NICE National Institute for Health and Care Excellence

The effectiveness and safety of ivermectin for acute symptoms and complications of COVID-19

Evidence review

Review date November 2021

Contents

Objective

This evidence review aims to review the effectiveness and safety of ivermectin for acute symptoms and complications of COVID-19.

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.

Due to the urgency of this work, data developed by the Australian Living Guidelines Taskforce was used to expedite the review. This included:

- Outcome data in Review Manager:
  - For this review, the original data provided by the Australian Living Guidelines Taskforce was separated into hospital and community settings, in line with the protocol for the review
  - For multi-arm trials identified by Australia, multiple treatment arms were treated as though they were one arm due to low numbers of events
  - For the new multi-arm study identified in surveillance (Buonfrate 2021), data from treatment arms was analysed separately due to high doses of ivermectin used in the trial
- Study risk of bias assessments were done in Review Manager so they have been assessed using the Cochrane risk of bias 1 tool, meaning risk of bias was assessed at the study level rather than outcome level.
- Study characteristics tables:
  - For this review, these tables were used as the basis for data extraction and the NICE team added some additional fields including setting, funder and outcomes to provide more detailed information.

Note that studies were checked against trial registry details (where available) to assess any deviations from protocols. This information fed into the risk of bias assessments.

As the recommendations developed by the Australian Living Guidelines Taskforce were published in August 2021, a search was conducted to identify any additional evidence that may have published and should be considered for inclusion (see below).

The searches for the effectiveness evidence were run on 14/09/2021. 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. Pre-prints were searched via EPPI reviewer v5.

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. Both procedures were adapted from the 2016 PRESS Checklist.

Summary of included studies

A literature search identified 163 references (see appendix B for full details). These references were screened using their titles and abstracts and 30 full text references were obtained and assessed for relevance.

12 studies were excluded. Details of excluded studies are in appendix C.

An additional study was subsequently identified in surveillance checks (Buonfrate 2021) and was considered eligible for inclusion. One study (Samaha 2021) that had been identified in our development and included was subsequently retracted (in November 2021) and excluded from this evidence review. In total, 18 studies are included in this evidence summary, all of which were identified by the Australian Living Guidelines Taskforce (with the exception of the Buonfrate 2021 study that was identified in surveillance checks). Two studies included as pre-prints in the Australian Living Guideline have been included as full publications as they are no longer pre-prints. A summary of the included studies and their quality assessment is shown in appendices D and E. Forest plots are in appendix F.

Study characteristics

Table 1: Hospital setting

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

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Abd-Elsalam 2021 Egypt **No. of participants: 164**	RCT	Mild/moderate	Adults PCR confirmed COVID-19 Exclusions: pregnancy/lactation, allergy or contraindication to the drugs in the study, pregnant and lactating mothers, and patients with cardiac problems. **Mean age ± SD (years):** Intervention - 42.38 ± 16.02 Comparator - 39.38 ± 16.92 **Average % female:** Intervention - 54.9 Comparator - 45.1	Oral ivermectin 12 mg once daily for 3 days Standard care 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 90% despite oxygen or non-invasive ventilation, progressive hypercapnia, respiratory acidosis (pH < 7.3), and progressive or	Mortality Invasive mechanical ventilation Adverse events Hospital length of stay

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
					refractory septic shock.	
Ahmed 2020 Bangladesh **No. of participants: 68**	RCT	Mild symptoms	Adults PCR confirmed COVID-19 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. **Average age (years):** 42 **Average % female:** 54	Subgroups: 1) oral ivermectin 12mg once daily (5 days) 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	Virological clearance
Bukhari 2021 Pakistan **No. of participants: 86**	RCT	Mild/moderate - severity was defined by WHO guidelines Chest x-ray was used to support “moderate” severity and if these patients had oxygen requirements	Adults and children 15 and above PCR confirmed COVID-19 Exclusions: pregnancy, severe symptoms, uncontrolled co-morbidities and immunocompromised, history of ivermectin allergy, patients taking CY3A4 inhibitors. **Mean age ± SD (years):** Intervention - 42.24 ± 12.0	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 Virological clearance

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
		equivalent to FiO2 ≥ 50%, they were excluded.	Comparator - 38.98 ± 12.61 **Average % female:** Intervention - 9.8 Comparator - 20			
Gonzalez 2021 Mexico **No. of participants: 73**	RCT	Severe (non-critically ill patients)	No information on whether paediatric patients or pregnant women excluded. 69 patients had typical infiltrates characteristic of SARS-CoV-2 infection pneumonia, defined by CO-RADS 5, while 24 patients had an image with a low probability of SARS-CoV-2 infection according to that scoring system, but they had a diagnostically compatible clinical presentation and/or a positive RT-PCR test for SARS-CoV-2. Exclusions: patient required high oxygen volumes or required mechanical ventilation. **Average age ± SD (years):** Intervention - 56 ± 16.5 Comparator – 53.8 ± 16.9 **Average % female:** Intervention - 41.7 Comparator – 37.9	Oral ivermectin single dose 12mg (if less than 80kg) OR 18mg (if more than 80kg) Antibiotics (58% of patients) All hospitalised patients received pharmacological thromboprophylaxis with low molecular weight heparin or unfractionated heparin according to local and international guidelines. During the last week of June 2020, based on the RECOVERY trial, initiated administration of dexamethasone, 6 mg IV every 24 hours, for 10 days or until discharge, in patients requiring oxygen therapy.	Placebo Antibiotics (51% of patients)	Mortality Hospital length of stay Hospital discharge
Kishoria 2020 India	RCT	Mild/asymptomatic. Mild illness stated to be 'as per WHO'.	Adults PCR confirmed COVID-19 (positive after standard care treatment)	Oral ivermectin 12 mg single dose	Hydroxychloroquine 400mg twice a day for 5 days	Hospital discharge Virological clearance

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
No. of participants: 32			Exclusions: pregnancy/lactation, allergy or hypersensitivity to 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; concomitant administration of enzyme inducers (such as carbamazepine) that could affect the effectiveness of the drug and those receiving CYP3A4 substrates (such as statins) due to the risk of increased toxicity. **Average age (years):** Intervention – 39.5 Comparator – 37.0 **Average % female:** Intervention – 26.3 Comparator – 30.7	Hydroxychloroquine 400 mg twice a day for 5 days Paracetamol 500mg as required Vitamin C 1 tab twice a day	Paracetamol 500mg as required Vitamin C 1 tab twice a day	
Krolewiecki 2020 Argentina	RCT	Mild/Moderate (WHO ordinal	Adults PCR confirmed COVID-19	Oral ivermectin 600microgram/kg (5 days)	Standard care (included	Invasive mechanical ventilation

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
No. of participants: 32		scale score of 3 or 4)	Exclusions: pregnancy/lactation, pre-existing hypersensitivity/allergy to ivermectin, use of immunomodulators within 30 days, poorly controlled comorbidities. **Mean age ± SD (years):** Intervention Ivermectin <160ng/mL – 50.9 ± 12.3 Ivermectin >160ng/mL – 39.8 ± 10.2 Comparator – 37.3 ± 12.7 **Average % female:** Intervention Ivermectin <160ng/mL -– 45 Ivermectin >160ng/mL – 56 Comparator - 42		hospitalisation of all symptomatic cases)	Adverse events Clinical evolution
Mohan 2021 India **No. of participants: 125**	RCT	Mild/moderate (WHO ordinal scale score of 3 or 4)	Adults Diagnosis of COVID-19 based on positive result on either PCR or a rapid antigen test. 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	Oral ivermectin by subgroup (single dose): 1) 24mg 2) 12mg	Placebo	Mortality Invasive mechanical ventilation Adverse events Hospital discharge Symptom resolution Virological clearance Clinical worsening

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
			days prior to enrolment, prolonged corrected QT interval (>450 ms) on electrocardiogram, any other severe comorbidity as per investigator's assessment, or enrolment in a concomitant clinical trial. **Mean age ± SD (years):** Intervention Ivermectin 24mg – 34.3 ± 10.45 Ivermectin 12mg – 36.3 ± 10.54 Comparator - 35.3 ± 10.52 **Average % female:** Intervention Ivermectin 24mg – 7.5 Ivermectin 12mg – 12.5 Comparator – 13.3			Note: primary outcomes were assessed in PCR confirmed group only (modified ITT group). Safety outcomes assessed in ITT population.
Pott-Junior 2021 Brazil **No. of participants: 31**	RCT	Mild clinical symptoms of COVID-19	Adults PCR confirmed COVID-19 Exclusions: pregnancy/ lactation, unable to ingest / absorb the drug orally through spontaneous ingestion or by gastro / enteral tubes; abnormal ECG findings that require additional evaluation; known hypersensitivity to the drug components; body weight <15 kg; an estimated glomerular filtration rate (CKD-Epidemiology Collaboration, CKD-EPI) below 30 mL/min; and values of aspartate aminotransaminase (AST) or alanine aminotransaminase (ALT)	Oral ivermectin 100 microgram/kg OR 200 microgram/kg OR 400 microgram/kg (duration not reported) Between 7.5mg and 30mg dose (based on 75kg person) Glucocorticoids (26% of patients) Antibiotics (22% of patients)	Standard care treatment was provided at the time of hospital admission according to the latest recommendations on managing COVID-19 Glucocorticoids (75% of patients) Antibiotics (75% of patients)	ICU admission for ventilatory support Adverse events Virological clearance

