24 mg).<br>• Those weighing more than 80 kg and up to 110 kg received 3 tablets of 6 mg each at inclusion and another 3 tablets of 6 mg each 24 h after the first dose (total 36 mg).<br>• Those weighing more than 110 kg received 4 tablets of 6 mg each at inclusion and another 4 tablets of 6 mg each 24 h after the first dose (total 48 mg). |
| **Comparator (where applicable)** | Placebo plus SOC (SOC in accordance with Argentina Ministry of Health)<br><br>Individuals randomised to placebo received the equivalent number of placebo tablets to the ivermectin weight-based dosage, at baseline and again after 24 h. |
| **Methods for population selection/allocation** | web-based system using randomly permuted blocks in a 1:1 ratio<br><br>Patients were consecutively assigned to the treatment kit in ascending order at inclusion. |
| **Methods of data analysis** | • Student's *t*-test or the Mann-Whitney test<br>• chi-square test<br>• logistic regression<br>• hospitalisation-free survival - log-rank test with its corresponding Kaplan-Meier curve and the Cox regression test |

| | |
|---|---|
| **Attrition/loss to follow-up** | 501 patients were included in intention-to-treat analysis (250 to ivermectin and 251 to placebo)<br><br>Placebo group: 248 had 100% compliance, 2 had 50% compliance and 1 patient has 0% compliance<br><br>Ivermectin group: 249 had 100% compliance and 1 had 50% compliance<br><br>There was no missing data |
| **Study limitations (Author)** | • the percentage of events in relation to the primary outcome was below the estimate, so this trial was under powered.<br>• the mean dose of ivermectin was 192.37 micrograms/kg/day (SD ± 24.56), which is below the doses proposed as probably effective<br>• middle-aged population was included so hospitalisation rate below 10% was set at the time of calculating sample size<br>• blood ivermectin levels were not measured, so author stated that they cannot know the bioavailability of the drug in these patients or the blood ivermectin levels that were reached.<br>• Lastly, authors did not include any scale to determine the severity of the patients who were enrolled |

**Study arms**
**Ivermectin (N = 250)**

**Placebo (N = 251)**

**Characteristics**
**Arm-level characteristics**

| Characteristic | Ivermectin (N = 250) | Placebo (N = 251) |
|---|---|---|
| **Age** (years)<br>Mean (SD) | 42.58 (15.29) | 42.4 (15.75) |
| **Sex - female**<br>No of events | n = 111 ; % = 44.4 | n = 126 ; % = 50.2 |
| **Weight** (kg)<br>Mean (SD) | 81.7 (18.5) | 81.3 (18.27) |
| **Dose micrograms/kg/day**<br>Individuals randomised to placebo received the equivalent number of placebo tablets to the ivermectin weight-based dosage, at baseline and again after 24 h.<br>Mean (SD) | 192.3 (24.5) | 190.6 (23.93) |
| **Hypertension %**<br>No of events | n = 53 ; % = 21.3 | n = 66 ; % = 26.3 |

| Characteristic | Ivermectin (N = 250) | Placebo (N = 251) |
|---|---|---|
| **Diabetes %**<br>No of events | n = 21 ; % = 8.4 | n = 27 ; % = 10.8 |
| **Days from symptom started to inclusion**<br>Median (IQR) | 4 (3 to 5) | 4 (3 to 6) |

## Outcomes

### Primary and secondary outcomes

| Outcome | Ivermectin , , N = 250 | Placebo , , N = 251 |
|---|---|---|
| **All-cause mortality**<br>No of events | n = 4 ; % = 1.6 | n = 3 ; % = 1.2 |
| **Hospitalisation**<br>No of events | n = 14 ; % = 5.6 | n = 12 ; % = 8.37 |
| **Invasive mechanical ventilation**<br>No of events | n = 4 ; % = 1.6 | n = 3 ; % = 1.2 |
| **Negative nasal swab day 3**<br>No of events | n = 113 ; % = 47.08 | n = 120 ; % = 49.09 |
| **Negative nasal swab at day 12**<br>No of events | n = 212 ; % = 89.08 | n = 221 ; % = 92.47 |
| **Adverse events**<br>No of events | n = 45 ; % = 18 | n = 53 ; % = 21.1 |
| **Serious adverse events**<br>No of events | n = 0 ; % = 0 | n = 0 ; % = 0 |
| **Discontinuation due to adverse events**<br>No of events | n = 0 ; % = 0 | n = 0 ; % = 0 |

# Appendix G: Risk of Bias

### Abbas K, 2022

| | |
|---|---|
| **Bibliographic Reference** | Abbas K, U; Muhammad, S; Ding S, F; The Effect of Ivermectin on Reducing Viral Symptoms in Patients with Mild COVID-19; Indian Journal of Pharmaceutical Sciences; 2022; vol. 84; 87-91 |

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Time of resolution of symptoms

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns *(discrepancies in reporting numbers in results text and abstract text, incomplete information on missing outcome data)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns *(No information available on pre-specified plan or per-protocol analyses)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(incomplete information on reporting of outcomes)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Symptoms resolved

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns *(discrepancies in reporting numbers in results text and abstract text, incomplete information on missing outcome data)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns *(No information available on pre-specified plan or per-protocol analyses)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(incomplete information on reporting of outcomes)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Deterioration of 2 or more points on 8 point scale of WHO

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns *(discrepancies in reporting numbers in results text and abstract text, incomplete information on missing outcome data)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns *(No information available on pre-specified plan or per-protocol analyses)* |

| Section | Question | Answer |
|---|---|---|
| Overall bias and Directness | Risk of bias judgement | Some concerns *(incomplete information on reporting of outcomes)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Mortality

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns *(discrepancies in reporting numbers in results text and abstract text, incomplete information on missing outcome data)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns *(No information available on pre-specified plan or per-protocol analyses)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(incomplete information on reporting of outcomes)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

### Abd-Elsalam, 2021

| | |
|---|---|
| **Bibliographic Reference** | Abd-Elsalam, Sherief; Noor, Rasha A; Badawi, Rehab; Khalaf, Mai; Esmail, Eslam S; Soliman, Shaimaa; Abd El Ghafar, Mohamed S; Elbahnasawy, Mohamed; Moustafa, Ehab F; Hassany, Sahar M; Medhat, Mohammed A; Ramadan, Haidi Karam-Allah; Eldeen, Maii A S; Alboraie, Mohamed; Cordie, Ahmed; Esmat, Gamal; Clinical study evaluating the efficacy of ivermectin in COVID-19 treatment: A randomized controlled study.; Journal of medical virology; 2021; vol. 93 (no. 10); 5833-5838 |

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Mortality

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns *(Unclear how many people received antivirals/steroids)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns *(Unclear how many people received antivirals/steroids)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns *(Outcomes on trial registry record were changed after study completion so unclear if pre-specified)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(Unclear use of antivirals/steroids. Potential retrospective change in outcomes)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Length of hospital stay

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns *(Unclear how many people received antivirals/steroids)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns *(Unclear how many people received antivirals/steroids)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns *(Outcome requires clinical judgement which may be* |

| Section | Question | Answer |
|---|---|---|
| | | *influenced by knowledge of intervention)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns *(Outcomes on trial registry record were changed after study completion so unclear if pre-specified)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(Knowledge of intervention allocation could impact this outcome. Unclear use of antivirals/steroids. Potential retrospective change in outcomes)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Need for mechanical ventilation

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns *(Unclear how many people received antivirals/steroids)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns *(Unclear how many people received antivirals/steroids)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns *(Outcome requires clinical judgement which may be influenced by knowledge of intervention)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns *(Outcomes on trial registry record were changed after study completion so unclear if pre-specified)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(Unclear use of antivirals/steroids. Potential retrospective change in outcomes)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Mild side effects

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns *(Unclear how many people received antivirals/steroids)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns *(Unclear how many people received antivirals/steroids)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns *(Outcome requires clinical judgement or self-reporting by patients which may be influenced by knowledge of intervention)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns *(Outcomes on trial registry record were changed after study completion so unclear if pre-specified)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(Knowledge of intervention allocation could impact this outcome. Unclear use of antivirals/steroids. Potential retrospective change in outcomes)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

**Ahmed, 2021**

| | |
|---|---|
| **Bibliographic Reference** | Ahmed, Sabeena; Karim, Mohammad Mahbubul; Ross, Allen G; Hossain, Mohammad Sharif; Clemens, John D; Sumiya, Mariya Kibtiya; Phru, Ching Swe; Rahman, Mustafizur; Zaman, Khalequ; Somani, Jyoti; Yasmin, Rubina; Hasnat, Mohammad Abul; Kabir, Ahmedul; Aziz, Asma Binte; Khan, Wasif Ali; A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness.; International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases; 2021; vol. 103; 214-216 |

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Duration of Hospitalisation

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns *(Unclear randomisation methods and no baseline characteristics)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns *(Mortality not reported although specified as an outcome)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns *(No data for mortality.)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(No randomisation methods reported and unclear outcome reporting)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Duration to virological clearance

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns *(Unclear randomisation methods and no baseline characteristics)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns *(Mortality not reported although specified as an outcome)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns *(No data for mortality.)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(No randomisation methods reported and unclear outcome reporting)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Adverse events

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns *(Unclear randomisation methods and no baseline characteristics)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns *(Mortality not reported although specified as an outcome)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns *(No data for mortality.)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(No randomisation methods reported and unclear outcome reporting)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

### Beltran, 2022

| | |
|---|---|
| **Bibliographic Reference** | Beltran, Gonzalez; Jose, Lenin; Gonzalez, Gamez; Mario; Mendoza Enciso Emanuel, Antonio; Esparza, Maldonado; Ramiro, Josue; Hernandez, Palacios; Daniel; Duenas, Campos; Samuel; Robles Itzel, Ovalle; Macias, Guzman; Mariana, Jocelyn; Garcia, Diaz; Andrea, Lucia; Gutierrez, Pena; Cesar, Mauricio; Martinez, Medina; Lucila; Monroy, Colin; Victor, Antonio; Arreola Guerra Jose, Manuel; Efficacy and Safety of Ivermectin and Hydroxychloroquine in Patients with Severe COVID-19: |

A Randomized Controlled Trial.; Infectious disease reports; 2022; vol. 14 (no. 2); 160-168

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Duration of Hospitalisation

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns *(method of randomisation is not given)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(lack of information on per-protocol analysis and randomisation)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Hospital Discharge

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns *(method of randomisation is not given)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(lack of information on per-protocol analysis and randomisation)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Discharge without respiratory deterioration

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns *(method of randomisation is not given)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(lack of information on per-protocol analysis and randomisation)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Respiratory deterioration or death

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns *(method of randomisation is not given)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended | Risk of bias judgement for deviations from the intended | Low |

| Section | Question | Answer |
|---|---|---|
| interventions (effect of adhering to intervention) | interventions (effect of adhering to intervention) | |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(lack of information on per-protocol analysis and randomisation)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Death

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns *(method of randomisation is not given)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(lack of information on per-protocol analysis and randomisation)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

**Biber et al.**

| | |
|---|---|
| **Bibliographic Reference** | Biber, Asaf; Mandelboim, Michal; Harmelin, Geva; Lev, Dana; Ram, Li; Shaham, Amit; Nemet, Ital; Kliker, Limor; Erster, Oran; Schwartz, Eli; Favorable outcome on viral load and culture viability using Ivermectin in |

early treatment of non-hospitalized patients with mild COVID-19, A double-blind, randomized placebo-controlled trial.; medrxiv preprint

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Number of patients requiring oxygen

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*("Randomization in a 1:1 ratio was done by computer-generated program using randomization. By Clinical Research Coordinator (CRC), blinded to the rest of study team")* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*("The investigators and patients were blinded to the assignment." Exclusion of positive RT-PCR test post randomisation (7 vs 14).)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns<br>*("The investigators and patients were blinded to the assignment." Exclusion of positive RT-PCR test post randomisation (7vs 14).)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(Patients with missing data along the follow up were carried over from the last data available. No evidence that the result is not biased.)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low<br>*(Method of measuring the outcome probably appropriate. Blinded study (outcome assessor).)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(Retrospective registry. Unclear if analysed as pre-specified. AEs an SAEs event data differed between analysis population and safety population)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Blinded study, some concerns surrounding exclusion post randomisation and retrospective registry.)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Hospitalisation

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*("Randomization in a 1:1 ratio was done by computer-generated program using randomization. By Clinical Research Coordinator (CRC), blinded to the rest of study team")* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*("The investigators and patients were blinded to the assignment." Exclusion of positive RT-PCR test post randomisation (7 vs 14).)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns<br>*("The investigators and patients were blinded to the assignment." Exclusion of positive RT-PCR test post randomisation (7 vs 14).)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(Patients with missing data along the follow up were carried over from the last data available. No evidence that the result is not biased.)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low<br>*(Method of measuring the outcome probably appropriate. Blinded study (outcome assessor).)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(Retrospective registry. Unclear if analysed as pre-specified. AEs an SAEs event numbers varied between analysis population and safety population)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Blinded study, some concerns surrounding exclusion post randomisation and retrospective registry.)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Viral clearance within 7-12 days

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*("Randomization in a 1:1 ratio was done by computer-generated program using randomization. By Clinical Research Coordinator (CRC), blinded to the rest of study team")* |

| Section | Question | Answer |
|---|---|---|
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low<br>*(“The investigators and patients were blinded to the assignment.” Exclusion of positive RT-PCR test post randomisation (7 vs 14).)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(Patients with missing data along the follow up were carried over from the last data available. No evidence that the result is not biased.)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low<br>*(Method of measuring the outcome probably appropriate. Blinded study (outcome assessor).)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(Retrospective registry. Unclear if analysed as pre-specified. AEs an SAEs event data and participant numbers vary from analysis population)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Blinded study, some concerns surrounding exclusion post randomisation and retrospective registry.)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Adverse events

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns<br>*("Randomization in a 1:1 ratio was done by computer-generated program using randomization. By Clinical Research Coordinator (CRC), blinded to the rest of study team")* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*(“The investigators and patients were blinded to the assignment.” Exclusion of positive RT-PCR test post randomisation (7 vs 14).)* |

| Section | Question | Answer |
|---|---|---|
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns<br>*("The investigators and patients were blinded to the assignment." Exclusion of positive RT-PCR test post randomisation (7 vs 14).)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(Patients with missing data along the follow up were carried over from the last data available. No evidence that the result is not biased.)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low<br>*(Method of measuring the outcome probably appropriate. Blinded study (outcome assessor).)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(Retrospective registry. Unclear if analysed as pre-specified. AEs an SAEs event numbers different between analysis population and safety population)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Blinded study, some concerns surrounding exclusion post randomisation and retrospective registry.)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

### Bukhari (preprint)

| | |
|---|---|
| **Bibliographic Reference** | Bukhari Syed Karamat Hussain, Shah; Asghar, Asma; Perveen, Najma; Hayat, Arshad; Mangat Sermad, Ahmad; Butt Kamil, Rehman; Abdullah, Mohammad; Fatima, Tehreem; Mustafa, Ahmad; Cheema, Talal; Merrill, Anna; Perlman, Stanley; Knudson, Mike; Kalyani, Suraj; Raut, Prathamesh; Bapte, Madhura; Mehta, Anshul; Reddy M, Sateesh; Bhayani, Krushnadas; Laxmi S, S; Vishnu P, D; Srivastava, Shipra; Khandelwal, Shubham; More, Sailee; Shinde, Rohit; Pawar, Mohit; Harshe, Amol; Kadam, Sagar; Mahajan, Uma; Joshi, Gaurav; Mane, Dilip; Efficacy of Ivermectin in COVID-19 Patients with Mild to Moderate Disease; medrxiv preprint |

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Virological clearance day 7

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns<br>*(randomisation methods were not sufficiently reported to be sure allocation sequence was random)* |

| Section | Question | Answer |
|---|---|---|
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*(Unblinded trial and no information on co-interventions)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns<br>*(Unblinded trial and no information on co-interventions. No analysis methods reported)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(14 people left against medical advice)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns<br>*(Unblinded study)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(The clinicaltrials.gov entry lists two outcomes: negative PCR and need for mechanical ventilation. Only negative PCR outcomes were reported)* |
| Overall bias and Directness | Risk of bias judgement | High<br>*(Unblinded study, several patients withdrew against medical advice. Potential reporting bias)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Adverse events

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns<br>*(randomisation methods were not sufficiently reported to be sure allocation sequence was random)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*(Unblinded trial and no information on co-interventions)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns<br>*(Unblinded trial and no information on co-interventions. No analysis methods reported)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(14 people left against medical advice)* |

| Section | Question | Answer |
|---|---|---|
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns<br>*(Unblinded study)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(The clinicaltrials.gov entry lists two outcomes: negative PCR and need for mechanical ventilation. Only negative PCR outcomes were reported)* |
| Overall bias and Directness | Risk of bias judgement | High<br>*(Unblinded study, several patients withdrew against medical advice. Potential reporting bias)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

### Buonfrate, 2022

| | |
|---|---|
| **Bibliographic Reference** | Buonfrate, D; Chesini, F; Martini, D; Roncaglioni M, C; Ojeda Fernandez, M.L; Alvisi M, F; De Simone, I; Rulli, E; Nobili, A; Casalini, G; Antinori, S; Gobbi, M; Campoli, C; Deiana, M; Pomari, E; Lunardi, G; Tessari, R; Bisoffi, Z; High-dose ivermectin for early treatment of COVID-19 (COVER study): a randomised, double-blind, multicentre, phase II, dose-finding, proof-of-concept clinical trial; International Journal of Antimicrobial Agents; 2022; 106516 |