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
			5-fold above the upper limit of normality. **Mean age ± SD (years):** 49.4 ± 14.6 **Average % female:** 54.8			
Ravikirti 2021 India **No. of participants: 112**	RCT	Mild/Moderate disease as defined by the Ministry of Health and Family Welfare (MOHFW), Government of India (GOI) guidelines Mild: No evidence of breathlessness or hypoxia (normal saturation) Moderate: Breathlessness and/or hypoxia (saturation 90-94% on room air), respiratory rate of 24 or more and no features of severe disease	Adults Diagnosis of COVID-19 based on positive result on either PCR or a rapid antigen test. 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. **Mean age ± SD (years):** Intervention - 50.7 ± 12.7 Comparator - 54.2 ± 16.3 **Average % female:** Intervention - 27.3 Comparator - 28.1	Oral ivermectin 12 mg daily for 2 days Hydroxychloroquine Antibiotics Tocilizumab (7% of patients) Remdesivir (22% of patients)	Placebo Hydroxychloroquine Antibiotics Tocilizumab (5% of patients) Remdesivir (19% of patients)	Mortality Invasive mechanical ventilation Admission to ICU Hospital discharge Symptom resolution Virological clearance

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Shahbaznejad 2021 Iran **No. of participants: 69**	RCT	Moderate/ Severe Severe disease was defined as tachypnea (respiratory rate of ≥24 breaths/min), need for mechanical ventilation, need for supplemental oxygen, and oxygen saturation of <94% in the ambient air. All other patients were considered to have moderate disease.	Adults and children aged above 5 years Diagnostic criteria for COVID-19 included any of the following: positive result on PCR test: clinical symptoms of COVID-19, with a history of contact with a patient with COVID-19; and/or abnormalities on CT scan compatible with COVID-19. 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. **Mean age ± SD age (years):** Intervention - 47.63 ± 22.20 Comparator – 45.18 ± 23.20 **Average % female:** Intervention - 48.6 Comparator – 47.1	Oral ivermectin single dose 200microgram/kg Hydroxychloroquine as part of standard care. Lopinavir-ritonavir (77% of patients) Azithromycin (66% of patients) Antibiotics as indicated (91% of patients).	Standard care Hydroxychloroquine as part of standard care. Lopinavir-ritonavir (82% of patients) Azithromycin (50% of patients) Antibiotics as indicated (88% of patients).	Invasive mechanical ventilation Adverse events Length of hospital stay Supplemental oxygen Duration of symptoms Virological clearance
Shakhsi Niaee 2020 Iran **No. of participants: 180**	RCT	Mild/Moderate/ Severe Disease severity was based on CT scan for all participants.	Adults COVID-19 confirmed by PCR or chest image tests. 80% of intervention groups diagnosed by PCR.	Subgroups Oral ivermectin (duration 5 days): 1) 200microgram/ kg once daily	Group 1: hydroxychloroquine 200 mg/kg twice per day Group 2: placebo plus	Mortality Duration of hospital stay

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
			53% of control groups diagnosed by PCR. 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. **Median age, IQR (years):** Ivermectin Arm 1: 61 (42, 68) Arm 2: 53 (42, 65) Arm 3: 54 (47, 60) Arm 4: 54 (46, 65) Comparator Standard care: 55 (45, 70) Standard care + placebo: 58 (45, 68) **Average % female:** Ivermectin Arm 1: 60 Arm 2: 36.7 Arm 3: 46.7 Arm 4: 56.7 Comparator Standard care: 46.7 Standard care + placebo: 53.3	2) 400microgram/ kg once daily 3) 200 microgram /kg days 1, 3 & 5 4) 400 microgram /kg days 1, 3 & 5 All groups: Hydroxychloroquine 200 mg twice per day	hydroxychloroquine 200 mg/kg twice per day	

Table 2: Community setting

Study	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Biber 2021 Israel **No. of participants: 89**	RCT	Asymptomatic/ mild/moderate	Adults PCR confirmed COVID-19 Exclusions: pregnancy/lactation, weighed below 40kg, known allergy to the drugs, unable to take oral medication, participating in another RCT for treatment of 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. **Median age, IQR (years):** Intervention - 36.0 (32·0-50·0) Comparator – 33.5 (26·0-47·0) **Average % female:** Intervention - 21.7 Comparator – 21.4	Oral ivermectin 200microgram/kg (daily for 3 days)	Placebo	Adverse events Hospitalisation Supplemental oxygen Virological clearance
Buonfrate 2021 (COVER) Italy **No. of participants: 59**	RCT	Asymptomatic/ mild/moderate COVID-19 severity score < 3	Adults PCR confirmed COVID-19 Exclusions: pregnant or lactating women, CNS diseases, people receiving dialysis, severe medical	High dose oral ivermectin (2 arms): Single dose 600 microgram/kg plus placebo for 5 days	Placebo	Serious adverse drug reactions Adverse events Serious adverse events

Study	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
		1 = no limitation of activities 2= limitation of activities	conditions with < 6 months prognosis, warfarin treatment, antiviral/chloroquine phosphate/hydroxychloroquine treatment **Median age (Q1 – Q3) (years):** Ivermectin 600 µg/kg 47.0 (31.0-62.0) Ivermectin 1200 µg/kg 44.5 (31.0-55.5) Comparator 50.0 (26.0-57.0) **Average % female:** Ivermectin 600 µg/kg 48.3 Ivermectin 1200 µg/kg 25.0 Comparator 53.1	Single dose 1200 microgram/kg for 5 days High dose - 75kg person would be taking 450mg (total)		Hospitalisation Time to clinical resolution Virological clearance
Chaccour 2021 Spain **No. of participants: 24**	RCT	Non-severe disease	Adults PCR confirmed COVID-19 Exclusions: pregnancy; known history of Ivermectin allergy; hypersensitivity to any component of Stromectol® ; COVID-19 Pneumonia: • Diagnosed by the attending physician • Identified in a chest X-ray 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,	Oral ivermectin 400 microgram/kg single dose	Placebo	Adverse events Virological clearance

Study	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
			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. **Age, median (IQR) [range] (years):** Intervention - 26 (19-36) [18-54] Comparator – 26 (21-44) [18-54] **Average % female:** Intervention - 42 Comparator – 58			
Chachar 2020 Pakistan **No. of participants: 50**	RCT	Mild	Adults PCR confirmed COVID-19 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 C **Mean age ±SD (years):** Intervention – 40.60± 17 Comparator – 43.08 ± 14.8 **Average % female:** Intervention - 16 Comparator - 22	Ivermectin 12mg loading dose and 12mg; 12 and 24 hours after initial dose and symptomatic treatment. Method of administration not reported.	Standard care – symptomatic treatment.	Adverse events Symptom resolution

Study	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
López-Medina 2021 Colombia **No. of participants: 398**	RCT	Mild disease defined as being at home or hospitalised but not receiving high-flow nasal oxygen or mechanical ventilation (invasive or non-invasive)	Adults PCR confirmed COVID-19 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. **Median age (IQR) (years):** Intervention - 37 (29 - 47.7) Comparator – 37 (28.7- 49.2) **Average % female:** Intervention - 61 Comparator - 55	Oral ivermectin 300 microgram/kg for 5 days Glucocorticoids (3% of patients) Antibiotics (7% of patients)	Placebo Glucocorticoids (6% of patients) Antibiotics (6% of patients)	Mortality Adverse events Clinical deterioration Symptom resolution
Podder 2020 Bangladesh **No. of participants: 62**	RCT	Mild/moderate according to WHO COVID-19 disease severity classification	Adults PCR confirmed COVID-19 Exclusions: pregnancy/lactation, pre-existing hypersensitivity to ivermectin, patients taking other antimicrobials or hydroxychloroquine. **Mean age ±SD (years):** Intervention – 38.41 ± 11.02 Comparator – 39.97 ± 13.24 **Average % female:** Intervention – 28.1 Comparator – 30.0	Oral ivermectin 200 microgram/kg single dose. Symptomatic treatment included antipyretics, cough suppressants, capsule doxycycline (100 mg every 12 hours for seven days).	Standard care Symptomatic treatment included antipyretics, cough suppressants, capsule doxycycline (100 mg every 12 hours for seven days).	Symptom resolution Viral clearance (7-10 days)

Study	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Vallejos 2021 Argentina **No. of participants: 501**	RCT	Mild/moderate No scale used to determine severity.	Adults PCR confirmed COVID-19 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. **Mean age ±SD (years):** Intervention – 42.58 ± 15.29 Comparator – 42.40 ± 15.75 **Average % female:** Intervention – 44.4 Comparator – 50.2	Oral ivermectin 2 doses in 2 days 12mg (≥80kg), 18mg (80-110kg), 24mg (≥110kg) Antibiotics (6% of patients)	Standard of care in accordance with the recommendations of the Argentine Ministry of Health Placebo Antibiotics (6% of patients)	Mortality Hospitalisation Invasive mechanical ventilation Adverse events Negative nasal swab

KEY: tables 1 and 2

ICU – intensive care unit

ITT – intention to treat

PCR - polymerase chain reaction

RCT – randomised control trial

SD – standard deviation

WHO – World Health Organization

Table 3: Trial funder and status details

Study	Trial registration details/no.	Funder details	Print status
Abd-Elsalam 2021	ClinicalTrial.gov (NCT04403555)	Not reported	Full publication
Ahmed 2020	Not applicable	Beximco Pharmaceutical Limited, Bangladesh	Full publication
Biber 2021	ClinicalTrials.gov NCT 044297411	No funding	Preprint
Bukhari 2021	Trial registration NCT04392713	Funding statement says: not applicable	Preprint
Buonfrate 2021	ClinicalTrials.gov Identifier: NCT04438850	Sponsored by IRCCS Sacro Cuore Don Calabria hospital, funded by Italian Ministry of Health, ivermectin and placebo tablets donated by Insud Pharma, Madrid	Preprint
Chaccour 2021	ClinicalTrials.gov: NCT04390022	ISGlobal, Barcelona Institute for Global Health and Clinica Universidad de Navarra	Full publication
Chachar 2020	Not applicable	Not reported	Full publication
Gonzalez 2021	Clinical Trials identifier NCT04391127	Sponsored by the Aguascalienes state health institute	Preprint
Kishoria 2020	Not applicable	Not reported	Full publication
Krolewiecki 2020	ClinicalTrials.gov: NCT04381884	Agencia Nacional de Promocion de la Investigacion, el Desarrollo Tecnologico y la Innovacion, Argentina and Laboratorio ELEA/Phoenix, Argentina.	Full publication
López-Medina 2021	ClinicalTrials.gov Identifier: NCT04405843	Unrestricted grant from Centro de Estudios en Infectología Pediátrica	Full publication
Mohan 2021	Clinical Trial Registry – India (CTRI) vide ref No CTRI/2020/06/026001	Science and Engineering Research Board , Department of Science and Technology , Government of India	Full publication
Podder 2020	Not applicable	Self-financed	Full publication
Pott-Junior 2021	ClinicalTrials.gov (NCT04431466)	Non-commercial phase 2a clinical trial conducted at the Federal University of São Carlos, Brazil.	Full publication
Ravikirti 2021	Clinical Trials Registry-India (CTRI) (registration number: CTRI/2020/08/027225).	Not reported	Full publication
Shahbaznejad 2021	Iranian Registry of Clinical Trials identifier: IRCT20111224008507N3	Not reported	Full publication
Shakhsi Niaee 2020	Iranian Registry of Clinical Trials website (ID: IRCT20200408046987N1)	Not reported	Full publication
Vallejos 2021	ClinicalTrials.gov NCT04529525	No funding	Full publication

Results

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

Hospital setting

Please see MAGICapp for the evidence profile for ivermectin in the hospital setting

Community setting

Please see MAGICapp for the evidence profile for ivermectin in the community setting.

References

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

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, 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.

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

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

Kishoria, N., Mathur, S., Parmar, V., Kaur, R., Agarwal, H., Parihar, B., & Verma S (2020) Ivermectin as adjuvant to hydroxychloroquine 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

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

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

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

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

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

Appendices

Appendix A: PICO table

PICO table

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 *Note: Standard care comprises best supportive care and in certain circumstances the use of additional drugs (such as dexamethasone, remdesivir).*
Outcomes	Critical outcomes: • Mortality (n/N) • Invasive mechanical ventilation (IMV) or intensive care admission (requirement and duration) • Adverse events

	• Hospitalisation (requirement and duration) Important outcomes: • Supplemental oxygen, high-flow oxygen, continuous positive airway pressure or non-invasive ventilation (requirement and duration) • Discontinuation due to adverse events • Symptom resolution or clinical recovery (number and time until) • Virological clearance (negative PCR) • Clinical worsening / deterioration (number and time until) • 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: **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) **Non-invasive ventilation:** includes HFNO, CPAP, CPAP via tracheostomy, and non-invasive bilevel ventilation. Note: oxygen via (low flow) nasal cannulae or face mask does not fall within the categories above.
Settings	All settings
Subgroups	• Adults > 50 years • Children <12 years of age • Disease severity (moderate/severe/critical) • Sex • Ethnic background • Pregnant women • Comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary

	heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity) • Time from symptom onset • Treatment with other therapeutics used for COVID-19 • Community vs hospital • Confirmed versus negative for COVID • Tested vs untested for COVID • PCR confirmed versus clinically confirmed COVID • Vaccination status • Different variants
Study types	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If no systematic reviews or RCT evidence is available progress to: • non-randomised controlled trials • systematic reviews of non-randomised controlled trials • cohort studies • before and after studies • interrupted time series studies 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: • non-English language papers, studies that are only available as abstracts, and narrative reviews • animal studies • editorials, letters, news items, case reports and commentaries, conference abstracts and posters

	• 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: Search strategies

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. 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

Appendix C: Excluded studies at full text screening

Study	Code [Reason]
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 *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 and study doesn't report any critical outcomes.*
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 *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 *Excluded as study investigated active comparators without proven efficacy. Also, no relevant outcomes reported.*
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	- Not a relevant study design *Not an RCT.*
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	- Study does not contain a relevant intervention *Combination treatment.*
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-	- Comparator in study does not match that specified in protocol *Exclude on basis of no relevant active comparator of proven efficacy plus phase 2.*

Study	Code [Reason]
CoV-2 infection. Pathogens and global health 115(4): 235-242	
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 *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 *This is a correction to an article we already included.*
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 *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, patients with odd numbers were grouped as the study group, and patients with even numbers as the control group.'*
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 *No relevant active comparator of proven efficacy.*
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 contain a population of people with COVID-19 *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 D: Data extraction

Abd-Elsalam 2021 (NCT04403555)			
	Ivermectin	**Standard care**	**P value**
Study Characteristics			
No. of patients (N)	82	82	
Age (years)	42.38	39.38	0.23
Gender (female; %)	54.9	45.1	0.21
Pregnant patients	Pregnant and lactating women were excluded.		
Paediatric patients	Excluded		
COVID-19 status	Confirmed by PCR test		
Primary exclusion criteria	Allergy or contraindication to the drugs in the study, pregnant and lactating mothers, and patients with cardiac problems.		
Setting	Hospital		
Country	Egypt		
Study dates	March 2020 to October 2020		
Funder	Not reported		
Dose and duration			
Dose (loading)	12mg	-	
Dose (maintenance)	12mg	-	
Duration	3 days	-	
Route of administration	Oral	Oral	
Disease severity			
Mild (%)	Not reported		
Moderate (%)			
Severe (%)	-		
Critical (%)	-		
Co-administered interventions			
Hydroxychloroquine (%)	NR	NR	
Lopinavir-ritonavir (%)	NR	NR	
Glucocorticoids (%)	NR	NR	
Tocilizumab (%)	NR	NR	
Azithromycin (%)	NR	NR	
Remdesivir (%)	NR	NR	
Antivirals, any (%)	NR	NR	
Antibiotics, any (%)	100 (part of SC)	100 (part of SC)	
Comorbidities			