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Serious adverse events/ serious adverse reactions Ivermectin 600micrograms/kg - Ivermectin 1200micrograms/kg

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |

| Section | Question | Answer |
|---|---|---|
| Overall bias and Directness | Overall Directness | Directly applicable |

Time to clinical resolution Ivermectin 600micrograms/kg -Ivermectin 1200micrograms/kg

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Reduction in Viral Load at day 7 Ivermectin 600micrograms/kg -Ivermectin 1200micrograms/kg

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |

| Section | Question | Answer |
|---|---|---|
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Virological Clearance within 14days Ivermectin 600micrograms/kg -Ivermectin 1200micrograms/kg

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Virological clearance within 30days Ivermectin 600micrograms/kg -Ivermectin 1200micrograms/kg

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Hospitalisation rate Ivermectin 600micrograms/kg -Ivermectin 1200micrograms/kg

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

### Chaccour, 2021

| | |
|---|---|
| **Bibliographic Reference** | Chaccour, Carlos; Casellas, Aina; Blanco-Di Matteo, Andres; Pineda, Inigo; Fernandez-Montero, Alejandro; Ruiz-Castillo, Paula; Richardson, Mary-Ann; Rodriguez-Mateos, Mariano; Jordan-Iborra, Carlota; Brew, Joe; Carmona-Torre, Francisco; Giraldez, Miriam; Laso, Ester; Gabaldon-Figueira, Juan C; Dobano, Carlota; Moncunill, Gemma; Yuste, Jose R; Del Pozo, Jose L; Rabinovich, N Regina; Schoning, Verena; Hammann, Felix; Reina, Gabriel; Sadaba, Belen; Fernandez-Alonso, Mirian; The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial.; EClinicalMedicine; 2021; vol. 32; 100720 |

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Adverse events

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns *("The randomization sequence was computer-generated by the trial statistician using blocks of four to ensure balance. Allocation was made by the attending investigator using opaque envelopes. The placebo tablets did not match ivermectin in appearance, therefore, in order for the clinical team to remain blinded, treatment was administered under direct supervision by a nurse not participating in patient´s care. There was a higher proportion of females in the placebo group (58 vs 42%). There was a good balance in terms of other demographics and disease characteristics (Table 1).At baseline, there were no differences in vital signs, inflammatory markers or full blood count between the groups (Table 1)." Some concerns regarding method of allocation concealment)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns *(Placebo-controlled; claims double-blinded study however details regarding blinding in patients are lacking. ITT analysis used.)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns *(Placebo-controlled; claims double-blinded study however details regarding blinding in patients are lacking. ITT analysis used.)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low *("All randomized patients received the corresponding study product and completed 28 days of follow-up (Figure 1).")* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low *(RT-PCR, SAEs, progression to severe low risk of bias. Self-reported symptoms and AEs, however blinded study so at low risk of bias.)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low *(All outcomes, with exception of progression to severe disease or death, pre-specified in trial registry, protocol and SAP, as well as exploratory analyses.)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(Outcomes of interest: AEs, SAEs. Some concerns)* |

| Section | Question | Answer |
|---|---|---|
| Overall bias and Directness | Overall Directness | Directly applicable |

Serious adverse events

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns *("The randomization sequence was computer-generated by the trial statistician using blocks of four to ensure balance. Allocation was made by the attending investigator using opaque envelopes. The placebo tablets did not match ivermectin in appearance, therefore, in order for the clinical team to remain blinded, treatment was administered under direct supervision by a nurse not participating in patient´s care. There was a higher proportion of females in the placebo group (58 vs 42%). There was a good balance in terms of other demographics and disease characteristics (Table 1).At baseline, there were no differences in vital signs, inflammatory markers or full blood count between the groups (Table 1)." Some concerns regarding method of allocation concealment)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns *(Placebo-controlled; claims double-blinded study however details regarding blinding in patients are lacking. ITT analysis used.)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns *(Placebo-controlled; claims double-blinded study however details regarding blinding in patients are lacking. ITT analysis used.)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low *("All randomized patients received the corresponding study product and completed 28 days of follow-up (Figure 1).")* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low *(RT-PCR, SAEs, progression to severe low risk of bias. Self-reported symptoms and AEs, however blinded study so at low risk of bias.)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for | Low *(All outcomes, with exception of progression to severe disease or death,* |

| Section | Question | Answer |
|---|---|---|
| | selection of the reported result | *pre-specified in trial registry, protocol and SAP, as well as exploratory analyses.)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Outcomes of interest: AEs, SAEs. Some concerns)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Viral clearance 1-7 days

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns<br>*("The randomization sequence was computer-generated by the trial statistician using blocks of four to ensure balance. Allocation was made by the attending investigator using opaque envelopes. The placebo tablets did not match ivermectin in appearance, therefore, in order for the clinical team to remain blinded, treatment was administered under direct supervision by a nurse not participating in patient´s care. There was a higher proportion of females in the placebo group (58 vs 42%). There was a good balance in terms of other demographics and disease characteristics (Table 1).At baseline, there were no differences in vital signs, inflammatory markers or full blood count between the groups (Table 1)." Some concerns regarding method of allocation concealment)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*(Placebo-controlled; claims double-blinded study however details regarding blinding in patients are lacking. ITT analysis used.)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns<br>*(Placebo-controlled; claims double-blinded study however details regarding blinding in patients are lacking. ITT analysis used.)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low<br>*("All randomized patients received the corresponding study product and completed 28 days of follow-up (Figure 1).")* |

| Section | Question | Answer |
|---|---|---|
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low<br>*(RT-PCR, SAEs, progression to severe low risk of bias. Self-reported symptoms and AEs, however blinded study so at low risk of bias.)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low<br>*(All outcomes, with exception of progression to severe disease or death, pre-specified in trial registry, protocol and SAP, as well as exploratory analyses.)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Outcomes of interest: AEs, SAEs. Some concerns)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

### Chachar, 2020

| | |
|---|---|
| **Bibliographic Reference** | Chachar, A.Z., Khan, K., Asif, M., Tanveer, K., Khaqan, A., & Basri R; Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients; International journal of sciences; 2020; vol. 9; 31-35 |

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Aysymptomatic at day 7

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns<br>*("Control group participants' were older than the case group statistically but there is no difference between the average ages of both groups ". Baseline factors between participants were similar and they were randomly allocated. "Participants were allocated randomly to the groups by computer generated number".)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*(Participants and personnel were not blinded)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns<br>*(Participants and personnel were not blinded)* |

| Section | Question | Answer |
|---|---|---|
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low<br>*(All participants and their data after randomization were included.)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns<br>*(Participants were not blinded)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | High<br>*("Response was recorded on the basis of clinical parameters (Fever, Cough, sore throat, Headache, Shortness of breath, lethargy, and fatigue. Any side effects noted after prescription of Ivermectin was recorded. " Recording of outcomes factors was not specified, potential for selective reporting.)* |
| Overall bias and Directness | Risk of bias judgement | High<br>*(Non-blinded study with subjective outcome. "Response was recorded on the basis of clinical parameters (Fever, Cough, sore throat, Headache, Shortness of breath, lethargy, and fatigue. Any side effects noted after prescription of Ivermectin was recorded. " Recording of outcomes factors was not specified, potential for selective reporting.)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

### Kishoria, 2020

| | |
|---|---|
| **Bibliographic Reference** | Kishoria, N., Mathur, S., Parmar, V., Kaur, R., Agarwal, H., Parihar, B., & Verma S; IVERMECTIN AS ADJUVANT TO HYDROXYCHOLOROQUINE IN PATIENTS RESISTANT TO STANDARD TREATMENT FOR SARS-CoV-2: RESULTS OF AN OPEN-LABEL RANDOMIZED CLINICAL STUDY; Paripex Indian Journal Of Research; 2020; vol. 9 (no. 8); 50-53 |

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Discharged from hospital

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*("The randomization list was generated by a computerized system by a unit independent of the study team. The randomization codes was kept in sealed sequentially numbered opaque envelopes.")* |

| Section | Question | Answer |
|---|---|---|
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*(Open-label (unblinded). Unclear co-interventions outside of those included in standard care.)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns<br>*(Open-label (unblinded). Unclear co-interventions outside of those included in standard care.)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(Data available for al, misreporting of participant numbers in text I 32 participants.)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns<br>*(Open-label (unblinded).)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(Protocol and registry were not available. Unclear if conducted as pre-specified.)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Trial was open label with some concerns regarding the reporting of original analysis plans as well as blinding of participants and adherence to trial regimen)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Viral clearance 1-7 days

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*("The randomization list was generated by a computerized system by a unit independent of the study team. The randomization codes was kept in sealed sequentially numbered opaque envelopes.")* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*(Open-label (unblinded). Unclear co-interventions outside of those included in standard care.)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions | Risk of bias judgement for deviations from the intended interventions | Some concerns<br>*(Open-label (unblinded). Unclear co-interventions outside of those included in standard care.)* |

| Section | Question | Answer |
|---|---|---|
| (effect of adhering to intervention) | (effect of adhering to intervention) | |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(Data available for al, misreporting of participant numbers in text I 32 participants.)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns<br>*(Open-label (unblinded).)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(Protocol and registry were not available. Unclear if conducted as pre-specified.)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Trial was open label with some concerns regarding the reporting of original analysis plans as well as blinding of participants and adherence to trial regimen)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

### Krolewiecki, 2021

| | |
|---|---|
| **Bibliographic Reference** | Krolewiecki, Alejandro; Lifschitz, Adrian; Moragas, Matias; Travacio, Marina; Valentini, Ricardo; Alonso, Daniel F; Solari, Ruben; Tinelli, Marcelo A; Cimino, Ruben O; Alvarez, Luis; Fleitas, Pedro E; Ceballos, Laura; Golemba, Marcelo; Fernandez, Florencia; Fernandez de Oliveira, Diego; Astudillo, German; Baeck, Ines; Farina, Javier; Cardama, Georgina A; Mangano, Andrea; Spitzer, Eduardo; Gold, Silvia; Lanusse, Carlos; Antiviral effect of high-dose ivermectin in adults with COVID-19: A proof-of-concept randomized trial.; EClinicalMedicine; 2021; vol. 37; 100959 |

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Adverse events

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*(Enrolled participants were randomly assigned (2:1) to either IVM group or untreated control group. Randomization was stratified for each Center. Randomization sequence was prepared by a centralized, web-based system in blocks of variable size (3, 6 or 9 cases per block) and communicated to the trial physicians that recruited the patients upon entry to the web system information on availability of* |

| Section | Question | Answer |
|---|---|---|
| | | *the signed Informed Consent Form and verification of all eligibility criteria.)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns *("Patients, nurses, and physicians were not blinded to the treatment arm. Outcome assessors (virology staff) were blinded to the treatment group by receiving the samples labeled with randomization code and visit number." Only outcome assessors blinded. (single blinded) AES reported for all participant, no information on co-interventions (standard of care))* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns *("Patients, nurses, and physicians were not blinded to the treatment arm. Outcome assessors (virology staff) were blinded to the treatment group by receiving the samples labeled with randomization code and visit number." Only outcome assessors blinded. (single blinded) AES reported for all participant, no information on co-interventions (standard of care))* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low *(For SAEs & AEs information reported for all participants)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns *(adverse events and serious adverse events may be affected by unblinding.)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low *(Outcomes reported as in the prespecified protocol. Unlikely that it affects the outcomes of interest.)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(Trial single blinded, only for viral load outcome evaluation. Co interventions not reported, for our outcomes of interest SAEs and AEs complete reporting although non blinding could affect their reporting)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Serious Adverse events

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low *(Enrolled participants were randomly assigned (2:1) to either IVM group or untreated control group. Randomization was stratified for each Center.* |

| Section | Question | Answer |
|---|---|---|
| | | *Randomization sequence was prepared by a centralized, web-based system in blocks of variable size (3, 6 or 9 cases per block) and communicated to the trial physicians that recruited the patients upon entry to the web system information on availability of the signed Informed Consent Form and verification of all eligibility criteria.)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*("Patients, nurses, and physicians were not blinded to the treatment arm. Outcome assessors (virology staff) were blinded to the treatment group by receiving the samples labeled with randomization code and visit number." Only outcome assessors blinded. (single blinded) AES reported for all participant, no information on co-interventions (standard of care))* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns<br>*("Patients, nurses, and physicians were not blinded to the treatment arm. Outcome assessors (virology staff) were blinded to the treatment group by receiving the samples labeled with randomization code and visit number." Only outcome assessors blinded. (single blinded) AES reported for all participant, no information on co-interventions (standard of care))* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low<br>*(For SAEs & AEs information reported for all participants)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns<br>*(adverse events and serious adverse events may be affected by unblinding.)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low<br>*(Outcomes reported as in the prespecified protocol. Unlikely that it affects the outcomes of interest.)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Trial single blinded, only for viral load outcome evaluation. Co interventions not reported, for our outcomes of interest SAEs and AEs complete reporting although non blinding could affect their reporting)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Invasive mechanical ventilation

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*(Enrolled participants were randomly assigned (2:1) to either IVM group or untreated control group. Randomization was stratified for each Center. Randomization sequence was prepared by a centralized, web-based system in blocks of variable size (3, 6 or 9 cases per block) and communicated to the trial physicians that recruited the patients upon entry to the web system information on availability of the signed Informed Consent Form and verification of all eligibility criteria.)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*("Patients, nurses, and physicians were not blinded to the treatment arm. Outcome assessors (virology staff) were blinded to the treatment group by receiving the samples labeled with randomization code and visit number." Only outcome assessors blinded. (single blinded) AES reported for all participant, no information on co-interventions (standard of care))* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns<br>*("Patients, nurses, and physicians were not blinded to the treatment arm. Outcome assessors (virology staff) were blinded to the treatment group by receiving the samples labeled with randomization code and visit number." Only outcome assessors blinded. (single blinded) AES reported for all participant, no information on co-interventions (standard of care))* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low<br>*(For SAEs & AEs information reported for all participants)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns<br>*(adverse events and serious adverse events may be affected by unblinding.)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low<br>*(Outcomes reported as in the prespecified protocol. Unlikely that it affects the outcomes of interest.)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Trial single blinded, only for viral load outcome evaluation. Co interventions not reported, for our outcomes of interest SAEs and AEs complete reporting although non blinding could affect their reporting)* |

| Section | Question | Answer |
|---|---|---|
| Overall bias and Directness | Overall Directness | Directly applicable |

### Lim Steven Chee, 2022

| | |
|---|---|
| **Bibliographic Reference** | Lim Steven Chee, Loon; Hor Chee, Peng; Tay Kim, Heng; Mat, Jelani; Anilawati; Tan Wen, Hao; Ker Hong, Bee; Chow Ting, Soo; Zaid, Masliza; Cheah Wee, Kooi; Lim Han, Hua; Khalid Khairil, Erwan; Cheng Joo, Thye; Mohd, Unit; Hazfadzila; An, Noralfazita; Nasruddin Azraai, Bahari; Low Lee, Lee; Khoo Song Weng, Ryan; Loh Jia, Hui; Zaidan Nor, Zaila; Ab, Wahab; Suhaila; Song Li, Herng; Koh Hui, Moon; King Teck, Long; Lai Nai, Ming; Chidambaram Suresh, Kumar; Peariasamy Kalaiarasu, M; I-TECH, Study; Group; Efficacy of Ivermectin Treatment on Disease Progression Among Adults With Mild to Moderate COVID-19 and Comorbidities: The I-TECH Randomized Clinical Trial.; JAMA internal medicine; 2022 |

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Progression to severe disease

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns *(due to open label design, subjective outcome assessment might have been influenced)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(due to open label design, subjective outcome assessment might have been influenced)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Time of progression to severe disease

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns *(due to open label design, subjective outcome assessment might have been influenced)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(due to open label design, subjective outcome assessment might have been influenced)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Patients who had mechanical ventilation

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns *(due to open label design, subjective outcome assessment might have been influenced)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |

| Section | Question | Answer |
|---|---|---|
| Overall bias and Directness | Risk of bias judgement | Some concerns *(due to open label design, subjective outcome assessment might have been influenced)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Patients admitted to ICU

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns *(due to open label design, subjective outcome assessment might have been influenced)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(due to open label design, subjective outcome assessment might have been influenced)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

ALL-Cause mortality

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Length of Hospital stay

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns *(due to open label design, subjective outcome assessment might have been influenced)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(due to open label design, subjective outcome assessment might have been influenced)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Complete symptom resolution

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns *(due to open label design, subjective outcome assessment might have been influenced)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(due to open label design, subjective outcome assessment might have been influenced)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Normal chest radiography

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns *(due to open label design, subjective outcome assessment might have been influenced)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(due to open label design, subjective outcome assessment might have been influenced)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

1 or more than 1 adverse events or serious adverse events

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns *(due to open label design, subjective outcome assessment might have been influenced)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(due to open label design, subjective outcome assessment might have been influenced)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

total serious adverse events

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |

| Section | Question | Answer |
|---|---|---|
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

### Lopez-Medina, 2021

| | |
|---|---|
| **Bibliographic Reference** | Lopez-Medina, Eduardo; Lopez, Pio; Hurtado, Isabel C; Davalos, Diana M; Ramirez, Oscar; Martinez, Ernesto; Diazgranados, Jesus A; Onate, Jose M; Chavarriaga, Hector; Herrera, Socrates; Parra, Beatriz; Libreros, Gerardo; Jaramillo, Roberto; Avendano, Ana C; Toro, Dilian F; Torres, Miyerlandi; Lesmes, Maria C; Rios, Carlos A; Caicedo, Isabella; Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial.; JAMA; 2021; vol. 325 (no. 14); 1426-1435 |

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Time to resolution of symptoms/recovery