Abd-Elsalam 2021 (NCT04403555)			
	Ivermectin	**Standard care**	**P value**
Cardiovascular disease (%)	NR	NR	
Hypertension (%)	21.9	17.1	0.52
Diabetes (%)	20.7	12.2	0.14
Obesity (%)	NR	NR	
Asthma (%)	NR	NR	
Outcomes			
Critical			
Mortality n (%)	3 (3.7)	4 (4.9)	1.00
Invasive mechanical ventilation (IMV) n (%)	3 (3.7)	3 (3.7)	1.00
Adverse events n (%)	3 (3.7)	0 (0)	NR
Length of hospital stay (days)	8.82	10.97	0.08
Important	NR		

Ahmed 2020				
	Ivermectin		**Placebo**	**P value**
Study Characteristics	**Ivermectin**	**Ivermectin + doxycycline (200mg day 1 + 100mg/12 hrs)**		
No. of patients (N)	22	23	23	
Age (years)	42			
Gender (female; %)	54			
Pregnant patients	Pregnant or lactating women were excluded.			
Paediatric patients	Excluded			
COVID-19 status	Confirmed by PCR test			
Primary exclusion criteria	Allergic to ivermectin or doxycycline, or if there was the potential for a drug–drug interaction with ivermectin or doxycycline; had chronic illnesses (e.g., ischemic heart disease, heart failure, documented cardiomyopathy, chronic kidney disease, chronic liver disease); had received ivermectin and/or doxycycline in the last 7 days; or had participated in any other clinical trial within the last month.			
Setting	Hospital			
Country	Bangladesh			
Study dates	NR. Published 26 November 2020			
Funder	Beximco Pharmaceutical Limited, Bangladesh			
Dose and duration				
Dose (loading)	12mg		N/A	

Ahmed 2020				
	Ivermectin		**Placebo**	**P value**
Dose (maintenance)	12mg once daily		N/A	
Duration	5 days		N/A	
Route of administration	Oral		N/A	
Disease severity				
Mild (%)	Only reported as mild symptoms – no further detail			
Moderate (%)	N/A			
Severe (%)				
Critical (%)				
Co-administered interventions				
Hydroxychloroquine (%)	Not reported			
Lopinavir-ritonavir (%)				
Glucocorticoids (%)				
Tocilizumab (%)				
Azithromycin (%)				
Remdesivir (%)				
Antivirals, any (%)				
Antibiotics, any (%)				
Comorbidities				
Cardiovascular disease (%)	Not reported			
Hypertension (%)				
Diabetes (%)				
Obesity (%)				
Asthma (%)				
Outcomes				
Critical				
Adverse events (n)	0	0	0	
Mean duration of hospitalisation after treatment (days)	9.6	10.1	9.7	
Important				
Need for oxygen	0	0	0	
Virological clearance (days)	9.7	11.5	12.7	0.02 (I) 0.27 (I+D)

Biber 2021			
	Ivermectin	**Placebo**	**P value**
Study Characteristics			
No. of patients (N)	47	42	
Median age (IQR) (years)	36.0 (32·0-50·0)	33.5 (26·0-47·0)	0.2446
Gender (female; %)	21.7	21.4	0.9718
Pregnant patients	Pregnant women were excluded.		
Paediatric patients	Excluded		
COVID-19 status	Confirmed by PCR test		
Primary exclusion criteria	Weighed below 40kg, were with known allergy to the drugs, unable to take oral medication, participating in another RCT for treatment of 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.		
Setting	Community		
Country	Israel		
Study dates	15 May 2020 to January 2021		
Funder	None		
Dose and duration			
Dose (loading)	200 microgram/kg	Placebo tablets (unspecified)	
Dose (maintenance)	200 microgram/kg	-	
Duration	3 days	3 days	
Route of administration	Oral	Oral	
Disease severity			
Mild (%)	Not reported		
Moderate (%)			
Severe (%)	-	-	
Critical (%)	-	-	
Co-administered interventions			
Hydroxychloroquine (%)	Not reported		
Lopinavir-ritonavir (%)			
Glucocorticoids (%)			
Tocilizumab (%)			
Azithromycin (%)			

Biber 2021			
	Ivermectin	**Placebo**	**P value**
Remdesivir (%)			
Antivirals, any (%)			
Antibiotics, any (%)			
Comorbidities			
Cardiovascular disease (%)	Not reported		
Hypertension (%)			
Diabetes (%)			
Obesity (%)			
Asthma (%)			
Critical			
Adverse events, n (%)	2 (4.2)	3 (7.1)	NR
Hospitalisation (duration range 1-11 days), n (%)	1 (2.1)	3 (7.1)	NR
Important			
Need for oxygen, n (%)	0 (0)	1 (2.3)	
Negative PCR at day 4, n (%)	15 (54)	7 (32)	0.12
Negative PCR at day 6, n (%)	34 (72)	21 (50)	0.03
Negative PCR at day 8, n (%)	39 (83)	25 (59)	0.01
Negative PCR at day 10, n (%)	40 (85)	29 (69)	0.07
Negative PCR test with non-viable cultures at day 4, n (%)	24 (86)	13 (59)	0.03
Negative PCR test with non-viable cultures at day 6, n (%)	44 (94)	31 (74)	0.01
Negative PCR test with non-viable cultures at day 8, n (%)	45 (96)	32 (76)	0.01
Negative PCR test with non-viable	45 (96)	36 (86)	0.14

Biber 2021			
	Ivermectin	**Placebo**	**P value**
cultures at day 10, n (%)			

Bukhari 2021 (NCT04392713)			
	Ivermectin	**Standard care**	**P value**
Study Characteristics			
No. of patients (N)	41	45	
Mean age ± SD (years)	42.24 ± 12.0	38.98 ± 12.61	0.394
Gender (female; %)	9.8	20	0.185
Pregnant patients	Excluded		
COVID-19 status	Confirmed by PCR test		
Paediatric patients	Children 15 and above included		
Primary exclusion criteria	Patients with severe symptoms, uncontrolled co-morbidities and immunocompromised, along with those with a history of ivermectin allergy. Along with those taking CY3A4 inhibitors.		
Setting	Hospital		
Country	Pakistan		
Study dates	15 March to 15 June 2020		
Funder	Funding statement says: not applicable		
Dose and duration			
Dose (loading)	12mg	NR	
Dose (maintenance)		NR	
Duration	Single dose	NR	
Route of administration	Oral	NR	
Disease severity			
Mild (%)	Not reported		
Moderate (%)			
Severe (%)	N/A		
Critical (%)			
Co-administered interventions			
Hydroxychloroquine (%)	Not reported		
Lopinavir-ritonavir (%)			
Glucocorticoids (%)			
Tocilizumab (%)			
Azithromycin (%)			

Bukhari 2021 (NCT04392713)			
	Ivermectin	**Standard care**	**P value**
Remdesivir (%)			
Antivirals, any (%)			
Antibiotics, any (%)			
Comorbidities			
Cardiovascular disease (%)	7	4	0.57
Hypertension (%)	12	16	0.653
Diabetes (%)	15	9	0.406
Obesity (%)	NR	NR	
Asthma (%)	NR	NR	
Outcomes			
Critical			
Adverse events n	0	Not reported	
Important			
Virological clearance at 72 hours n (%)	17 (41.4)	2 (4.4)	0.001
Virological clearance at day 7 n (%)	20 (48.7)	18 (40.0)	
Virological clearance at day 14 n (%)	4 (9.7)	25 (55.5)	

Buonfrate 2021 (COVER) (NCT04438850)				
	Ivermectin (high dose)		**Placebo**	**P value**
Study Characteristics	Single dose 600 µg/kg plus placebo for 5 days	Single dose 1200 µg/kg for 5 days		
No. of patients (N)	Randomised n=29 Safety analysis set n=28 Primary efficacy analysis n=28	Randomised n=32 Safety analysis set n=30 Primary efficacy analysis n=30	Randomised n=32 Safety analysis set n=31 Primary efficacy analysis n=29	
Age (years)	Median (Q1 to Q3) 47.0 (31.0 to 62.0)	Median (Q1 to Q3) 44.5 (31.0 to 55.5)	Median (Q1 to Q3) 50.0 (26.0 to 57.0)	NR
Gender (female; %)	14/29 (48.3%)	8/32 (25.0%)	17/32 (53.1%)	
Pregnant patients	Exclusion of pregnant or lactating women			
Paediatric patients	Excluded			
COVID-19 status	Newly diagnosed with SARS-CoV-2 infection by Real-Time PCR analysis of nasopharyngeal swabs			