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*("Patients were randomized in permuted blocks of 4 in a randomization sequence prepared by the unblinded pharmacist in Microsoft Excel version 19.0 who provided masked ivermectin or placebo to a field nurse for home or hospital patient visits." Allocation assignment was concealed from investigators and patients.)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*(Unclear who/if anyone was blinded to outcomes. labeling error also occurred for a period of the trial resulting in all participants receiving ivermectin and none receiving placebo during this time frame.)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns<br>*(Unclear who/if anyone was blinded to outcomes. labeling error also occurred for a period of the trial resulting in all participants receiving ivermectin and none receiving placebo during this time frame.)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(476 participants randomized; 398 participants analyzed. Reasons for missing data: error in labeling, which resulted in 38 placebo group participants receiving treatment.)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for | Some concerns<br>*(“The primary outcome was originally defined as the time from randomization* |

| Section | Question | Answer |
|---|---|---|
| | measurement of the outcome | *until worsening by 2 points on the 8-category ordinal scale… the principal investigator proposed to the data and safety monitoring board to modify the primary end point to time from randomization to complete resolution of symptoms within the 21-day follow-up period". Primary outcome measures were changed during the study.)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(Primary outcome measures unclear if reported as pre-specified.)* |
| Overall bias and Directness | Risk of bias judgement | High<br>*(Concerns with trial conduct and adherence to intervention and labelling error in study which may have impacted outcomes for patients)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Death

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*("Patients were randomized in permuted blocks of 4 in a randomization sequence prepared by the unblinded pharmacist in Microsoft Excel version 19.0 who provided masked ivermectin or placebo to a field nurse for home or hospital patient visits." Allocation assignment was concealed from investigators and patients.)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*(Unclear who/if anyone was blinded to outcomes. labeling error also occurred for a period of the trial resulting in all participants receiving ivermectin and none receiving placebo during this time frame.)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns<br>*(Unclear who/if anyone was blinded to outcomes. labeling error also occurred for a period of the trial resulting in all participants receiving ivermectin and none receiving placebo during this time frame.)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(476 participants randomized; 398 participants analyzed. Reasons for missing data: error in labeling, which resulted in 38* |

| Section | Question | Answer |
|---|---|---|
| | | *placebo group participants receiving treatment.)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns<br>*("The primary outcome was originally defined as the time from randomization until worsening by 2 points on the 8-category ordinal scale… the principal investigator proposed to the data and safety monitoring board to modify the primary end point to time from randomization to complete resolution of symptoms within the 21-day follow-up period". Primary outcome measures were changed during the study.)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(Primary outcome measures unclear if reported as pre-specified.)* |
| Overall bias and Directness | Risk of bias judgement | High<br>*(Concerns with trial conduct and adherence to intervention and labelling error in study which may have impacted outcomes for patients)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Clinical progression/deterioration by 2 or more points

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*("Patients were randomized in permuted blocks of 4 in a randomization sequence prepared by the unblinded pharmacist in Microsoft Excel version 19.0 who provided masked ivermectin or placebo to a field nurse for home or hospital patient visits." Allocation assignment was concealed from investigators and patients.)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*(Unclear who/if anyone was blinded to outcomes. labeling error also occurred for a period of the trial resulting in all participants receiving ivermectin and none receiving placebo during this time frame.)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns<br>*(Unclear who/if anyone was blinded to outcomes. labeling error also occurred for a period of the trial resulting in all participants receiving ivermectin and none receiving placebo during this time frame.)* |

| Section | Question | Answer |
|---|---|---|
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(476 participants randomized; 398 participants analyzed. Reasons for missing data: error in labeling, which resulted in 38 placebo group participants receiving treatment.)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns<br>*("The primary outcome was originally defined as the time from randomization until worsening by 2 points on the 8-category ordinal scale… the principal investigator proposed to the data and safety monitoring board to modify the primary end point to time from randomization to complete resolution of symptoms within the 21-day follow-up period". Primary outcome measures were changed during the study.)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(Primary outcome measures unclear if reported as pre-specified.)* |
| Overall bias and Directness | Risk of bias judgement | High<br>*(Concerns with trial conduct and adherence to intervention and labelling error in study which may have impacted outcomes for patients)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Adverse events

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*("Patients were randomized in permuted blocks of 4 in a randomization sequence prepared by the unblinded pharmacist in Microsoft Excel version 19.0 who provided masked ivermectin or placebo to a field nurse for home or hospital patient visits." Allocation assignment was concealed from investigators and patients.)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*(Unclear who/if anyone was blinded to outcomes. labeling error also occurred for a period of the trial resulting in all participants receiving ivermectin and none receiving placebo during this time frame.)* |
| Domain 2b: Risk of bias due to deviations | Risk of bias judgement for | Some concerns<br>*(Unclear who/if anyone was blinded to* |

| Section | Question | Answer |
|---|---|---|
| from the intended interventions (effect of adhering to intervention) | deviations from the intended interventions (effect of adhering to intervention) | *outcomes. labeling error also occurred for a period of the trial resulting in all participants receiving ivermectin and none receiving placebo during this time frame.)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(476 participants randomized; 398 participants analyzed. Reasons for missing data: error in labeling, which resulted in 38 placebo group participants receiving treatment.)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns<br>*("The primary outcome was originally defined as the time from randomization until worsening by 2 points on the 8-category ordinal scale… the principal investigator proposed to the data and safety monitoring board to modify the primary end point to time from randomization to complete resolution of symptoms within the 21-day follow-up period". Primary outcome measures were changed during the study.)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(Primary outcome measures unclear if reported as pre-specified.)* |
| Overall bias and Directness | Risk of bias judgement | High<br>*(Concerns with trial conduct and adherence to intervention and labelling error in study which may have impacted outcomes for patients)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Serious adverse events

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*("Patients were randomized in permuted blocks of 4 in a randomization sequence prepared by the unblinded pharmacist in Microsoft Excel version 19.0 who provided masked ivermectin or placebo to a field nurse for home or hospital patient visits." Allocation assignment was concealed from investigators and patients.)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of | Risk of bias for deviations from the intended interventions | Some concerns<br>*(Unclear who/if anyone was blinded to outcomes. labeling error also occurred for a period of the trial resulting in all participants* |

| Section | Question | Answer |
|---|---|---|
| assignment to intervention) | (effect of assignment to intervention) | *receiving ivermectin and none receiving placebo during this time frame.)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns<br>*(Unclear who/if anyone was blinded to outcomes. labeling error also occurred for a period of the trial resulting in all participants receiving ivermectin and none receiving placebo during this time frame.)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(476 participants randomized; 398 participants analyzed. Reasons for missing data: error in labeling, which resulted in 38 placebo group participants receiving treatment.)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Some concerns<br>*("The primary outcome was originally defined as the time from randomization until worsening by 2 points on the 8-category ordinal scale… the principal investigator proposed to the data and safety monitoring board to modify the primary end point to time from randomization to complete resolution of symptoms within the 21-day follow-up period". Primary outcome measures were changed during the study.)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(Primary outcome measures unclear if reported as pre-specified.)* |
| Overall bias and Directness | Risk of bias judgement | High<br>*(Concerns with trial conduct and adherence to intervention and labelling error in study which may have impacted outcomes for patients)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

### Manomaipiboon, 2022

| | |
|---|---|
| **Bibliographic Reference** | Manomaipiboon, Anan; Pholtawornkulchai, Kitisak; Pupipatpab, Sujaree; Suraamornkul, Swangjit; Maneerit, Jakravoot; Ruksakul, Wiroj; Phumisantiphong, Uraporn; Trakarnvanich, Thananda; Efficacy and safety of ivermectin in the treatment of mild-to-moderate COVID-19 infection: A randomized, double blind, placebo, controlled trial; 2022 |

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT RT-PCR Negative

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low *(Outcomes have been reported for all patients randomised)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns *(Pre-print, not peer-reviewed)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(Pre-print, not peer-reviewed)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

RT-PCR Negative Day14

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low *(Outcomes have been reported for all patients randomised)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns *(Pre-print, not peer-reviewed)* |

| Section | Question | Answer |
|---|---|---|
| Overall bias and Directness | Risk of bias judgement | Some concerns *(Pre-print, not peer-reviewed)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Mortality at day 28

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low *(Outcomes have been reported for all patients randomised)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns *(Pre-print, not peer-reviewed)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(Pre-print, not peer-reviewed)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Adverse events day 14

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low *(Outcomes have been* |

| Section | Question | Answer |
|---|---|---|
| | | *reported for all patients randomised)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns *(Pre-print, not peer-reviewed)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(Pre-print, not peer-reviewed)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Adverse Events Day 28

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low *(Outcomes have been reported for all patients randomised)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns *(Pre-print, not peer-reviewed)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(Pre-print, not peer-reviewed)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

## Mohan, 2021

| | |
|---|---|
| **Bibliographic Reference** | Mohan, Anant; Tiwari, Pawan; Suri, Tejas Menon; Mittal, Saurabh; Patel, Ankit; Jain, Avinash; Velpandian, Thirumurthy; Das, Ujjalkumar Subhash; Boppana, Tarun Krishna; Pandey, Ravindra Mohan; Shelke, Sushil Suresh; Singh, Angel Rajan; Bhatnagar, Sushma; Masih, Shet; Mahajan, Shelly; Dwivedi, Tanima; Sahoo, Biswajeet; Pandit, Anuja; Bhopale, Shweta; Vig, Saurabh; Gupta, Ritu; Madan, Karan; Hadda, Vijay; Gupta, |

Nishkarsh; Garg, Rakesh; Meena, Ved Prakash; Guleria, Randeep; Single-dose oral ivermectin in mild and moderate COVID-19 (RIVET-COV): A single-centre randomized, placebo-controlled trial.; Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy; 2021

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Mortality

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low *("A variable block randomisation stratified based on disease severity (mild or moderate illness) was done using a centralised telephone-based system")* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low *("Patients, investigators, caregivers, and statisticians were blinded to the allocation")* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns *(Withdrawn consent of 5. A further 20 vs 7 participants were excluded from the analysis of clinical improvement and viral negative)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low *("Patients, investigators, caregivers, and statisticians were blinded to the allocation")* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns *(Some concern for outcomes and if assessed as pre-specified.)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns *(Concerns around missing data and outcome reporting)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Invasive mechanical ventilation

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low *("A variable block randomisation stratified based on disease severity (mild or moderate illness)* |

| Section | Question | Answer |
|---|---|---|
| | | *was done using a centralised telephone-based system")* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low<br>*("Patients, investigators, caregivers, and statisticians were blinded to the allocation")* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(Withdrawn consent of 5. A further 20 vs 7 participants were excluded from the analysis of clinical improvement and viral negative)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low<br>*("Patients, investigators, caregivers, and statisticians were blinded to the allocation")* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(Some concern for outcomes and if assessed as pre-specified.)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Concerns around missing data and outcome reporting)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Adverse events

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*("A variable block randomisation stratified based on disease severity (mild or moderate illness) was done using a centralised telephone-based system")* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low<br>*("Patients, investigators, caregivers, and statisticians were blinded to the allocation")* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(Withdrawn consent of 5. A further 20 vs 7 participants were excluded from the analysis of clinical improvement and viral negative)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low<br>*("Patients, investigators, caregivers, and statisticians were blinded to the allocation")* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(Some concern for outcomes and if assessed as pre-specified.)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Concerns around missing data and outcome reporting)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Negative PCR day 3

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*("A variable block randomisation stratified based on disease severity (mild or moderate illness) was done using a centralised telephone-based system")* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low<br>*("Patients, investigators, caregivers, and statisticians were blinded to the allocation")* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(Withdrawn consent of 5. A further 20 vs 7 participants were excluded from the analysis of clinical improvement and viral negative)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low<br>*("Patients, investigators, caregivers, and statisticians were blinded to the allocation")* |

| Section | Question | Answer |
|---|---|---|
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(Some concern for outcomes and if assessed as pre-specified.)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Concerns around missing data and outcome reporting)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Negative PCR day 5-

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*("A variable block randomisation stratified based on disease severity (mild or moderate illness) was done using a centralised telephone-based system")* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low<br>*("Patients, investigators, caregivers, and statisticians were blinded to the allocation")* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(Withdrawn consent of 5. A further 20 vs 7 participants were excluded from the analysis of clinical improvement and viral negative)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low<br>*("Patients, investigators, caregivers, and statisticians were blinded to the allocation")* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(Some concern for outcomes and if assessed as pre-specified.)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Concerns around missing data and outcome reporting)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Negative PCR day 7

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*("A variable block randomisation stratified based on disease severity (mild or moderate illness) was done using a centralised telephone-based system")* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low<br>*("Patients, investigators, caregivers, and statisticians were blinded to the allocation")* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(Withdrawn consent of 5. A further 20 vs 7 participants were excluded from the analysis of clinical improvement and viral negative)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low<br>*("Patients, investigators, caregivers, and statisticians were blinded to the allocation")* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(Some concern for outcomes and if assessed as pre-specified.)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Concerns around missing data and outcome reporting)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Serious adverse events

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*("A variable block randomisation stratified based on disease severity (mild or moderate illness) was done using a centralised telephone-based system")* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low<br>*("Patients, investigators, caregivers, and statisticians were blinded to the allocation")* |

| Section | Question | Answer |
|---|---|---|
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(Withdrawn consent of 5. A further 20 vs 7 participants were excluded from the analysis of clinical improvement and viral negative)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low<br>*("Patients, investigators, caregivers, and statisticians were blinded to the allocation")* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(Some concern for outcomes and if assessed as pre-specified.)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Concerns around missing data and outcome reporting)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

**Podder, 2021**

| | |
|---|---|
| **Bibliographic Reference** | Podder, C., Chowdhury, N., Sina, M.I., & Haque W; Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study; IMC Journal of Medical Science; 2021; vol. 14 (no. 2); 11-18 |

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Time to resolution of symptoms from date of enrolment

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | High<br>*(Randomisation methods concerns)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*(Open label trial so intervention allocation was known by all)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of | Risk of bias judgement for deviations from the intended interventions | Some concerns<br>*(Open label trial so intervention allocation was known by all)* |

| Section | Question | Answer |
|---|---|---|
| adhering to intervention) | (effect of adhering to intervention) | |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | High<br>*(No information on proportions of missing data or reasons for missing data between groups.“ Some parameters are excluded from the analysis due to inadequate data” Could mean that for some symptom sets, insufficient data, so excluded for entire symptom set (and possibly from overall Recovery outcomes).)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | High<br>*(Recovery outcomes based on symptoms that were self-reported/self-assessed, and open-label trial. Data were collected in a semi-structured questionnaire devised for the study by the research team. Both face-to-face and telephonic communication were used for follow-up and data collection.)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(analysis plan / protocol not available)* |
| Overall bias and Directness | Risk of bias judgement | High<br>*(Concerns regarding randomisation, missing data and lack of analysis plan)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Time to resolution of symptoms from date of illness onset

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | High<br>*(Randomisation methods concerns)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*(Open label trial so intervention allocation was known by all)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns<br>*(Open label trial so intervention allocation was known by all)* |

| Section | Question | Answer |
|---|---|---|
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | High<br>*(No information on proportions of missing data or reasons for missing data between groups.“ Some parameters are excluded from the analysis due to inadequate data” Could mean that for some symptom sets, insufficient data, so excluded for entire symptom set (and possibly from overall Recovery outcomes).)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | High<br>*(Recovery outcomes based on symptoms that were self-reported/self-assessed, and open-label trial. Data were collected in a semi-structured questionnaire devised for the study by the research team. Both face-to-face and telephonic communication were used for follow-up and data collection.)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(analysis plan / protocol not available)* |
| Overall bias and Directness | Risk of bias judgement | High<br>*(Concerns regarding randomisation, subjective measure in an open label trial, missing data and lack of analysis plan)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Viral clearance on 10th day

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | High<br>*(Randomisation methods concerns)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*(Open label trial so intervention allocation was known by all)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns<br>*(Open label trial so intervention allocation was known by all)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | High<br>*(No information on proportions of missing data or reasons for missing data between* |

| Section | Question | Answer |
|---|---|---|
| | | *groups.“ Some parameters are excluded from the analysis due to inadequate data” Could mean that for some symptom sets, insufficient data, so excluded for entire symptom set (and possibly from overall Recovery outcomes).)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(analysis plan / protocol not available)* |
| Overall bias and Directness | Risk of bias judgement | High<br>*(Concerns regarding randomisation, missing data and lack of analysis plan)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

**Ravikirti, 2021**

| | |
|---|---|
| **Bibliographic Reference** | Ravikirti; Roy, Ranjini; Pattadar, Chandrima; Raj, Rishav; Agarwal, Neeraj; Biswas, Bijit; Manjhi, Pramod Kumar; Rai, Deependra Kumar; Shyama; Kumar, Anjani; Sarfaraz, Asim; Evaluation of Ivermectin as a Potential Treatment for Mild to Moderate COVID-19: A Double-Blind Randomized Placebo Controlled Trial in Eastern India.; Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques; 2021; vol. 24; 343-350 |

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Symptom free on day 6

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | High<br>*(Not knowing COVID status at* |

| Section | Question | Answer |
|---|---|---|
| | | *baseline could impact this outcome)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | High<br>*(Those with no or an inconclusive RT-PCR report were included in the analysis which may have impacted this outcome)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Negative RT-PCR on day6

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | High<br>*(Not knowing COVID status at baseline could impact this outcome)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | High<br>*(Those with no or an inconclusive RT-PCR report were included in the analysis which may have impacted this outcome)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Discharged by day10

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | High<br>*(Not knowing COVID status at baseline could impact this outcome)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | High<br>*(Those with no or an inconclusive RT-PCR report were included in the analysis which may have impacted this outcome)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Admission to ICU