Buonfrate 2021 (COVER) (NCT04438850)				
	Ivermectin (high dose)		**Placebo**	**P value**
Primary exclusion criteria	Pregnant or lactating women, CNS diseases, people receiving dialyvsis, severe medical conditions with < 6 months prognosis, warfarin treatment, antiviral/chloroquine phosphate/hydroxychloroquine			
Setting	Outpatients			
Country	Italy			
Study dates	31 July 2020 to 29 June 2021			
Funder	Sponsored by IRCCS Sacro Cuore Don Calabria hospital, funded by Italian Ministry of Health, ivermectin and placebo tablets donated by Insud Pharma, Madrid			
Dose and duration				
Dose (loading)	Single dose 600 microgram/kg plus placebo for 5 days	Single dose 1200 µg/kg for 5 days	N/A	
Dose (maintenance)	Single dose 600 microgram/kg plus placebo for 5 days	Single dose 1200 µg/kg for 5 days	N/A	
Duration	5 days	5 days	5 days	
Route of administration	Oral tablet	Oral tablet	Oral tablet	
Disease severity				
Mild (%)	COVID-19 Severity Score 1 (no limitation of activities) 24/29 (82.8%)	COVID-19 Severity Score 1 (no limitation of activities) 27/32 (84.4%)	COVID-19 Severity Score 1 (no limitation of activities) 27/32 (84.4%)	
Moderate (%)	COVID-19 Severity Score 2 (limitation of activities) 5/29 (17.2%)	COVID-19 Severity Score 2 (limitation of activities) 5/32 (15.6%)	COVID-19 Severity Score 2 (limitation of activities) 5/32 (15.6%)	
Severe (%)	NR	NR	NR	
Critical (%)	NR	NR	NR	
Co-administered interventions				
Hydroxychloroquine (%)	0			
Lopinavir-ritonavir (%)	Not reported			
Glucocorticoids (%)				
Tocilizumab (%)				
Azithromycin (%)				
Remdesivir (%)				
Antivirals, any (%)	0			
Antibiotics, any (%)	Not reported			
Comorbidities				

Buonfrate 2021 (COVER) (NCT04438850)				
	Ivermectin (high dose)		Placebo	P value
Comorbidity	11/29 (37.9%)	12/32 (37.5%)	8/32 (25.0%)	
Respiratory	4/29 (36.4%)	2/32 (16.7%)	0	
Cardiovascular	7/29 (63.6%)	8/32 (66.7%)	7/32 (87.5%)	
Diabetes	0	1/32 (8.3%)	2/32 (25.0)	
Outcomes				
Critical				
Serious adverse drug reactions	0	0	0	
Adverse events	69 (30.1%)	114 (49.8%)	46 (20.1%)	NR
Serious adverse events	1	3	0	NR
Hospitalisation	1/29	3/30	0	NR
Important				
Time to clinical resolution (days)	29	14	14	
Virological clearance (within 14 days)	70%	58%	59% (no statistically significant difference between arms)	NR

Chaccour 2021 (SAINT) (NCT04390022)			
	Ivermectin	Placebo	P value
Study Characteristics			
No. of patients (N)	12	12	NR
Age, median (IQR)[range] (years)	26 (19-36) [18-54]	26 (21-44) [18-54]	
Gender (female; %)	42	58	
Pregnant patients	Excluded		
COVID-19 status	Confirmed by PCR test		
Paediatric patients	Excluded		
Primary exclusion criteria	1. Known history of Ivermectin allergy 2. Hypersensitivity to any component of Stromectol® 3. COVID-19 Pneumonia • Diagnosed by the attending physician • Identified in a chest X-ray 4. Fever or cough present for more than 72 hours 5. Positive IgG against SARS-CoV-2 by rapid test 6. Age under 18 or over 60 years 7. The following co-morbidities (or any other disease that might interfere with the study in the eyes of the investigator):		

Chaccour 2021 (SAINT) (NCT04390022)			
	Ivermectin	**Placebo**	**P value**
	Immunosuppression, COPD, diabetes, hypertension, obesity, acute/ chronic renal failure, history of coronary disease, history of cerebrovascular disease, current neoplasm. 8. Recent travel history to countries that are endemic for Loa loa 9. Current use of CYP 3A4 or P-gp inhibitor drugs such as quinidine, amiodarone, diltiazem, spironolactone, verapamil, clarithromycin, erythromycin, itraconazole, ketoconazole, cyclosporine, tacrolimus, indinavir, ritonavir or cobicistat. Use of critical CYP3A4 substrate drugs such as warfarin.		
Setting	Emergency room, not specified if patients admitted to hospital. However, trial protocol states that patients were isolated at home. Categorised as a community setting on this basis		
Country	Spain		
Study dates	31 July 2020 to 11 September 2020		
Funder	ISGlobal, Barcelona Institute for Global Health and Clinica Universidad de Navarra		
Dose and duration			
Dose (loading)	400 microgram/kg	N/A	
Dose (maintenance)	Single dose	N/A	
Duration	1 day	N/A	
Route of administration	Oral	N/A	
Disease severity			
Mild (%)	Not reported		
Moderate (%)			
Severe (%)			
Critical (%)			
Co-administered interventions			
Hydroxychloroquine (%)	Not reported		
Lopinavir-ritonavir (%)			
Glucocorticoids (%)			
Tocilizumab (%)			
Azithromycin (%)			
Remdesivir (%)			
Antivirals, any (%)			
Antibiotics, any (%)			
Comorbidities			

Chaccour 2021 (SAINT) (NCT04390022)			
	Ivermectin	**Placebo**	**P value**
Cardiovascular disease (%)	Not reported		
Hypertension (%)			
Diabetes (%)			
Obesity (%)			
Asthma (%)			
Outcomes			
Critical			
Severe adverse events	0	0	
Adverse events n (%) of patients	5 (41.6)	5 (41.6)	
Important			
Virological clearance 7 days post treatment n (%)	Positive 12 (100) Negative 0 (0)	Positive 12 (100) Negative 0 (0)	
Clinical worsening	No patient from either group progressed to severe disease.		

Chachar 2020			
	Ivermectin	**Standard care**	**P value**
Study Characteristics			
No. of patients (N)	25	25	
Mean age ±SD (years)	40.60 ± 17	43.08 ± 14.8	0.582
Gender (female; %)	16	22	0.561
Pregnant patients	Pregnant or lactating women were excluded.		
COVID-19 status	Confirmed by PCR test		
Paediatric patients	Excluded		
Primary exclusion criteria	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 C		
Setting	Patients reported to COVID-19 clinics and medical outpatient department		
Country	Pakistan		
Study dates	1 May 2020 to 30 June 2020		
Funder	Not reported		
Dose and duration			
Dose (loading)	12mg	N/A	
Dose (maintenance)	12mg; 12 and 24 hours after initial dose	N/A	
Duration		N/A	

Chachar 2020			
	Ivermectin	**Standard care**	**P value**
Route of administration		N/A	
Disease severity			
Mild (%)	Mild cases only		
Moderate (%)			
Severe (%)			
Critical (%)			
Co-administered interventions			
Hydroxychloroquine (%)	Not reported		
Lopinavir-ritonavir (%)			
Glucocorticoids (%)			
Tocilizumab (%)			
Azithromycin (%)			
Remdesivir (%)			
Antivirals, any (%)			
Antibiotics, any (%)			
Comorbidities			
Cardiovascular disease (%)	4	4	NR
Hypertension (%)	14	12	NR
Diabetes (%)	22	18	NR
Obesity (%)	4	8	NR
Asthma (%)	NR	NR	NR
Outcomes			
Critical			
Adverse event n (%) of patients	8 (32)	NR	NR
Important			
Symptom resolution at day 7 n (%)	Asymptomatic 16 (64) Symptomatic 9 (36)	15 (60) Symptomatic 10 (40)	0.500

Gonzalez 2021 (NCT04391127)			
	Ivermectin	**Placebo**	**P value**
Study Characteristics			
No. of patients (N)	36	37	
Age ± SD (years)	56 ± 16.5	53.8 ± 16.9	0.15

Gonzalez 2021 (NCT04391127)			
	Ivermectin	**Placebo**	**P value**
Gender (female; %)	41.7	37.9	0.77
Pregnant patients	Not reported		
Paediatric patients	Not reported		
COVID-19 status	69 patients had typical infiltrates characteristic of SARS-CoV-2 infection pneumonia, defined by CO-RADS 5, while 24 patients had an image with a low probability of SARS-CoV-2 infection according to that scoring system, but they had a diagnostically compatible clinical presentation and/or a positive RT-PCR test for SARS-CoV-2.		
Primary exclusion criteria	If patient required high oxygen volumes or required mechanical ventilation.		
Setting	Hospital		
Country	Mexico		
Study dates	4 May 2020 to 6 November 2020		
Funder	Sponsored by the Aguascalienes state health institute.		
Dose and duration			
Dose (loading)	12mg (if less than 80kg) OR 18mg (if more than 80kg)	NR	
Dose (maintenance)	NR	NR	
Duration	NR	NR	
Route of administration	Oral	NR	
Disease severity			
Mild (%)	N/A		
Moderate (%)			
Severe (%)	NR		
Critical (%)	N/A		
Co-administered interventions			
Hydroxychloroquine (%)	NR	NR	
Lopinavir-ritonavir (%)	NR	NR	
Glucocorticoids (%)	NR	NR	
Tocilizumab (%)	NR	NR	
Azithromycin (%)	NR	NR	
Remdesivir (%)	NR	NR	
Antivirals, any (%)	NR	NR	
Antibiotics, any (%)	58	51	
Comorbidities			
Cardiovascular disease (%)	NR	NR	
Hypertension (%)	33	38	0.47

Gonzalez 2021 (NCT04391127)			
	Ivermectin	**Placebo**	**P value**
Diabetes (%)	25	43	0.25
Obesity (%)	NR	NR	
Asthma (%)	NR	NR	
Outcomes			
Critical			
Mortality day 28, n (%)	5 (13.8)	6 (16.2)	0.42
Duration of Hospitalisation, median (IQR)	6 (4 – 11)	5 (4 – 7)	0.43
Hospital discharge, n (%)	32 (88.8)	34 (91.8)	0.91
Important	Not reported		

	Kishoria 2020		
	Ivermectin + HCQ	**HCQ**	**P value**
Study Characteristics			
No. of patients (N)	19	13	
Age (years)	39.5	37.0	0.560 (I+HCQ) 0.783 (HCQ)
Gender (female; %)	26.3	30.7	
Pregnant patients	Pregnant and lactating women were excluded.		
COVID-19 status	PCR confirmed COVID-19 (positive after standard care treatment)		
Paediatric patients	Excluded		
Primary exclusion criteria	Allergy or hypersensitivity to ivermectin and/or its inactive ingredients; respiratory distress or requiring intensive care; used immunosuppressants (including systemic corticosteroids) in the last 30 days; known HIV infection with CD4 count <300 cell/ L; medical conditions such as mal-absorption syndromes affecting proper ivermectin absorption; 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; concomitant administration of enzyme inducers (such as carbamazepine) that could affect the effectiveness of the drug and those receiving CYP3A4 substrates (such as statins) due to the risk of increased toxicity.		
Setting	Hospital		
Country	India		

	Kishoria 2020		
	Ivermectin + HCQ	**HCQ**	**P value**
Study dates	Not reported. Paper published August 2020.		
Funder	Not reported		
Dose and duration			
Dose (loading)	Ivermectin 12 mg single dose Hydroxychloroquine 400 mg twice a day	Hydroxychloroquine 400mg twice a day	
Dose (maintenance)	Hydroxychloroquine 400 mg twice a day	Hydroxychloroquine 400 mg twice a day	
Duration	5 days	5 days	
Route of administration	Oral	Oral	
Disease severity			
Mild (%)	Not reported		
Moderate (%)			
Severe (%)			
Critical (%)			
Co-administered interventions			
Hydroxychloroquine (%)	100	100	
Lopinavir-ritonavir (%)	Not reported		
Glucocorticoids (%)			
Tocilizumab (%)			
Azithromycin (%)			
Remdesivir (%)			
Antivirals, any (%)			
Antibiotics, any (%)			
Comorbidities			
Cardiovascular disease (%)	Not reported		
Hypertension (%)			
Diabetes (%)			
Obesity (%)			
Asthma (%)			
Outcomes			
Critical			
Discharge from hospital, n (%)	8 (42.2)	6 (46.2)	

Important			
Viral clearance day 3, n (%)	8 (42.2)	6 (46.2)	
Viral clearance day 5, n (%)	4 (80)	6 (100)	0.820

Krolewiecki 2020 (NCT04381884)				
	Ivermectin		**Standard care**	**P value**
Study Characteristics	<160ng/mL	>160ng/mL		
No. of patients (N)	11	9	12	
Mean age ± SD (years)	50.9 ± 12.3	39.8 ± 10.2	37.3 ± 12.7	0.03
Gender (female; %)	45	56	42	0.81
Pregnant patients	Exclusion of pregnant or lactating women.			
COVID-19 status	Confirmed by PCR test			
Paediatric patients	Excluded			
Primary exclusion criteria	Use of immunomodulators within 30 days, poorly controlled comorbidities.			
Setting	Hospital			
Country	Argentina			
Study dates	18 May to 29 September 2020			
Funder	Agencia Nacional de Promocion de la Investigacion, el Desarrollo Tecnologico y la Innovacion, Argentina and Laboratorio ELEA/Phoenix, Argentina.			
Dose and duration				
Dose (loading)	600microgram/kg	600microgram/kg	N/A	
Dose (maintenance)	600microgram/kg	600microgram/kg	N/A	
Duration	5 days	5 days	N/A	
Route of administration	Oral tablet	Oral tablet	N/A	
Disease severity				
Mild (%)	100	89%	100	
Moderate (%)	0	11%	0	
Severe (%)	0	0	0	
Critical (%)	0	0	0	
Co-administered interventions				
Hydroxychloroquine (%)	Not reported			
Lopinavir-ritonavir (%)				
Glucocorticoids (%)				

Krolewiecki 2020 (NCT04381884)				
	Ivermectin		Standard care	P value
Tocilizumab (%)				
Azithromycin (%)				
Remdesivir (%)				
Antivirals, any (%)				
Antibiotics, any (%)				
Comorbidities				
Cardiovascular disease (%)	NR	NR	NR	
Hypertension (%)	18	11	25	0.72
Diabetes (%)	27	11	8	0.42
Obesity (%)	45	56	25	NR
Asthma (%)	NR	NR	NR	
Outcomes				
Critical				
IMV n	1		0	
Serious adverse events n (%)	1		0	
Adverse events n (%) of patients	13 (43)		5 (33)	
Important				
Clinical evolution	No significant differences in clinical evolution at day-7 and day-30 between groups.			

López-Medina 2021 (NCT04405843)			
	Ivermectin	Placebo	P value
Study Characteristics			
No. of patients (N)	200	198	
Median age (IQR) (years)	37 (29-47.7)	37 (28.7-49.2)	NR
Gender (female; %)	61	55	NR
Pregnant patients	Pregnant and breastfeeding women were excluded.		
COVID-19 status	Confirmed by PCR test		
Paediatric patients	Excluded		
Primary exclusion criteria	If they were asymptomatic, had severe pneumonia, had received ivermectin within the previous 5 days, or had hepatic dysfunction or liver function test results more than 1.5 times the normal level.		
Setting	Community & hospital		
Country	Colombia		
Study dates	15 July 2020 to 21 December 2020		
Funder	Unrestricted grant from Centro de Estudios en Infectología Pediátrica		

López-Medina 2021 (NCT04405843)			
	Ivermectin	**Placebo**	**P value**
Dose and duration			
Dose (loading)	300 microgram/kg	NR	
Dose (maintenance)	300 microgram/kg	NR	
Duration	5 days	NR	
Route of administration	Oral	NR	
Disease severity			
Mild (%)	Mild only		
Moderate (%)			
Severe (%)			
Critical (%)			
Co-administered interventions			
Hydroxychloroquine (%)	NR	NR	
Lopinavir-ritonavir (%)	NR	NR	
Glucocorticoids (%)	3	6	
Tocilizumab (%)	NR	NR	
Azithromycin (%)	NR	NR	
Remdesivir (%)	NR	NR	
Antivirals, any (%)	NR	NR	
Antibiotics, any (%)	7	6	
Comorbidities			
Cardiovascular disease (%)	2	2	NR
Hypertension (%)	14	13	NR
Diabetes (%)	5	6	NR
Obesity (%)	19	19	NR
Asthma (%)	NR	NR	
Outcomes			
Critical			
Mortality day 28, n (%)	0 (0)	1 (0.5)	NR
Adverse events - No. of patients with ≥1 solicited adverse events, n (%)	154 (77.0)	161 (81.3)	NR
Serious adverse events - No. of patients with ≥1 serious adverse events, n (%)	2 (1.0)	2 (1.0)	NR
Clinical progression - Deterioration by ≥2	4 (2.0)	7 (3.5)	NR

López-Medina 2021 (NCT04405843)			
	Ivermectin	**Placebo**	**P value**
points in an ordinal 8-point scale, n (%)			
Discontinuation due to adverse event n (%)	15 (7.5)	5 (2.5)	NR
Important			
Time to resolution of symptoms, median No. of days (IQR)	10 (9-13)	12 (9-13)	.53
Symptoms resolved at 21 d, n (%)	164 (82.0)	156 (79.0)	NR