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | High<br>*(Not knowing COVID status at baseline could impact this outcome)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | High<br>*(Those with no or an inconclusive RT-PCR report were included in the analysis which may have impacted this outcome)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Invasive ventilation

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | High<br>*(Not knowing COVID status at baseline could impact this outcome)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(No timepoint reported for this outcome)* |
| Overall bias and Directness | Risk of bias judgement | High<br>*(Those with no or an inconclusive RT-PCR report were included in the analysis which may have impacted this outcome. Timepoint not reported)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

In-hospital mortality-

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | High<br>*(Not knowing COVID status at baseline could impact this outcome)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(No timepoint reported for this outcome)* |
| Overall bias and Directness | Risk of bias judgement | High<br>*(Those with no or an inconclusive RT-PCR report were included in the analysis which may have impacted this outcome. Timepoint not reported)* |
| Overall bias and Directness | Overall Directness | Directly applicable. |

Discharged

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | High<br>*(Not knowing COVID status at* |

| Section | Question | Answer |
|---|---|---|
| | | *baseline could impact this outcome)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(No timepoint reported for this outcome)* |
| Overall bias and Directness | Risk of bias judgement | High<br>*(Those with no or an inconclusive RT-PCR report were included in the analysis which may have impacted this outcome. Timepoint not reported)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

### Reis, 2022

| | |
|---|---|
| **Bibliographic Reference** | Reis, Gilmar; Silva Eduardo A S, M; Silva Daniela C, M; Thabane, Lehana; Milagres Aline, C; Ferreira Thiago, S; Dos, Santos; Castilho V, Q; Campos Vitoria H, S; Nogueira Ana M, R; de Almeida Ana P F, G; Callegari Eduardo, D; Neto Adhemar D, F; Savassi Leonardo C, M; Simplicio Maria I, C; Ribeiro Luciene, B; Oliveira, Rosemary; Harari, Ofir; Forrest Jamie, I; Ruton, Hinda; Sprague, Sheila; McKay, Paula; Guo Christina, M; Rowland-Yeo, Karen; Guyatt Gordon, H; Boulware David, R; Rayner Craig, R; Mills Edward, J; TOGETHER, Investigators; Effect of Early Treatment with Ivermectin among Patients with Covid-19.; The New England journal of medicine; 2022 |

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Hospitalisation for COVID-19

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Emergency room visit

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Primary outcome event (intention-to-treat analysis): hospitalisation due to COVID-19 or an emergency department visit of >6 hours, due to clinical worsening of COVID-19

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Primary outcome event (modified intention-to-treat analysis): hospitalisation due to COVID-19 or an emergency department visit of >6 hours, due to clinical worsening of COVID-19

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Primary outcome event (per-protocol population): hospitalisation due to COVID-19 or an emergency department visit of >6 hours, due to clinical worsening of COVID-19

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Viral clearance day 3

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Viral Clearance day 7

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Hospitalisation for any cause

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Median no of days of hospitalisation

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Median no of days to clinical recovery

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Mortality

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Mechanical Ventilation

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Median no of days with mechanical ventilation

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

100% adherence to assigned regimen

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Adverse Event during treatment period

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Adverse Event during treatment period Grade1

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Adverse Event during treatment period Grade2

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Adverse Event during treatment period Grade 3

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Adverse Event during treatment period Grade 4

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Adverse Event during treatment period Grade 5

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

### Shahbaznejad, 2021

| | |
|---|---|
| **Bibliographic Reference** | Shahbaznejad, Leila; Davoudi, Alireza; Eslami, Gohar; Markowitz, John S; Navaeifar, Mohammad Reza; Hosseinzadeh, Fatemeh; Movahedi, Faeze Sadat; Rezai, Mohammad Sadegh; Effects of Ivermectin in Patients With COVID-19: A Multicenter, Double-blind, Randomized, Controlled Clinical Trial.; Clinical therapeutics; 2021; vol. 43 (no. 6); 1007-1019 |

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Invasive mechanical ventilation

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns *("The patients were randomly divided into 2 groups (ivermectin and control) by a simple randomization method using a table of* |

| Section | Question | Answer |
|---|---|---|
| | | *random numbers. Neither the participants nor the evaluators were aware of the randomization process or group allocation." Methods/measures of randomisation and allocation unclear.)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(Some missing data from 4 withdrawals, No evidence bias did not occur.)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(The protocol and statistical analysis plan were not available, the registry was retrospective)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Some missing data with unclear allocation and randomising methods.)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Length of hospital stay

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns<br>*("The patients were randomly divided into 2 groups (ivermectin and control) by a simple randomization method using a table of random numbers. Neither the participants nor the evaluators were aware of the randomization process or group allocation." Methods/measures of randomisation and allocation unclear.)* |
| Domain 2a: Risk of bias due to deviations | Risk of bias for deviations from the | Low |

| Section | Question | Answer |
|---|---|---|
| from the intended interventions (effect of assignment to intervention) | intended interventions (effect of assignment to intervention) | |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(Some missing data from 4 withdrawals, No evidence bias did not occur.)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(The protocol and statistical analysis plan were not available, the registry was retrospective)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Some missing data with unclear allocation and randomising methods.)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Needed supplemental oxygen

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns<br>*("The patients were randomly divided into 2 groups (ivermectin and control) by a simple randomization method using a table of random numbers. Neither the participants nor the evaluators were aware of the randomization process or group allocation." Methods/measures of randomisation and allocation unclear.)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended | Risk of bias judgement for deviations from the | Low |

| Section | Question | Answer |
|---|---|---|
| interventions (effect of adhering to intervention) | intended interventions (effect of adhering to intervention) | |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(Some missing data from 4 withdrawals, No evidence bias did not occur.)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(The protocol and statistical analysis plan were not available, the registry was retrospective)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Some missing data with unclear allocation and randomising methods.)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Duration of symptoms

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns<br>*("The patients were randomly divided into 2 groups (ivermectin and control) by a simple randomization method using a table of random numbers. Neither the participants nor the evaluators were aware of the randomization process or group allocation." Methods/measures of randomisation and allocation unclear.)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(Some missing data from 4 withdrawals, No evidence bias did not occur.)* |

| Section | Question | Answer |
|---|---|---|
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(The protocol and statistical analysis plan were not available, the registry was retrospective)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Some missing data with unclear allocation and randomising methods.)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Adverse events

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns<br>*("The patients were randomly divided into 2 groups (ivermectin and control) by a simple randomization method using a table of random numbers. Neither the participants nor the evaluators were aware of the randomization process or group allocation." Methods/measures of randomisation and allocation unclear.)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Some concerns<br>*(Some missing data from 4 withdrawals, No evidence bias did not occur.)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for | Some concerns<br>*(The protocol and statistical analysis plan* |

| Section | Question | Answer |
|---|---|---|
| | selection of the reported result | *were not available, the registry was retrospective)* |
| Overall bias and Directness | Risk of bias judgement | Some concerns<br>*(Some missing data with unclear allocation and randomising methods.)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

### Shakhsi Niaee, 2021

| | |
|---|---|
| **Bibliographic Reference** | Shakhsi Niaee, Morteza; Cheraghi, Fatemeh; Namdar, Peyman; Allami, Abbas; Karampour, Amin; Zolghadr, Leila; Javadi, Amir; Varnaseri, Mehran; Karamyan, Masoumeh; Yadyad, Mohammad; Jamshidian, Ramin; Bijani, Behzad; Naderi, Yazdan; Gheibi, Nematollah; Amini, Fatemeh; Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial; Asian Pacific Journal of Tropical Medicine; 2021; vol. 14 (no. 6); 266-273 |

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Duration of hospital stay

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | High<br>*(Concealment method has not been explained and there has been imbalance in allocating patients who were PCR negative to intervention arms and control arms)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*(Full information is not given for deviations)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | High<br>*(no information on pre-specified outcomes)* |

| Section | Question | Answer |
|---|---|---|
| Overall bias and Directness | Risk of bias judgement | High<br>*(imbalance in PCR positive patients across arms and cause bias in outcomes)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

Mortality

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | High<br>*(Concealment method has not been explained and there has been imbalance in allocating patients who were PCR negative to intervention arms and control arms)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*(Full information is not given for deviations)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(For mortality outcome, it is less likely to be affected by pre-defined protocol or pre-specified outcomes of the trial)* |
| Overall bias and Directness | Risk of bias judgement | High<br>*(imbalance in PCR positive patients across arms and cause bias in outcomes)* |
| Overall bias and Directness | Overall Directness | Directly applicable |

## Vallejos, 2021

| | |
|---|---|
| **Bibliographic Reference** | Vallejos, Julio; Zoni, Rodrigo; Bangher, Maria; Villamandos, Silvina; Bobadilla, Angelina; Plano, Fabian; Campias, Claudia; Chaparro Campias, Evangelina; Medina, Maria Fernanda; Achinelli, Fernando; Guglielmone, Hector Andres; Ojeda, Jorge; Farizano Salazar, Diego; |

Andino, Gerardo; Kawerin, Pablo; Dellamea, Silvana; Aquino, Antonia Cristina; Flores, Victor; Martemucci, Carolina N; Martinez, Silvina Maria; Segovia, Juan Emanuel; Reynoso, Paola Itati; Sosa, Noelia Carolina; Robledo, Mariana Elizabeth; Guarrochena, Joaquina Maria; Vernengo, Maria Mercedes; Ruiz Diaz, Natalia; Meza, Elba; Aguirre, Maria Gabriela; Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial.; BMC infectious diseases; 2021; vol. 21 (no. 1); 635

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
All-cause mortality

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*(Permuted block randomisation through web-based system in 1:1 ratio)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low<br>*(all patients were included in intention to treat analysis)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Hospitalisation

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*(Permuted block randomisation through web-based system in 1:1 ratio)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low<br>*(all patients were included in intention to treat analysis)* |
| Domain 2b: Risk of bias due to deviations from the intended | Risk of bias judgement for deviations from the intended | Low |

| Section | Question | Answer |
|---|---|---|
| interventions (effect of adhering to intervention) | interventions (effect of adhering to intervention) | |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Invasive mechanical ventilation

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*(Permuted block randomisation through web-based system in 1:1 ratio)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low<br>*(all patients were included in intention to treat analysis)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Negative nasal swab at day 3

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*(Permuted block randomisation through web-based system in 1:1 ratio)* |
| Domain 2a: Risk of bias due to deviations from the intended | Risk of bias for deviations from the intended interventions | Low<br>*(all patients were* |

| Section | Question | Answer |
|---|---|---|
| interventions (effect of assignment to intervention) | (effect of assignment to intervention) | *included in intention to treat analysis)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Negative nasal swab at day 12

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*(Permuted block randomisation through web-based system in 1:1 ratio)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low<br>*(all patients were included in intention to treat analysis)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Adverse events

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*(Permuted block randomisation through* |

| Section | Question | Answer |
|---|---|---|
| | | *web-based system in 1:1 ratio)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low<br>*(all patients were included in intention to treat analysis)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

Serious adverse events

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*(Permuted block randomisation through web-based system in 1:1 ratio)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low<br>*(all patients were included in intention to treat analysis)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

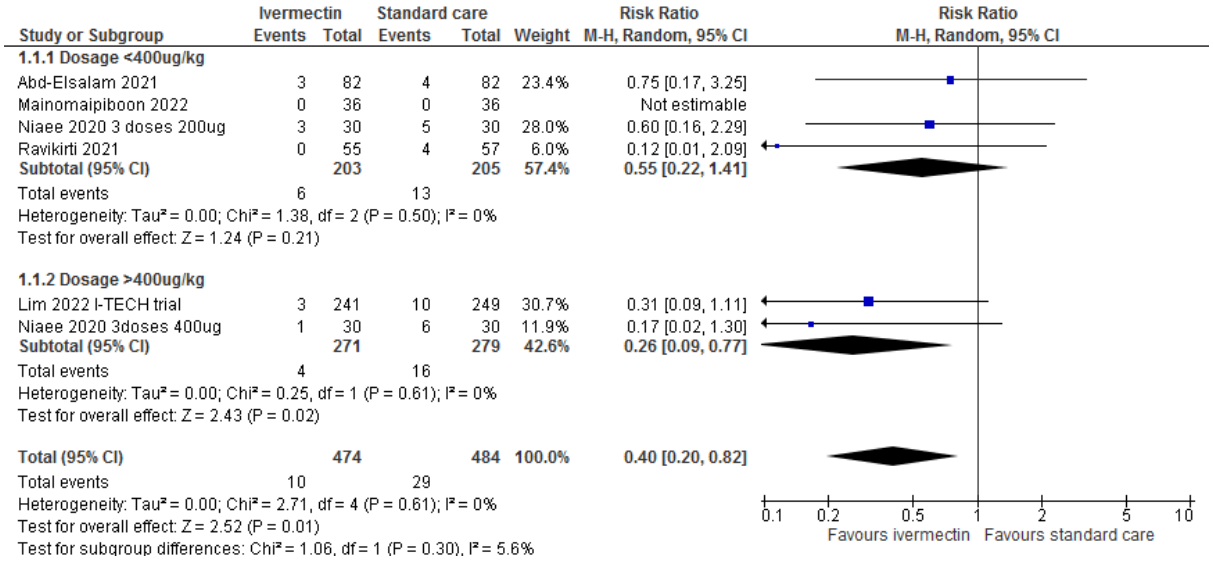
Discontinuation due to adverse events

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low<br>*(Permuted block randomisation through web-based system in 1:1 ratio)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low<br>*(all patients were included in intention to treat analysis)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| Overall bias and Directness | Overall Directness | Directly applicable |