Mohan 2021 (CTRI/2020/06/026001)				
	Ivermectin		**Placebo**	**P value**
	24mg	**12mg**		
Study Characteristics				
No. of patients (N)	40	40	45	
Mean age ± SD (years)	34.3 ± 10.45	36.3 ± 10.54	35.3 ± 10.52	0.64
Gender (female; %)	8	13	13	0.77
Pregnant patients	Pregnant or lactating women were excluded.			
COVID-19 status	Diagnosis of COVID-19 based on positive result on either PCR or a rapid antigen test.			
Paediatric patients	Excluded			
Primary exclusion criteria	Known hypersensitivity to ivermectin, chronic kidney disease with creatinine clearance <30 mL/min, elevated transaminase levels (>5 x 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 as per investigator's assessment, or enrolment in a concomitant clinical trial.			
Setting	Hospital			
Country	India			
Study dates	28 July to 29 September 2020 (patients screened and randomised). Article published August 2021.			
Funder	Science and Engineering Research Board , Department of Science and Technology , Government of India			
Dose and duration				
Dose (loading)	24mg	12mg	NR	
Dose (maintenance)			NR	
Duration	Single dose		NR	
Route of administration	Oral		NR	

Mohan 2021 (CTRI/2020/06/026001)				
	Ivermectin		Placebo	P value
	24mg	12mg		
Disease severity				
Mild (%)	60	68	64	0.80
Moderate (%)	40	33	36	
Severe (%)	N/A			
Critical (%)				
Co-administered interventions				
Hydroxychloroquine (%)	Not reported			
Lopinavir-ritonavir (%)				
Glucocorticoids (%)				
Tocilizumab (%)				
Azithromycin (%)				
Remdesivir (%)				
Antivirals, any (%)				
Antibiotics, any (%)				
Comorbidities				
Cardiovascular disease (%)	NR		NR	
Hypertension (%)	8	15	11	0.60
Diabetes (%)	5	10	11	0.63
Obesity (%)	NR		NR	
Asthma (%)	NR		NR	
Outcomes				
Critical				
Mortality n (%)	NR			
IMV n (%)	NR			
Serious adverse events	No serious adverse events reported during the study			
Adverse events n (%) of patients	6 (11.8)	8 (16.3)	6 (11.5)	0.76
Discharge by day 14 n (%)	38 (95.0)	37 (92.5)	39 (86.7)	0.42
Important				0.77
Days to symptom resolution, mean (SD)	4.26 (2.65)	4.76 (2.44)	4.58 (2.94)	
Clinical recovery at day 14 – WHO ordinal scale n (%) Decrease by 2 Decrease by 3	 35 (87.5) 2 (5.0)	 32 (80.0) 5 (12.5)	 37 (82.2) 2 (4.4)	 0.67
Virological clearance at day 5 n (%)	19 (47.5)	14 (35.0)	14 (31.1)	0.30

Mohan 2021 (CTRI/2020/06/026001)				
	Ivermectin		Placebo	P value
	24mg	12mg		
Virological clearance at day 7 n (%)	16 (44.4)	13 (36.1)	16 (38.1)	0.79
Clinical worsening n (%)	3 (7.5)	2 (5.0)	5 (11.1)	0.65

Podder 2020			
	Ivermectin	Standard care	P value
Study Characteristics			
No. of patients (N)	32	30	
Mean age ±SD (years)	38.41 ± 11.02	39.97 ± 13.24	
Gender (female; %)	28.1	30.0	>.05
Pregnant patients	Exclusion of pregnant or lactating women.		
COVID-19 status	Confirmed by PCR test		
Paediatric patients	Excluded		
Primary exclusion criteria	Pre-existing hypersensitivity to ivermectin, patients taking other antimicrobials or hydroxychloroquine.		
Setting	Outpatients		
Country	Bangladesh		
Study dates	1 May 2020 to end of July 2020		
Funder	Self-financed		
Dose and duration			
Dose (loading)	200 microgram/kg	N/A	
Dose (maintenance)	N/A	N/A	
Duration	1 day	N/A	
Route of administration	Oral tablet	N/A	
Disease severity			
Mild (%)	81	80	>.05
Moderate (%)	19	20	
Severe (%)	0	0	
Critical (%)	0	0	
Co-administered interventions	Standard care: symptomatic treatment which included antipyretics, cough suppressants, and capsule doxycycline (100 mg every 12 hours for seven days).		
Hydroxychloroquine (%)	EXCL	EXCL	
Lopinavir-ritonavir (%)	NR	NR	

Podder 2020			
	Ivermectin	**Standard care**	**P value**
Glucocorticoids (%)	NR	NR	
Tocilizumab (%)	NR	NR	
Azithromycin (%)	NR	NR	
Remdesivir (%)	NR	NR	
Antivirals, any (%)	NR	NR	
Antibiotics, any (%)	100% doxycycline as per standard care		
Comorbidities			
Cardiovascular disease (%)	Not reported		
Hypertension (%)			
Diabetes (%)			
Obesity (%)			
Asthma (%)			
Outcomes			
Critical	Not reported		
Important			
Symptom resolution from date of enrolment (days)	Complete recovery 5.31 Fever 3.33 Shortness of breath 4.83 Fatigue 6	Complete recovery 6.33 Fever 3.18 Shortness of breath 6.33 Fatigue 5.67	
Symptom resolution from date of onset of illness (days)	Complete recovery 10.09 Fever 6.48 Cough 9.23 Shortness of breath 6.67 Fatigue 9.0	Complete recovery 11.50 Fever 6.43 Cough 10.45 Shortness of breath 8.86 Fatigue 9.57	
Viral clearance (day 10) n (%)	Positive 2 (10) Negative 18 (90)	1 (5) 19 (95)	>.05

Pott-Junior 2021 (NCT04431466)			
	Ivermectin	**Standard care**	**P value**
Study Characteristics			
No. of patients (N)	27	4	
Mean age ± SD (years)	49.4 ± 14.6		NR
Gender (female; %)	54.8		NR
Pregnant patients	Pregnant and lactating women were excluded.		
COVID-19 status	Confirmed by PCR test		
Paediatric patients	Excluded		
Primary exclusion criteria	Not able to ingest / absorb the drug orally through spontaneous ingestion or by gastro / enteral tubes; any clinical observation (clinical / physical evaluation) or laboratory findings which, in the investigator's opinion, would have put the patient at risk to		

Pott-Junior 2021 (NCT04431466)			
	Ivermectin	**Standard care**	**P value**
	participate in the study; any abnormal ECG findings that require additional evaluation; known hypersensitivity to the drug components used during the study; body weight less than 15 kg; an estimated glomerular filtration rate (CKD-Epidemiology Collaboration, CKD-EPI) below 30 mL/min; and values of aspartate aminotransaminase (AST) or alanine aminotransaminase (ALT) 5-fold above the upper limit of normality.		
Setting	Hospital		
Country	Brazil		
Study dates	Not reported by study. Trial registry states 1 July 2020 as start date. Article published 6 March 2021.		
Funder	Non-commercial phase 2a clinical trial conducted at the Federal University of São Carlos, Brazil.		
Dose and duration			
Dose (loading)	100 microgram/kg OR 200 microgram/kg OR 400 microgram/kg	Standard of care treatment was provided at the time of hospital admission according to the latest recommendations on managing COVID-19	
Dose (maintenance)	Dose reductions, changes in dosage or changes in dosing frequency were not permitted at any time during the study	NR	
Duration	NR	NR	
Route of administration	Oral	NR	
Disease severity			
Mild (%)	Mild symptoms only		
Moderate (%)	N/A		
Severe (%)			
Critical (%)			
Co-administered interventions			
Hydroxychloroquine (%)	Not reported		
Lopinavir-ritonavir (%)			
Glucocorticoids (%)	26	75	
Tocilizumab (%)	Not reported		
Azithromycin (%)			
Remdesivir (%)			

Pott-Junior 2021 (NCT04431466)			
	Ivermectin	**Standard care**	**P value**
Antivirals, any (%)			
Antibiotics, any (%)	22	75	
Comorbidities			
Cardiovascular disease (%)	Not reported		
Hypertension (%)			
Diabetes (%)			
Obesity (%)			
Asthma (%)			
Outcomes			
Critical			NR
ICU admission for ventilatory support, n (%)	1 (3.7)	1 (50)	
Adverse events, n (%)	7 (25.9)	2 (50)	
Important			
Viral clearance, n (%)	17 (63)	2 (66.7)	