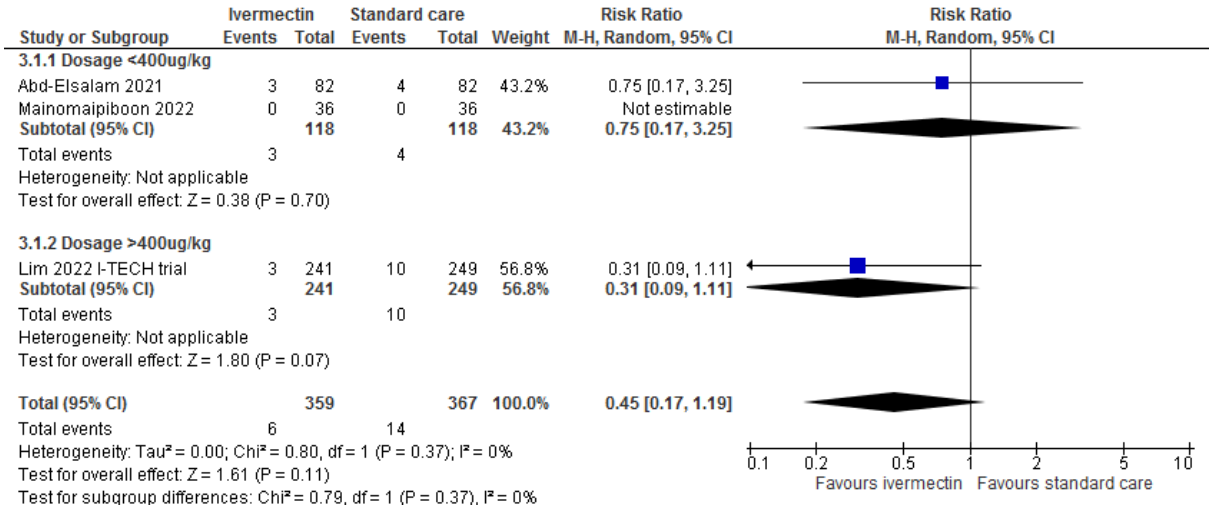
# Appendix H: Forest Plots

## Hospital setting: Multiple doses of ivermectin

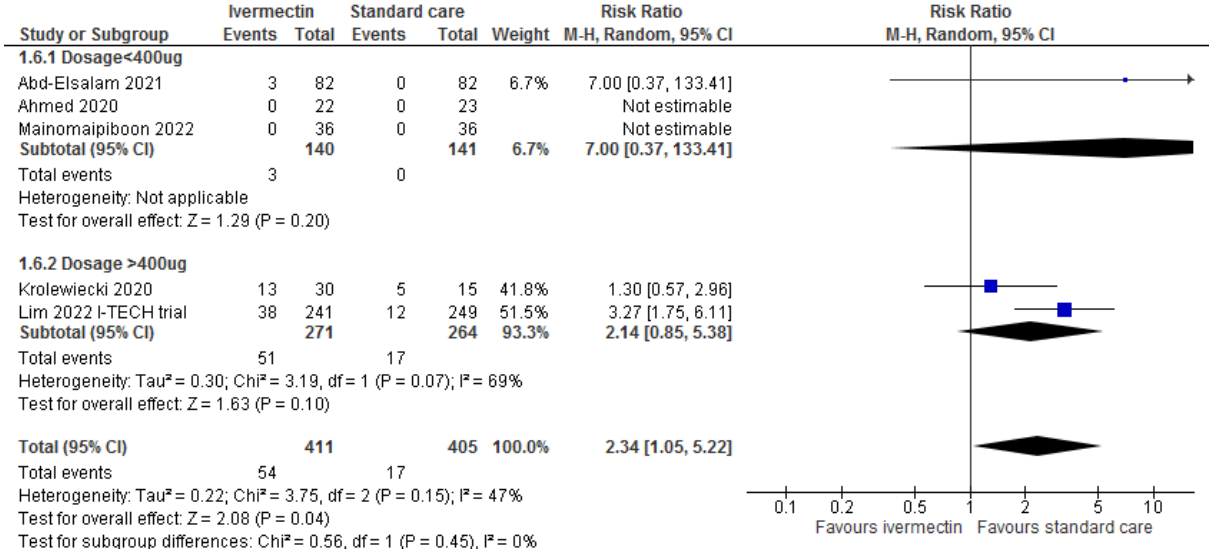
### All-cause mortality



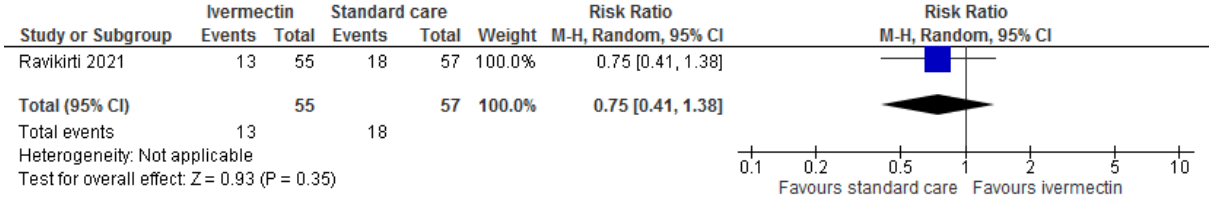

### All-cause mortality sensitivity analysis (High ROB removed from analysis)



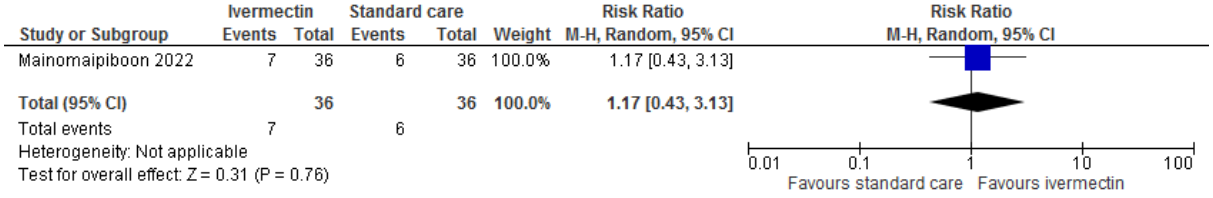
## Adverse events



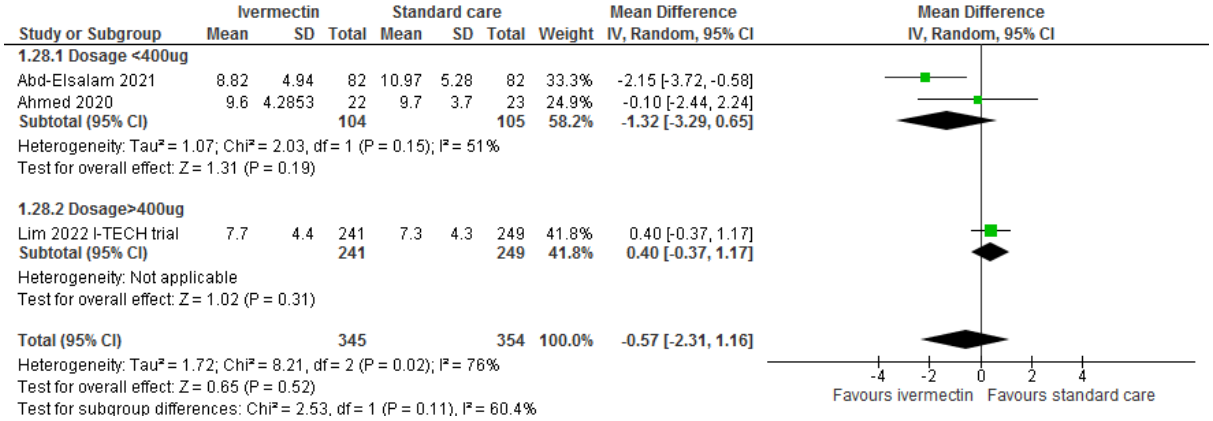

## Viral clearance day 1-6



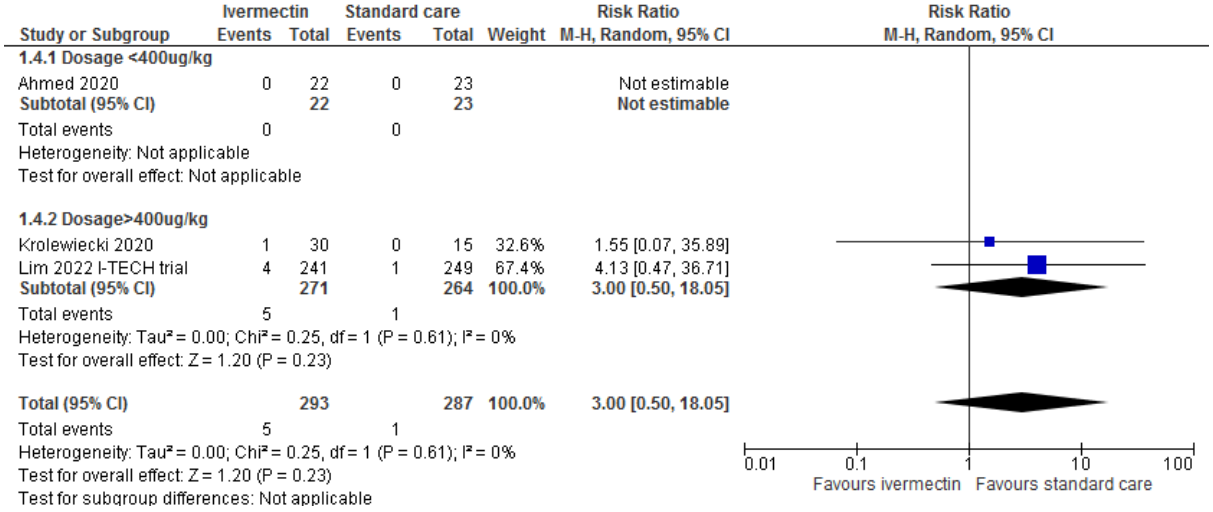

## Viral clearance day 7-14



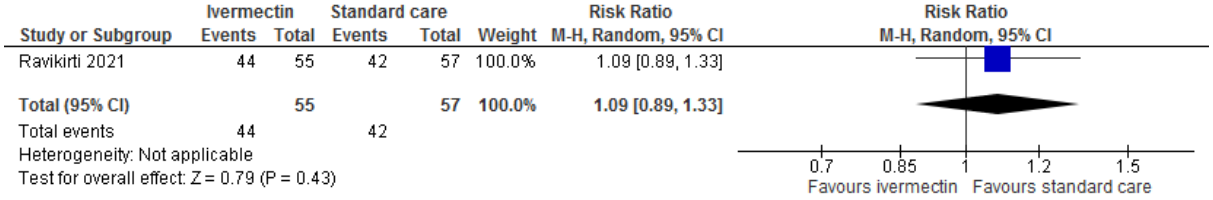

## Duration of hospitalisation



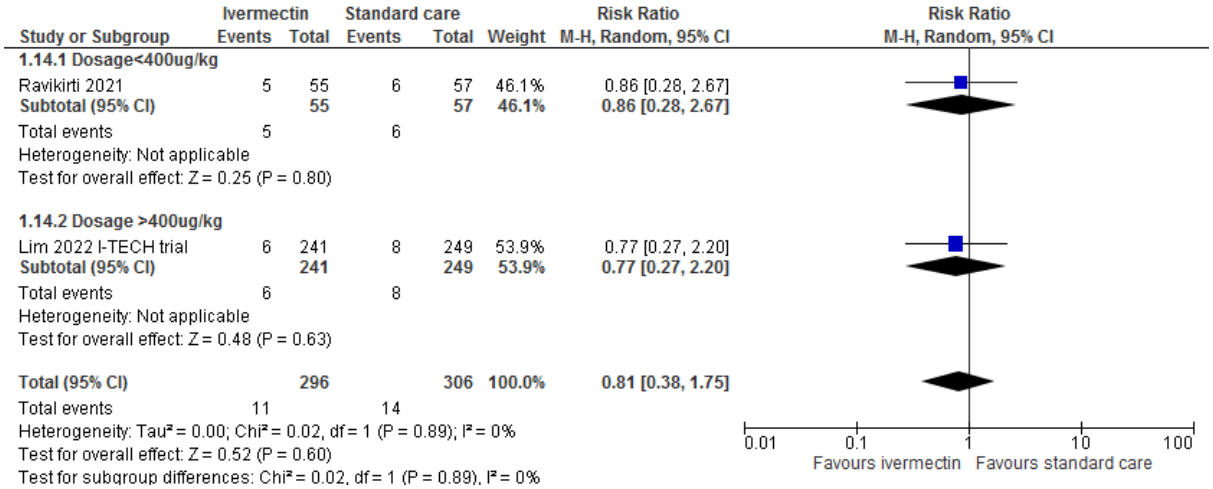
## Serious adverse events



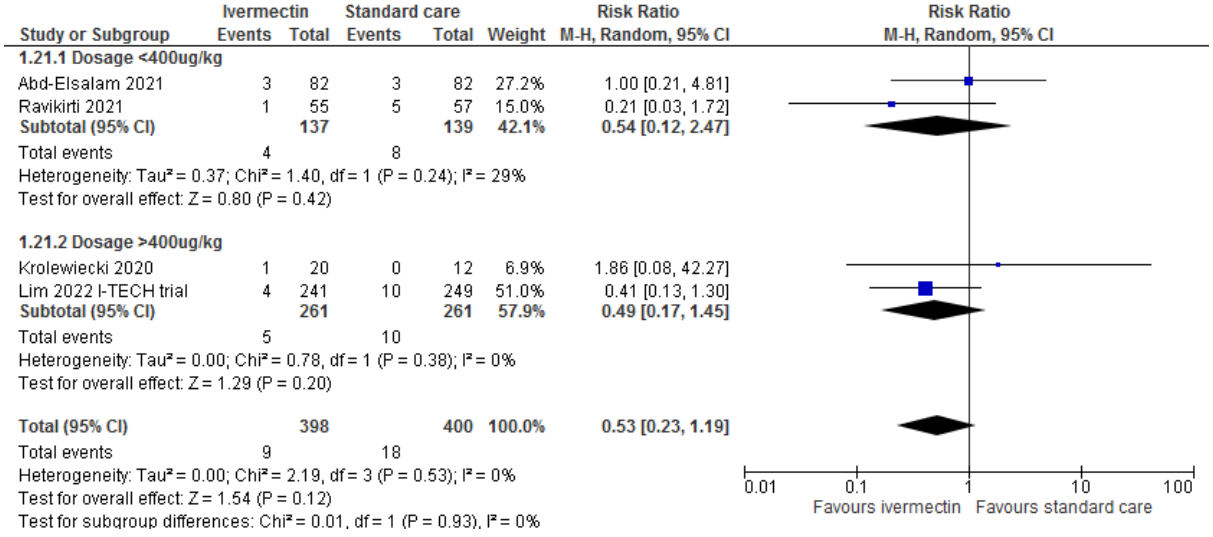

## Discharge from hospital



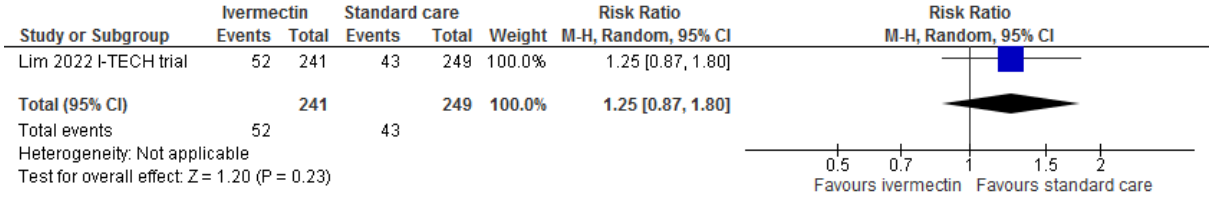

## Admission to ICU



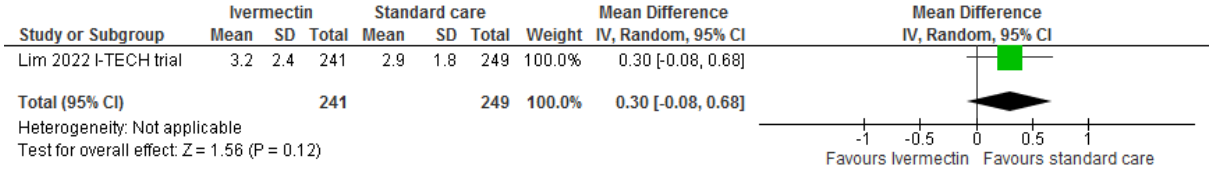
## Invasive mechanical ventilation



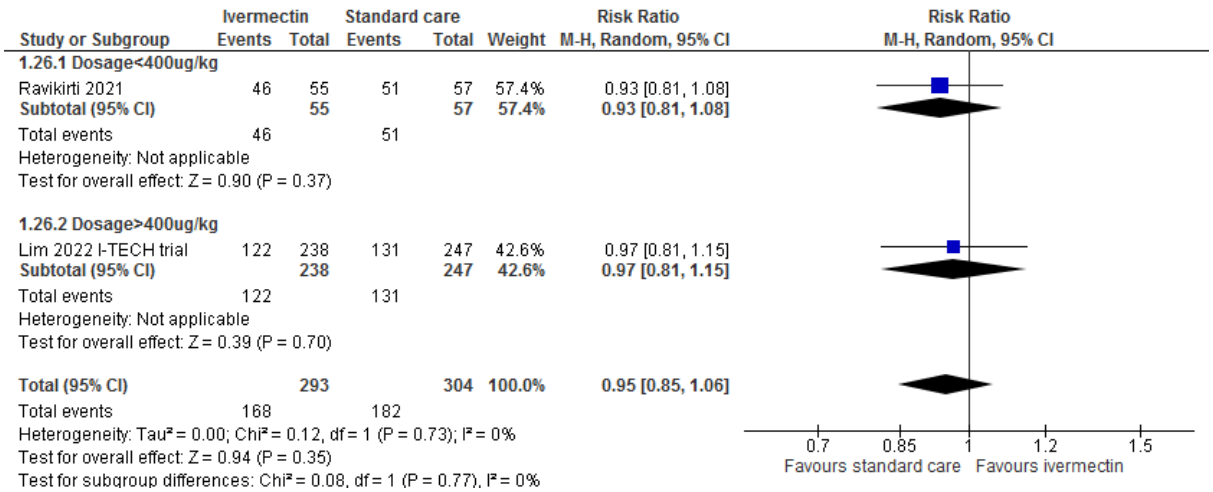

## Clinical Progression




## Time to progression to severe disease

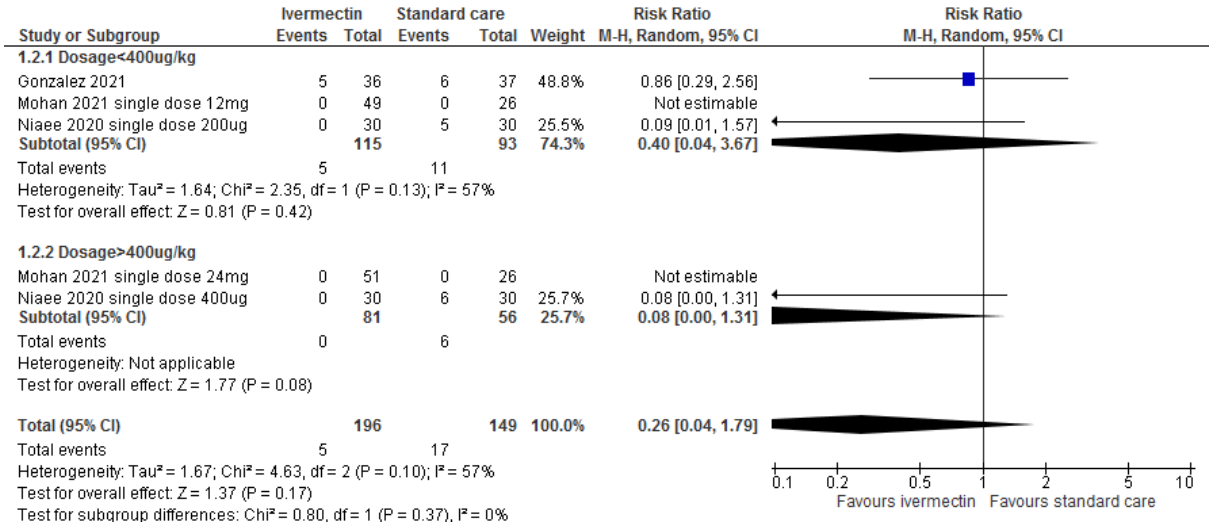



## Symptom resolution

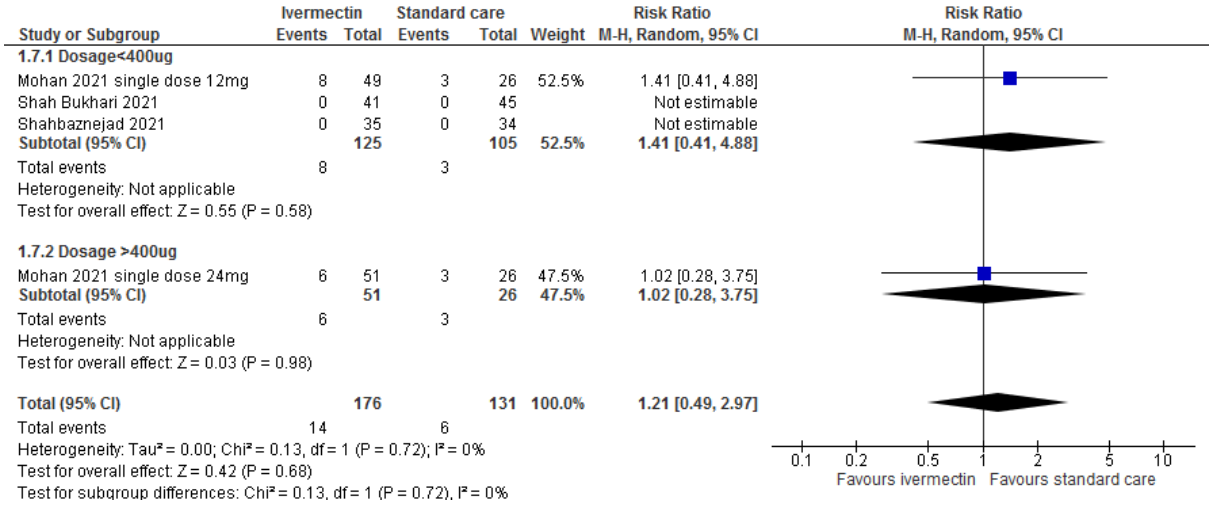


# Hospital setting: Single dose of ivermectin

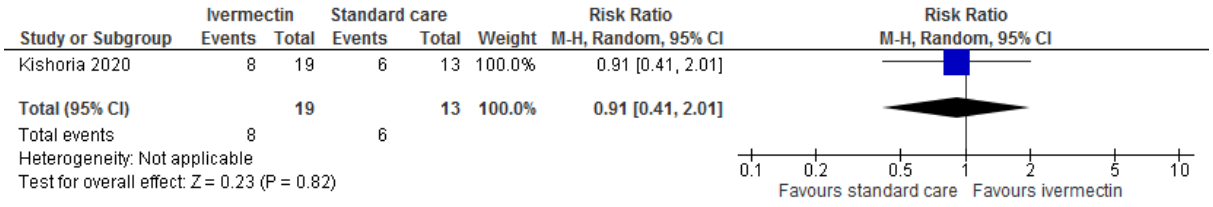
## All-cause mortality



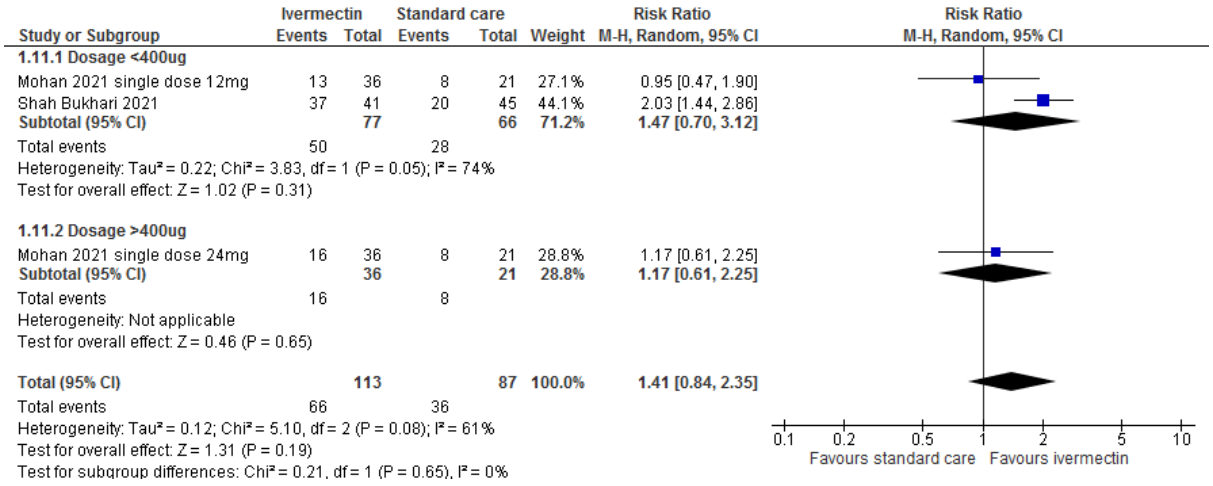

## Adverse events



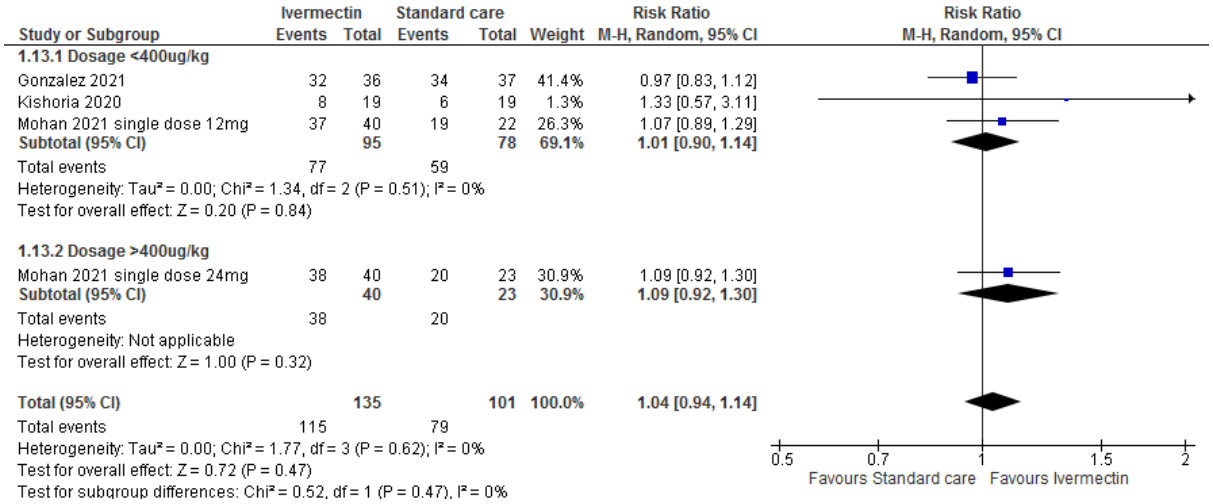

## Viral clearance day 1-6



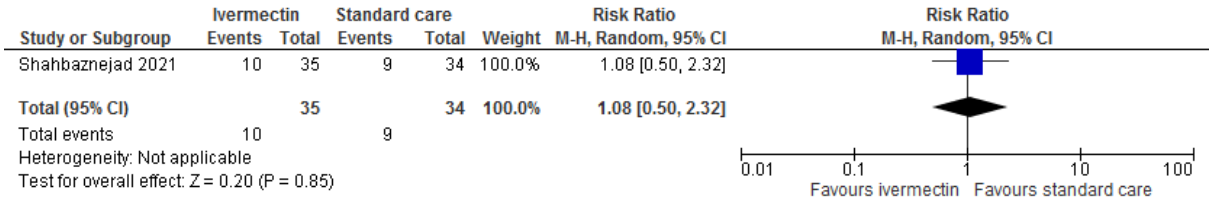
## Viral clearance day 7-14



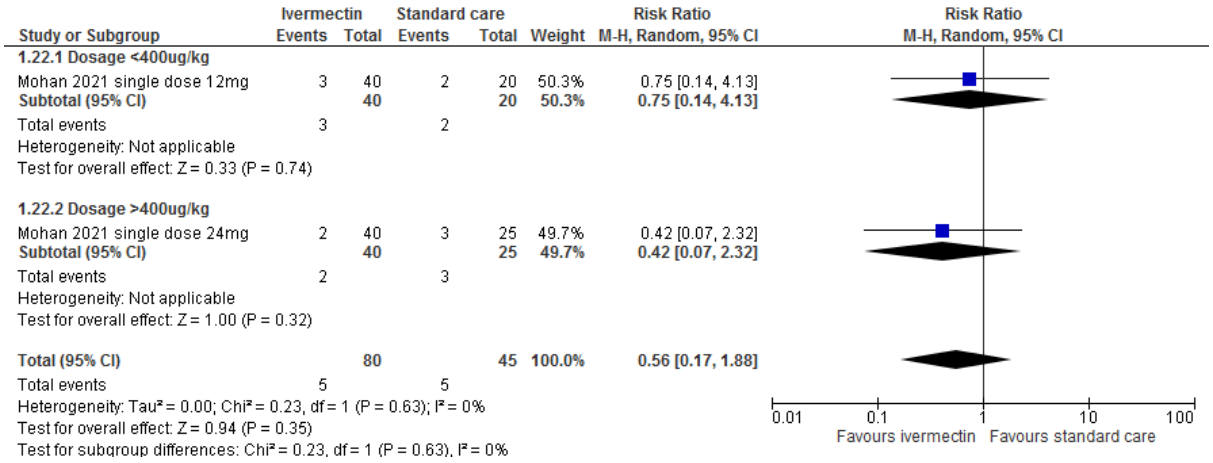

## Discharge from hospital



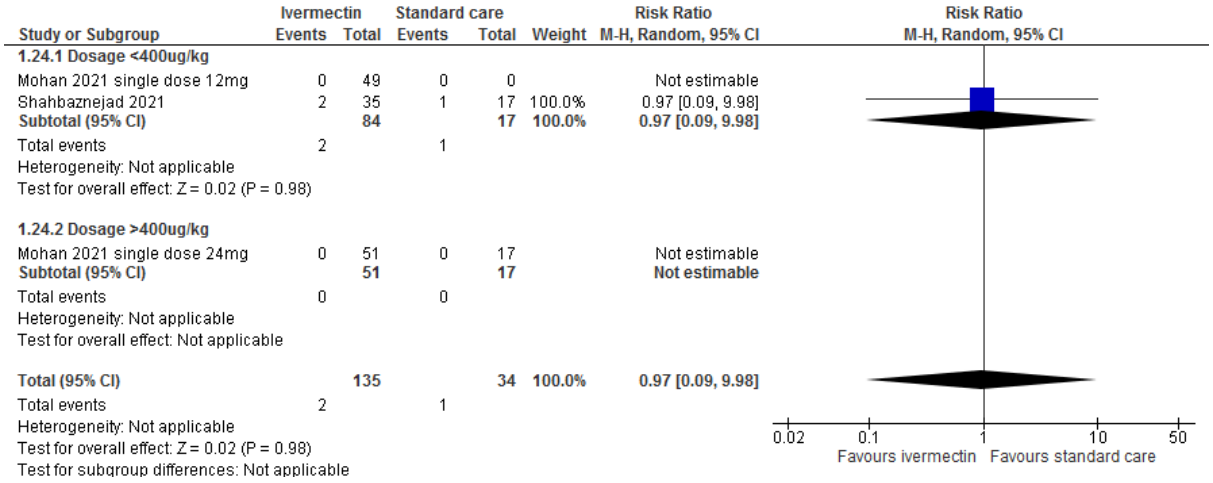

## Supplemental oxygen



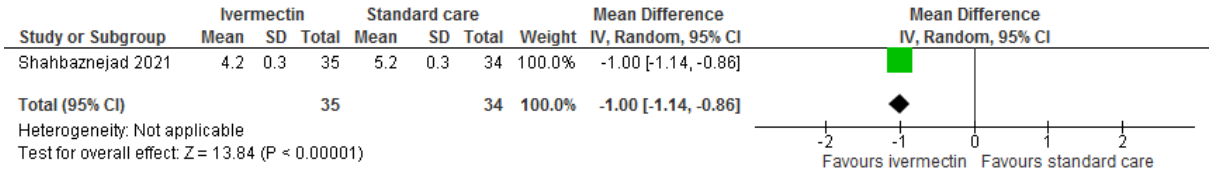
## Clinical progression



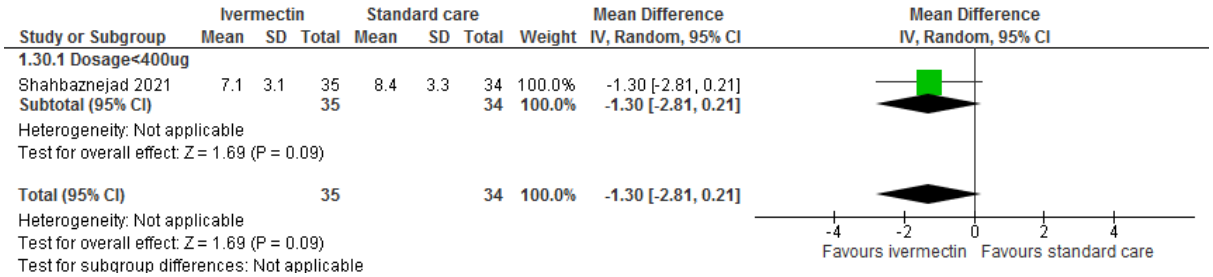

## Invasive mechanical ventilation



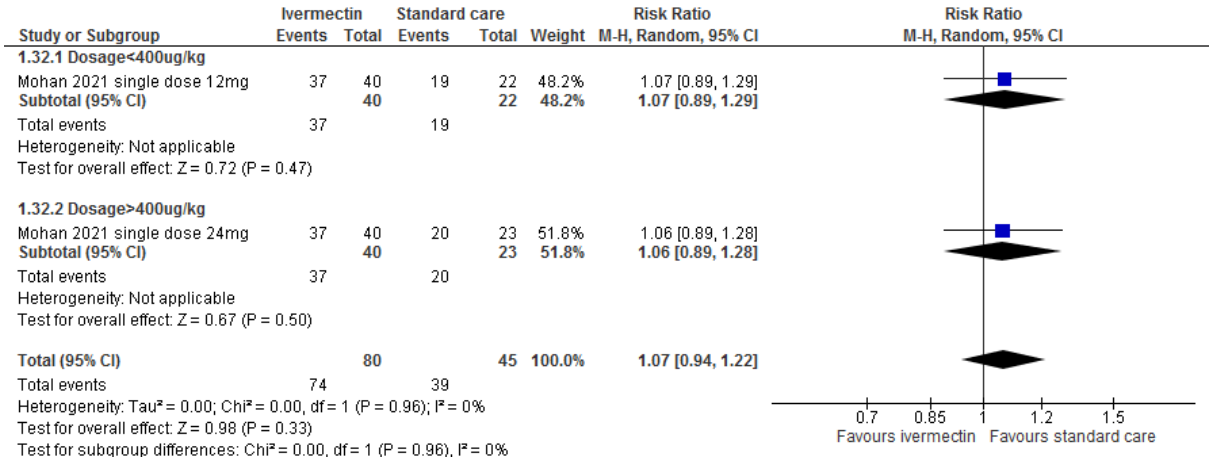

## Duration of symptoms



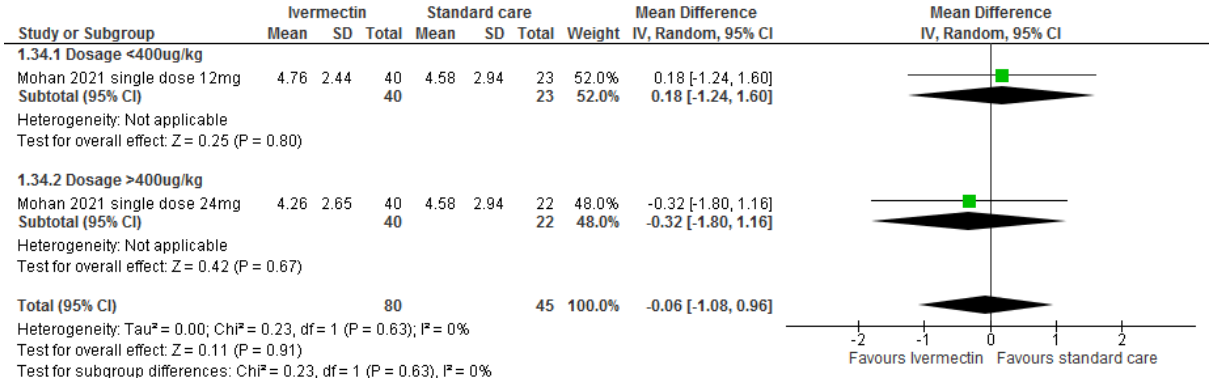

## Duration of hospitalisation



## Clinical improvement (2 or more point decrease in WHO scale)

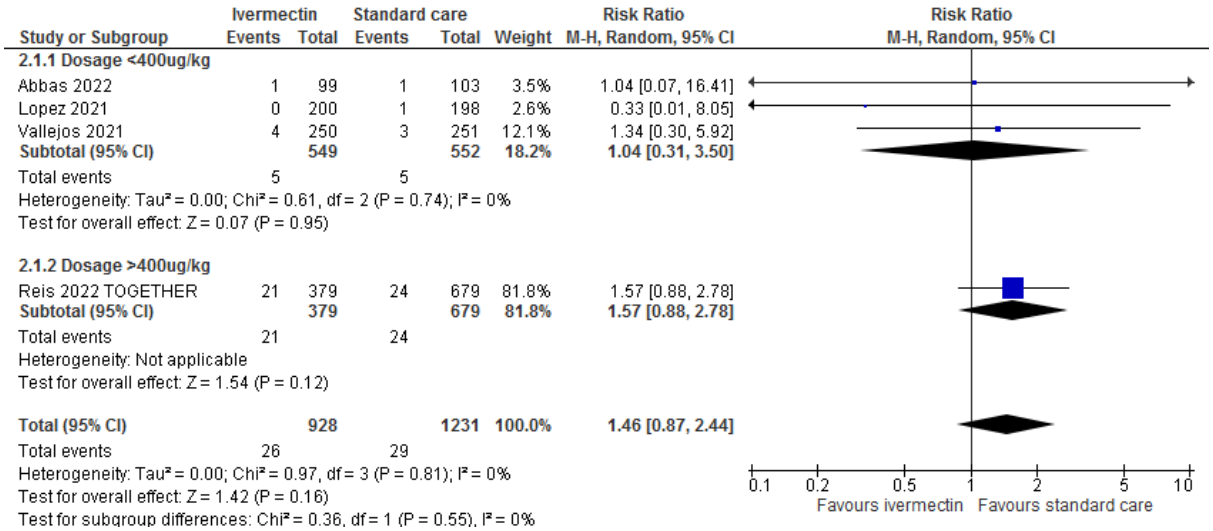



## Time to recovery (resolution of symptoms)

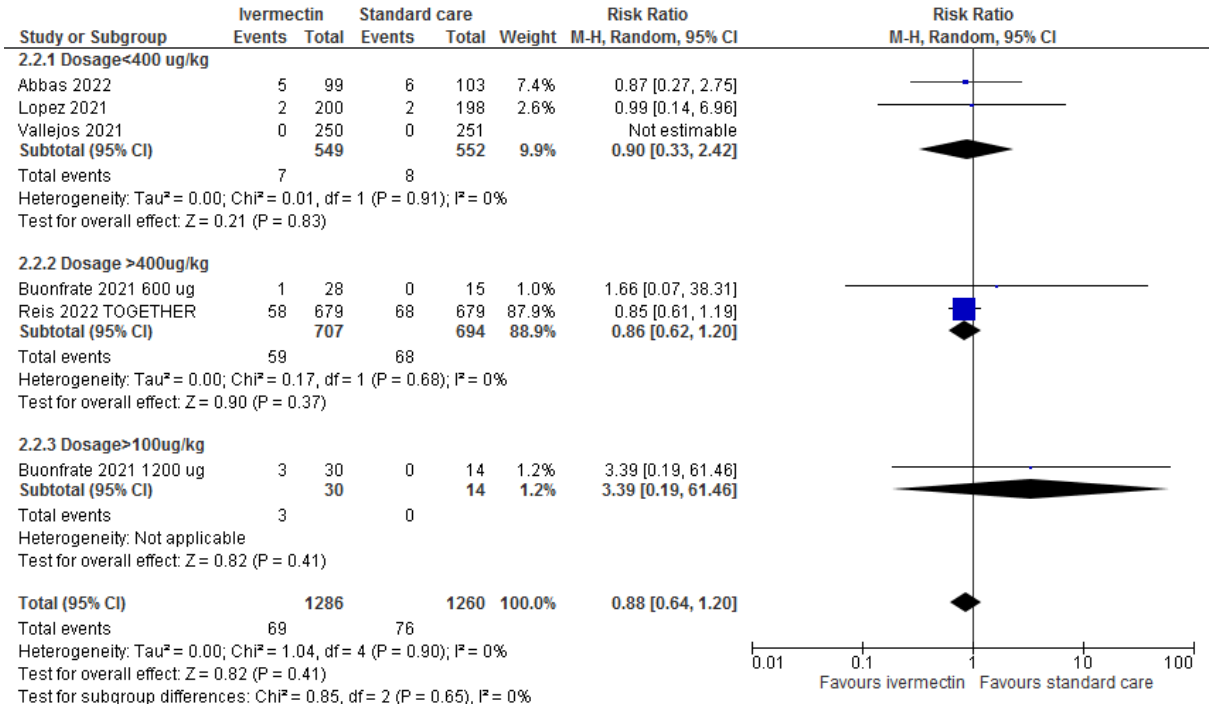



# Community setting: Multiple doses of ivermectin

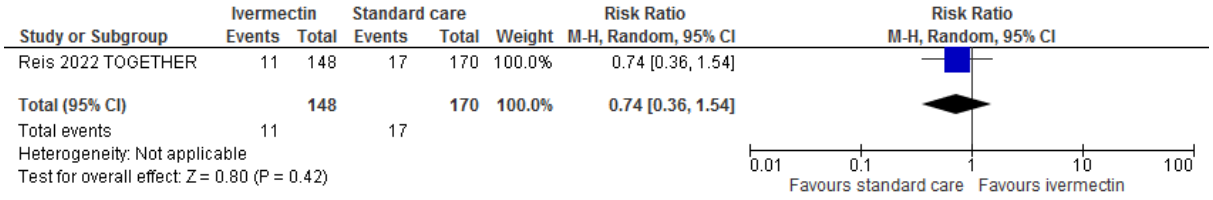
## All-cause mortality



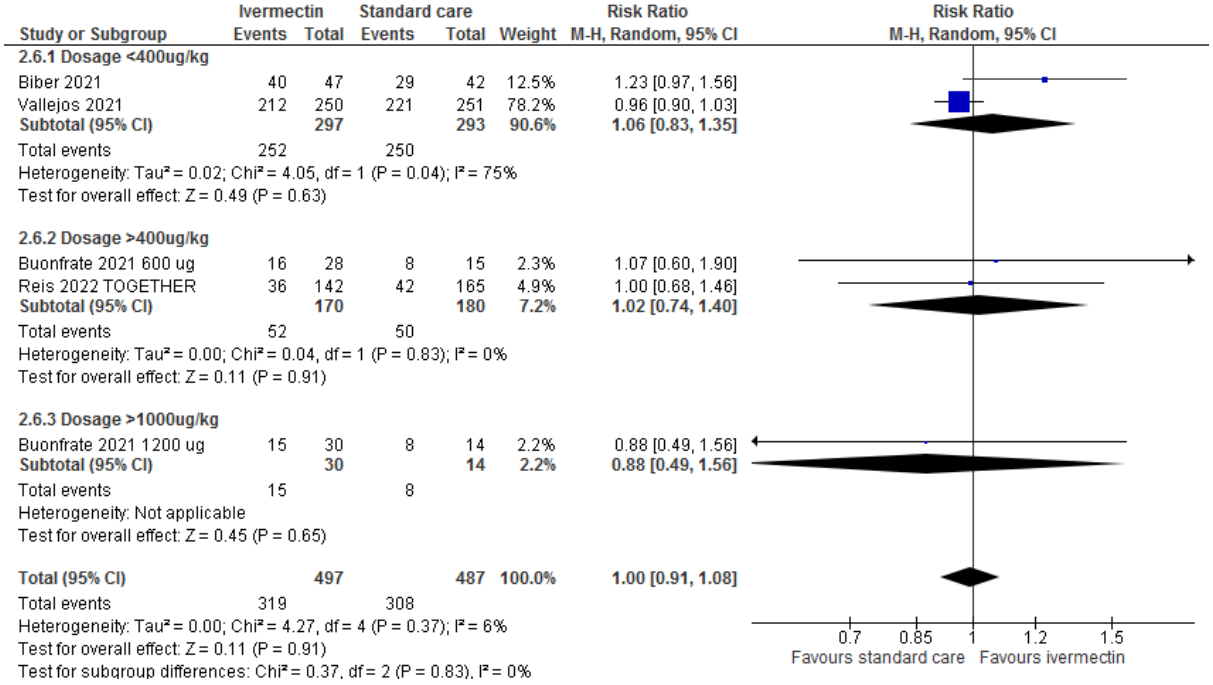
## Serious adverse events



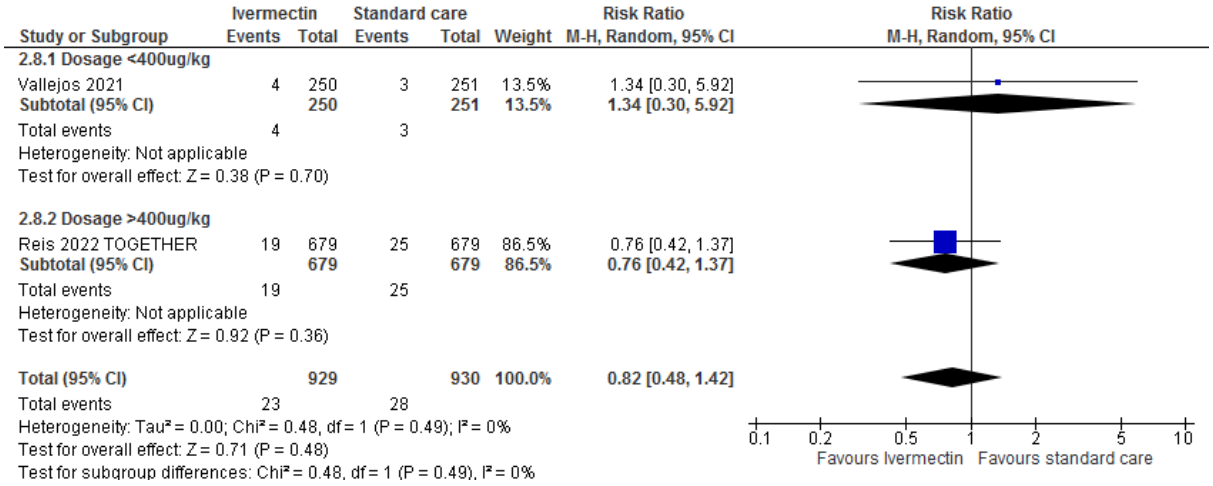

## Viral clearance day 1-6



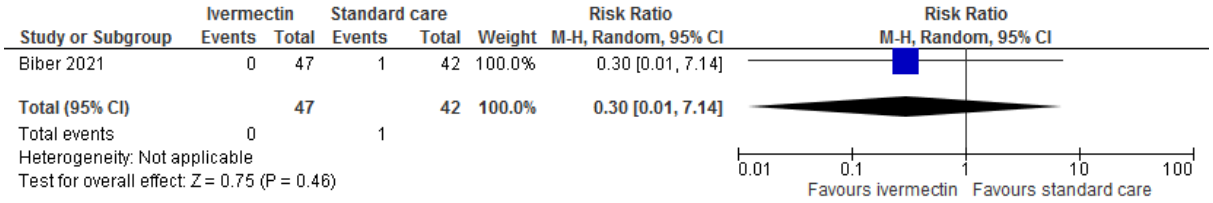
## Viral clearance day 7-14



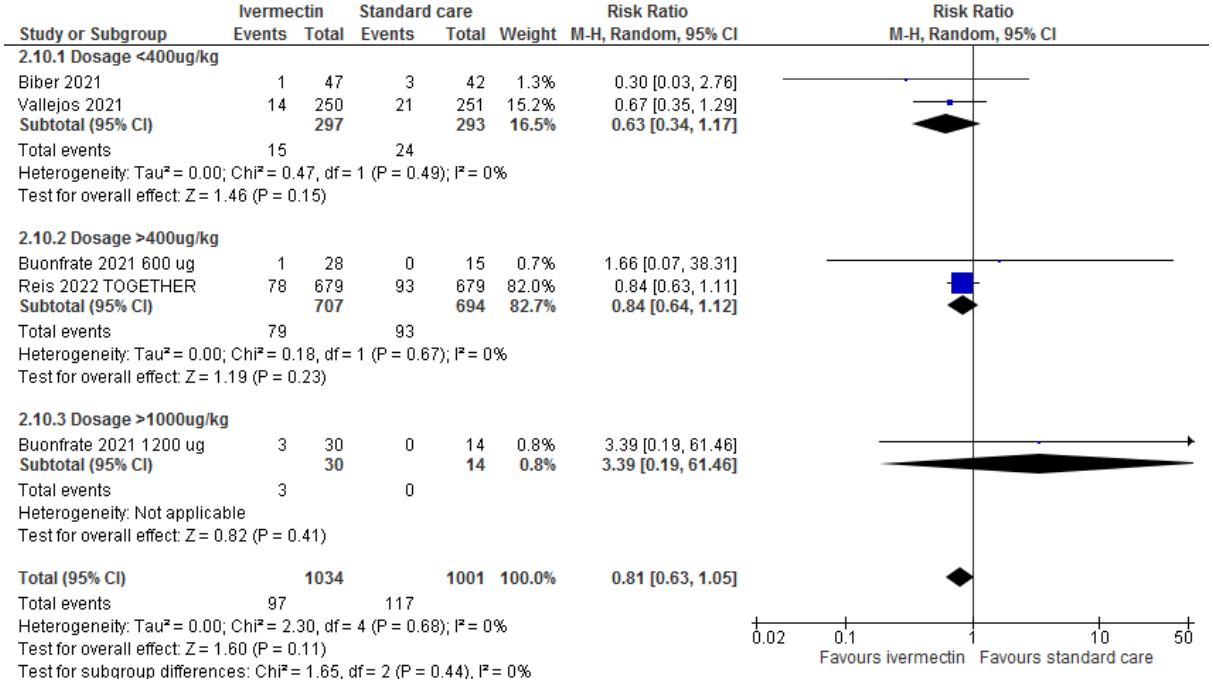

## Invasive mechanical ventilation



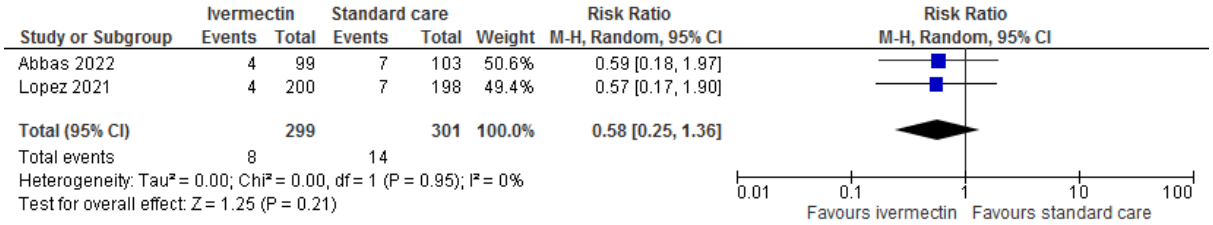

## No. of patients requiring oxygen



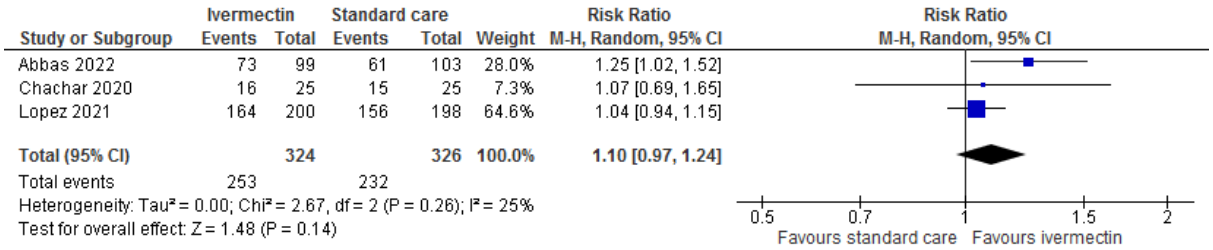
## Hospitalisation



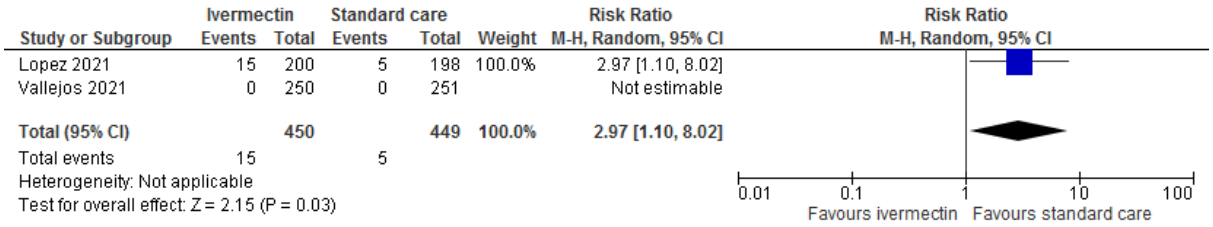

## Clinical deterioration



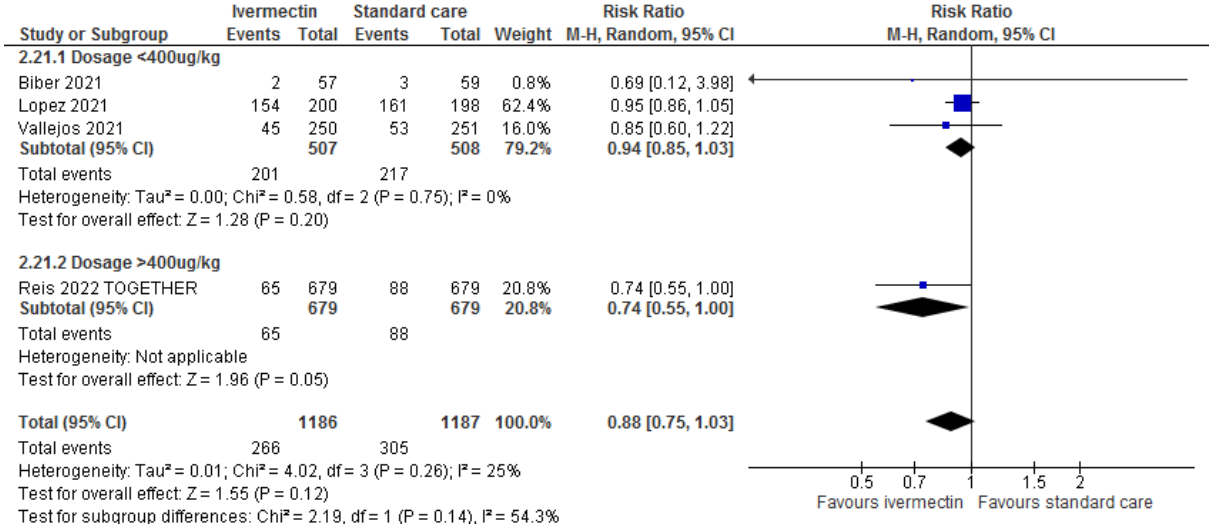

## Clinical recovery




## Discontinuation due to adverse events

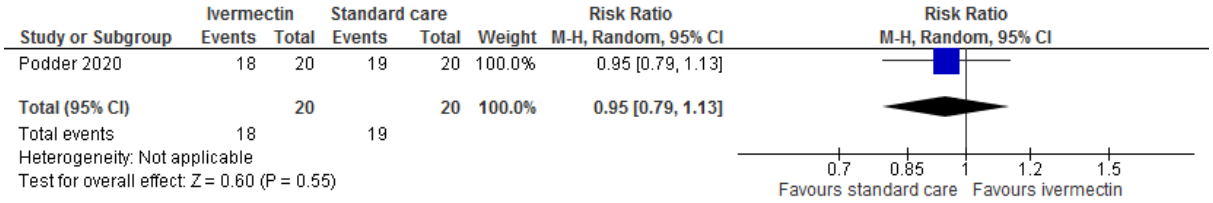


## Adverse events

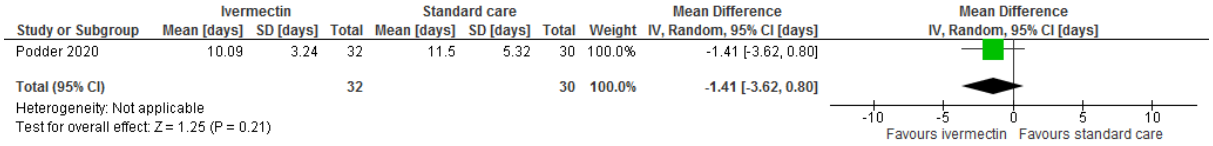



# Community setting single dose of ivermectin

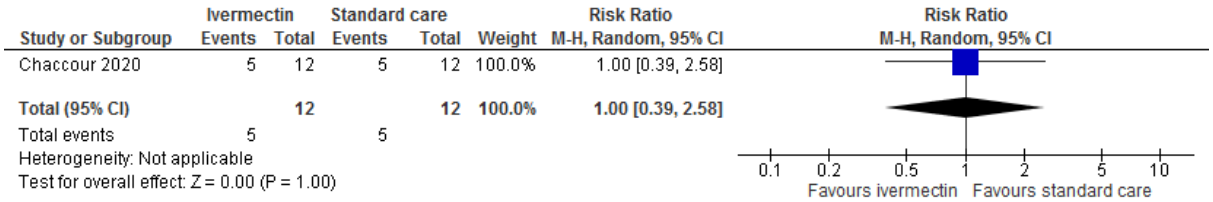
## Viral clearance day 7-14




## Recovery from date of illness onset (days)




## Adverse events



# Appendix I: GRADE profiles

## Ivermectin (multiple doses) compared to standard care in people hospitalised with COVID-19

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Study event rates (%) | | | Anticipated absolute effects | |
| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | With standard care | With ivermectin (multiple doses) | Relative effect (95% CI) | Risk with standard care | Risk difference with ivermectin (multiple doses) |
| All-cause mortality (day 28) | | | | | | | | | | | |
| 958 (6 RCTs) | very serious[a] | not serious | serious[b] | not serious | none | Very low | 29/484 (6.0%) | 10/474 (2.1%) | **RR 0.40** (0.20 to 0.82) | 60 per 1,000 | **36 fewer per 1,000** (from 48 fewer to 11 fewer) |
| All-cause mortality (day 28) | | | | | | | | | | | |
| 726 (3 RCTs) | not serious | not serious | not serious | serious[c] | none | Moderate | 14/367 (3.8%) | 6/359 (1.7%) | **RR 0.45** (0.17 to 1.19) | 38 per 1,000 | **21 fewer per 1,000** (from 32 fewer to 7 more) |
| Serious adverse events | | | | | | | | | | | |
| 580 (3 RCTs) | serious[d] | not serious | not serious | serious[c] | none | Low | 1/287 (0.3%) | 5/293 (1.7%) | **RR 3.00** (0.50 to 18.05) | 3 per 1,000 | **7 more per 1,000** (from 2 fewer to 59 more) |
| Adverse events | | | | | | | | | | | |

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 816 (5 RCTs) | serious[e] | not serious | not serious | not serious | none | Moderate | 17/405 (4.2%) | 54/411 (13.1%) | **RR 2.34** (1.05 to 5.22) | 42 per 1,000 | **56 more per 1,000** (from 2 more to 177 more) |

Viral clearance 1-6 days

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 112 (1 RCT) | serious[f] | not serious | serious[g] | serious[c] | none | Very low | 18/57 (31.6%) | 13/55 (23.6%) | **RR 0.75** (0.41 to 1.38) | 316 per 1,000 | **79 fewer per 1,000** (from 186 fewer to 120 more) |

Viral clearance 7-14 days

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 72 (1 RCT) | serious[h] | not serious | not serious | serious[c] | none | Low | 6/36 (16.7%) | 7/36 (19.4%) | **RR 1.17** (0.43 to 3.13) | 167 per 1,000 | **28 more per 1,000** (from 95 fewer to 355 more) |

Discharge from hospital

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 112 (1 RCT) | serious[f] | not serious | serious[g] | serious[c] | none | Very low | 42/57 (73.7%) | 44/55 (80.0%) | **RR 1.09** (0.89 to 1.33) | 737 per 1,000 | **66 more per 1,000** (from 81 fewer to 243 more) |

Admission to ICU

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 602 (2 RCTs) | serious[f] | not serious | not serious | serious[c] | none | Low | 14/306 (4.6%) | 11/296 (3.7%) | **RR 0.81** (0.38 to 1.75) | 46 per 1,000 | **9 fewer per 1,000** (from 28 fewer to 34 more) |

Invasive mechanical ventilation

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 798 (4 RCTs) | serious[i] | not serious | not serious | serious[c] | none | Low | 18/400 (4.5%) | 9/398 (2.3%) | **RR 0.53** (0.23 to 1.19) | 45 per 1,000 | **21 fewer per 1,000** (from 35 fewer to 9 more) |

Clinical progression

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 490 (1 RCT) | serious[j] | not serious | not serious | serious[c] | none | Low | 43/249 (17.3%) | 52/241 (21.6%) | **RR 1.25** (0.87 to 1.80) | 173 per 1,000 | **43 more per 1,000** (from 22 fewer to 138 more) |

Time to progression to severe disease

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 490 (1 RCT) | serious[j] | not serious | not serious | serious[c] | none | Low | 249 | 241 | - | | MD 0.3 more (0.08 fewer to 0.68 more) |

Symptom resolution

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 597 (2 RCTs) | serious[k] | not serious | serious[g] | serious[c] | none | Very low | 182/304 (59.9%) | 168/293 (57.3%) | **RR 0.95** (0.85 to 1.06) | 599 per 1,000 | **30 fewer per 1,000** (from 90 fewer to 36 more) |

Duration of hospitalisation

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 699 (3 RCTs) | serious[j] | serious[l] | not serious | serious[c] | none | Very low | 354 | 345 | - | | MD 0.57 fewer (2.31 fewer to 1.16 more) |

**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

## Explanations

a. Niaee and Ravikiriti have 'high ROB' and Abd-Elsalam and Manomaipiboon have unclear ROB
b. comparator in some studies was different to the UK standard of care
c. CIs cross line of no effect
d. all three studies have some concerns on ROB

e. Lim 2022 has some concerns on ROB due to open label RCT Kroleweicki 2020 has unclear ROB due to single blinding and concerns on reporting of AEs and SAEs (Lim and Kroleweicki contribute more than 33.3% of weight in meta analysis
f. Ravikirti 2021 has moderate risk in ROB
g. hydroxychloroquine in SOC
h. Mainomaipiboon 2022 is a preprint with incomplete information on pre-specified analysis
i. Lim contributing more than 33.3% with some concerns on ROB
j. Lim was an open label trial with some concerns on ROB
k. Ravikirti 2021 contributing to the meta-analysis for more than 33.3% and same applies for Lim trial
l. I square greater than 50% and point estimates are not in one direction

## Ivermectin (single dose) compared to standard care for people hospitalised with COVID-19

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Study event rates (%) | | | Anticipated absolute effects | |
| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | With standard care | With ivermectin (single dose) | Relative effect (95% CI) | Risk with standard care | Risk difference with ivermectin (single dose) |
| All-cause mortality (day 28) | | | | | | | | | | | |
| 345 (5 RCTs) | not serious | not serious[a] | serious[b] | serious[c] | none | Low | 17/149 (11.4%) | 5/196 (2.6%) | **RR 0.26** (0.04 to 1.79) | 114 per 1,000 | **84 fewer per 1,000** (from 110 fewer to 90 more) |
| Adverse events | | | | | | | | | | | |
| 307 (4 RCTs) | serious[d] | not serious | serious[e] | serious[c] | none | Very low | 6/131 (4.6%) | 14/176 (8.0%) | **RR 1.21** (0.49 to 2.97) | 46 per 1,000 | **10 more per 1,000** (from 23 fewer to 90 more) |
| Viral clearance 1-6 days | | | | | | | | | | | |
| 32 (1 RCT) | serious[f] | not serious | serious[b] | serious[c] | none | Very low | 6/13 (46.2%) | 8/19 (42.1%) | **RR 0.91** (0.41 to 2.01) | 462 per 1,000 | **42 fewer per 1,000** (from 272 fewer to 466 more) |
| Viral clearance 7-14 days | | | | | | | | | | | |

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 200 (3 RCTs) | serious[d] | serious[a] | not serious | serious[c] | none | Very low | 36/87 (41.4%) | 66/113 (58.4%) | **RR 1.41** (0.84 to 2.35) | 414 per 1,000 | **170 more per 1,000** (from 66 fewer to 559 more) |

Discharge from hospital

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 236 (4 RCTs) | not serious | not serious | not serious | serious[c] | none | Moderate | 79/101 (78.2%) | 115/135 (85.2%) | **RR 1.04** (0.94 to 1.14) | 782 per 1,000 | **31 more per 1,000** (from 47 fewer to 110 more) |

Supplemental oxygen

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 69 (1 RCT) | serious[g] | not serious | serious[b] | serious[c] | none | Very low | 9/34 (26.5%) | 10/35 (28.6%) | **RR 1.08** (0.50 to 2.32) | 265 per 1,000 | **21 more per 1,000** (from 132 fewer to 349 more) |

Clinical progression

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 125 (2 RCTs) | serious[d] | not serious | not serious | serious[c] | none | Low | 5/45 (11.1%) | 5/80 (6.3%) | **RR 0.56** (0.17 to 1.88) | 111 per 1,000 | **49 fewer per 1,000** (from 92 fewer to 98 more) |

Invasive mechanical ventilation

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 169 (3 RCTs) | serious[h] | not serious | serious[b] | serious[c] | none | Very low | 1/34 (2.9%) | 2/135 (1.5%) | **RR 0.97** (0.09 to 9.98) | 29 per 1,000 | **1 fewer per 1,000** (from 27 fewer to 264 more) |

Duration of symptoms

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 69 (1 RCT) | serious[g] | not serious | serious[b] | not serious | none | Low | 34 | 35 | - | | MD 1 fewer (1.14 fewer to 0.86 fewer) |

Duration of hospitalisation

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 69 (1 RCT) | serious[g] | not serious | serious[b] | serious[c] | none | Very low | 34 | 35 | - | | MD 1.3 fewer (2.81 fewer to 0.21 more) |

Clinical Improvement (2 or more decrease WHO)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 125 (2 RCTs) | serious[d] | not serious | not serious | serious[c] | none | Low | 39/45 (86.7%) | 74/80 (92.5%) | **RR 1.07** (0.94 to 1.22) | 867 per 1,000 | **61 more per 1,000** (from 52 fewer to 191 more) |

Time to recovery (resolution of symptoms)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 125 (2 RCTs) | serious[d] | not serious | not serious | serious[c] | none | Low | 45 | 80 | - | | MD 0.06 lower (1.08 lower to 0.96 higher) |

**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

## Explanations

a. I square greater than 50% but point estimates are in same direction
b. hydroxychloroquine as standard care
c. CIs cross line of no effect
d. Mohan study had ROB rating as uncertain
e. Differences between the intervention/comparator of interest and those studied
f. Kishoria 2020 - uncertain ROB
g. Shahbaznejad 2021 - ROB unclear
h. Shahbaznejad contributing more than 33.3% and has uncertain ROB

## Ivermectin (multiple doses) compared to standard care for people in the community COVID-19

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Study event rates (%) | | | Anticipated absolute effects | |
| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | With standard care | With ivermectin (multiple doses) | Relative effect (95% CI) | Risk with standard care | Risk difference with ivermectin (multiple doses) |
| All-cause mortality (day 28) | | | | | | | | | | | |
| 2159 (4 RCTs) | not serious | not serious | not serious | serious[a] | none | Moderate | 29/1231 (2.4%) | 26/928 (2.8%) | **RR 1.46** (0.87 to 2.44) | 24 per 1,000 | **11 more per 1,000** (from 3 fewer to 34 more) |
| Serious adverse events (end of follow up) | | | | | | | | | | | |
| 2546 (6 RCTs) | not serious | not serious | not serious | serious[a] | none | Moderate | 76/1260 (6.0%) | 69/1286 (5.4%) | **RR 0.88** (0.64 to 1.20) | 60 per 1,000 | **7 fewer per 1,000** (from 22 fewer to 12 more) |
| Viral clearance (1-6 days) | | | | | | | | | | | |
| 318 (1 RCT) | not serious | not serious | not serious | serious[a] | none | Moderate | 17/170 (10.0%) | 11/148 (7.4%) | **RR 0.74** (0.36 to 1.54) | 100 per 1,000 | **26 fewer per 1,000** (from 64 fewer to 54 more) |
| Viral clearance (7-14 days) | | | | | | | | | | | |

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 984 (5 RCTs) | not serious | serious[b] | not serious | serious[a] | none | Low | 308/487 (63.2%) | 319/497 (64.2%) | **RR 1.00** (0.91 to 1.08) | 632 per 1,000 | **0 fewer per 1,000** (from 57 fewer to 51 more) |

Invasive mechanical ventilation

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1859 (2 RCTs) | not serious | not serious | serious[c] | serious[a] | none | Low | 28/930 (3.0%) | 23/929 (2.5%) | **RR 0.82** (0.48 to 1.42) | 30 per 1,000 | **5 fewer per 1,000** (from 16 fewer to 13 more) |

Supplemental oxygen

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 89 (1 RCT) | serious[d] | not serious | not serious | very serious[e] | none | Very low | 1/42 (2.4%) | 0/47 (0.0%) | **RR 0.30** (0.01 to 7.14) | 24 per 1,000 | **17 fewer per 1,000** (from 24 fewer to 146 more) |

Hospitalisation

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2035 (5 RCTs) | not serious | serious[f] | not serious | serious[a] | none | Low | 117/1001 (11.7%) | 97/1034 (9.4%) | **RR 0.81** (0.63 to 1.05) | 117 per 1,000 | **22 fewer per 1,000** (from 43 fewer to 6 more) |

Clinical deterioration

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 600 (2 RCTs) | very serious[g] | not serious | not serious | serious[a] | none | Very low | 14/301 (4.7%) | 8/299 (2.7%) | **RR 0.58** (0.25 to 1.36) | 47 per 1,000 | **20 fewer per 1,000** (from 35 fewer to 17 more) |

Clinical recovery (21 days)

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 650 (3 RCTs) | very serious[g] | not serious | not serious | serious[a] | none | Very low | 232/326 (71.2%) | 253/324 (78.1%) | **RR 1.10** (0.97 to 1.24) | 712 per 1,000 | **71 more per 1,000** (from 21 fewer to 171 more) |

Discontinuation due to adverse event

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 899 (2 RCTs) | very serious[h] | not serious | not serious | not serious | none | Low | 5/449 (1.1%) | 15/450 (3.3%) | **RR 2.97** (1.10 to 8.02) | 11 per 1,000 | **22 more per 1,000** (from 1 more to 78 more) |

Adverse events (end of follow up)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2373 (4 RCTs) | very serious[i] | not serious | not serious | serious[a] | none | Very low | 305/1187 (25.7%) | 266/1186 (22.4%) | **RR 0.88** (0.75 to 1.03) | 257 per 1,000 | **31 fewer per 1,000** (from 64 fewer to 8 more) |

**CI:** confidence interval; **RR:** risk ratio

## Explanations

a. CIs cross line of no effect
b. I square greater than 75% time since onset of symptoms was different across the trials
c. High risk population in Reis 2022
d. Biber study has unclear risk of bias due to insufficient information on: if analysed as per protocol analyses and involved retrospective data registry
e. CIs cross line of no effect; less than 300 people contributing to the outcome
f. time since onset of symptoms was different across the trials
g. Lopez 2021 has high ROB due to incomplete information on blinding and missing outcome data. Abbas 2022 has moderate ROB due to insufficient information on pre-specified analysis plan
h. Lopez 2021 has high risk of bias due to insufficient information on blinding and prespecified analysis plan and is contributing 100% to the analysis
i. Lopez 2021 has high ROB due to incomplete information on blinding and missing outcome data. Lopez contributing more than 33.3% to the analysis of this outcome

## Ivermectin (single dose) compared to standard dose for people in the community COVID-19

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Study event rates (%) | | | Anticipated absolute effects | |
| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | With standard dose | With ivermectin (single dose) | Relative effect (95% CI) | Risk with standard dose | Risk difference with ivermectin (single dose) |
| Viral clearance (7-14 days) Single dose | | | | | | | | | | | |
| 40 (1 RCT) | serious[a] | not serious | not serious | serious[b] | none | Low | 19/20 (95.0%) | 18/20 (90.0%) | **RR 0.95** (0.79 to 1.13) | 950 per 1,000 | **48 fewer per 1,000** (from 199 fewer to 123 more) |
| Adverse events (end of follow up) Single dose | | | | | | | | | | | |
| 24 (1 RCT) | serious[c] | not serious | not serious | serious[b] | none | Low | 5/12 (41.7%) | 5/12 (41.7%) | **RR 1.00** (0.39 to 2.58) | 417 per 1,000 | **0 fewer per 1,000** (from 254 fewer to 658 more) |

**CI:** confidence interval; **RR:** risk ratio

### Explanations

a. Podder 2020 study has high risk of bias; no information on missing data and per-protocol analysis plan
b. CIs cross line of no effect
c. Chaccour 2020 has unclear ROB, with incomplete information on blinding