Ravikirti 2021 (CTRI/2020/08/027225)			
	Ivermectin	**Placebo**	**P value**
Study Characteristics			
No. of patients (N)	55	57	
Mean age ± SD (years)	50.7 ± 12.7	54.2 ± 16.3	0.218
Gender (female; %)	27.3	28.1	0.925
Pregnant patients	Pregnant or lactating women were excluded.		
COVID-19 status	Diagnosis of COVID-19 based on positive result on either PCR or a rapid antigen test.		
Paediatric patients	Excluded		
Primary exclusion criteria	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.		
Setting	Hospital		
Country	India		
Study dates	1 August 2020 and 31 October 2020		
Funder	Not reported		
Dose and duration			

Ravikirti 2021 (CTRI/2020/08/027225)			
	Ivermectin	**Placebo**	**P value**
Dose (loading)	12 mg	NR	
Dose (maintenance)	12 mg daily	NR	
Duration	2 days	NR	
Route of administration	Oral	NR	
Disease severity			
Mild (%)	76	81	0.576
Moderate (%)	24	19	
Severe (%)	N/A		
Critical (%)			
Co-administered interventions			
Hydroxychloroquine (%)	100	100	
Lopinavir-ritonavir (%)	NR	NR	
Glucocorticoids (%)	NR	NR	
Tocilizumab (%)	7	5	0.660
Azithromycin (%)	NR	NR	
Remdesivir (%)	22	19	0.741
Antivirals, any (%)	NR	NR	
Antibiotics, any (%)	100	100	
Comorbidities			
Cardiovascular disease (%)	4	14	
Hypertension (%)	38	32	0.463
Diabetes (%)	38	33	0.592
Obesity (%)	NR	NR	
Asthma (%)	2	0	0.306
Outcomes			
Critical			
In hospital mortality n (%)	0 (0)	4 (7)	
IMV n (%)	1 (1.8)	5 (8.8)	0.102
Admission to ICU n (%)	5 (9.1)	6 (10.5)	0.799
Discharged by day 10 n (%)	44 (80.0)	42 (73.7)	0.429
Discharge (end of follow up)	55 (100.0)	53 (93.0)	0.045
Important			

Ravikirti 2021 (CTRI/2020/08/027225)			
	Ivermectin	**Placebo**	**P value**
Symptom resolution at day 6 n (%)	46 (83.6)	51 (89.5)	0.365
Virological clearance at day 6 n (%)	13 (23.6)	18 (31.6)	0.348

Shahbaznejad 2021 (IRCT20111224008507N3)			
	Ivermectin	**Standard care**	**P value**
Study Characteristics			
No. of patients (N)	35	34	
Mean age ± SD (years)	47.63 ± 22.20	45.18 ± 23.20	0.65
Gender (female; %)	48.6	47.1	0.90
Pregnant patients	Pregnant and lactating women were excluded.		
COVID-19 status	Diagnostic criteria for COVID-19 included any of the following: positive result on PCR test: clinical symptoms of COVID-19, with a history of contact with a patient with COVID-19; and/or abnormalities on CT scan compatible with COVID-19.		
Paediatric patients	Included (above 5 years old)		
Primary exclusion criteria	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.		
Setting	Hospital		
Country	Iran		
Study dates	23 May 2020 to 31 July 2020		
Funder	Not reported		
Dose and duration			
Dose (loading)	200 microgram/kg	-	
Dose (maintenance)	-	-	
Duration	Single dose	-	
Route of administration	Oral	-	
Disease severity			
Mild (%)	-		
Moderate (%)	62.9	47.1	NR
Severe (%)	37.1	52.9	0.19

Shahbaznejad 2021 (IRCT20111224008507N3)			
	Ivermectin	**Standard care**	**P value**
Critical (%)	-		
Co-administered interventions			
Hydroxychloroquine (%)	Part of SC	Part of SC	
Lopinavir-ritonavir (%)	77.14	82.35	1.00
Glucocorticoids (%)	NR	NR	
Tocilizumab (%)	NR	NR	
Azithromycin (%)	65.71	0.50	0.21
Remdesivir (%)	NR	NR	
Antivirals, any (%)	NR	NR	
Antibiotics, any (%)	91.43	88.24	0.24
Comorbidities			
Cardiovascular disease (%)	NR	NR	
Hypertension (%)	NR	NR	
Diabetes (%)	NR	NR	
Obesity (%)	NR	NR	
Asthma (%)	NR	NR	
Outcomes			
Critical			
IMV n (%)	2 (5.7)	1 (2.9)	1.000
Adverse events	None observed		
Mean duration of hospital stay (days)	7.1	8.4	0.016
Important			
Supplemental oxygen n (%)	10 (28.6)	9 (26.5)	0.84
Mean duration of symptoms (days)	4.2	5.2	0.023

Shakhsi Niaee 2020 (IRCT20200408046987N1)			
	Ivermectin	**Standard care/Placebo**	**P value**
Study Characteristics			
No. of patients (N)	120 (30 per arm)	60 (30 per arm)	
Median age, interquartile range (years)	Arm 1: 61 (42, 68) Arm 2: 53 (42, 65) Arm 3: 54 (47, 60) Arm 4: 54 (46, 65)	Standard care: 55 (45, 70) Standard care + placebo: 58 (45, 68)	0.958

Shakhsi Niaee 2020 (IRCT20200408046987N1)			
	Ivermectin	**Standard care/Placebo**	**P value**
Gender (female; %)	Arm 1: 60 Arm 2: 36.7 Arm 3: 46.7 Arm 4: 56.7	Standard care: 46.7 Standard care + placebo: 53.3	
Pregnant patients	Exclusion of pregnant or lactating women.		
COVID-19 status	Confirmed by PCR or chest image tests.		
Paediatric patients	Excluded		
Primary exclusion criteria	Known allergic reaction to the intervention drugs, severe immunosuppression, chronic kidney disease, cancer, severe COVID-19 patients and indications that the patients were unable and/or unlikely to comprehend and/or follow the protocol.		
Setting	Hospital		
Country	Iran		
Study dates	1 June 2020 to 15 July 2020		
Funder	NR		
Dose and duration			
Dose (loading)	1) 200 microgram/kg single dose 2) 400 microgram /kg single dose 3) 200 microgram/kg 4) 400 microgram/kg	N/A	
Dose (maintenance)	3) 200 microgram/kg days 3 & 5 4) 200 microgram/kg days 3 & 5	N/A	
Duration	5 days	N/A	
Route of administration	Oral tablet	N/A	
Disease severity			
Mild (%)	13	15	
Moderate (%)	70	77	
Severe (%)	14	8	
Critical (%)	NR	NR	
Co-administered interventions			
Hydroxychloroquine (%)	200 mg twice per day		
Lopinavir-ritonavir (%)	NR	NR	
Glucocorticoids (%)	NR	NR	
Tocilizumab (%)	NR	NR	
Azithromycin (%)	NR	NR	
Remdesivir (%)	NR	NR	
Antivirals, any (%)	NR	NR	

Shakhsi Niaee 2020 (IRCT20200408046987N1)			
	Ivermectin	**Standard care/Placebo**	**P value**
Antibiotics, any (%)	NR	NR	
Comorbidities			
Cardiovascular disease (%)	Not reported		
Hypertension (%)			
Diabetes (%)			
Obesity (%)			
Asthma (%)			
Outcomes			
Critical			
Mortality n (%)	4 (3.3)	11 (18.3)	
Duration of hospital stay (mean number of days)	6.5	7.5	0.006*
Important	Not reported		

*Compared with standard care/placebo group.

Vallejos 2021 (NCT04529525)			
	Ivermectin	**Placebo**	**P value**
Study Characteristics			
No. of patients (N)	250	251	
Mean age ±SD (years)	42.58 ± 15.29	42.40 ± 15.75	NR
Gender (female; %)	44.4	50.2	NR
Pregnant patients	Pregnant and breastfeeding women were excluded.		
COVID-19 status	Confirmed by PCR test		
Paediatric patients	Excluded		
Primary exclusion criteria	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		
Setting	Community		
Country	Argentina		
Study dates	19 August 2020 to 22 February 2021		
Funder	None		
Dose and duration			
Dose (loading)	12mg (≤80kg), 18mg (80-110kg), 24mg (≥110kg)	NR	
Dose (maintenance)	Second dose 24 hours after first	NR	
Duration	2 days	NR	

Vallejos 2021 (NCT04529525)			
	Ivermectin	**Placebo**	**P value**
Route of administration	Oral	NR	
Disease severity			
Mild (%)	NR		
Moderate (%)	NR		
Severe (%)	-		
Critical (%)	-		
Co-administered interventions			
Hydroxychloroquine (%)	NR	NR	
Lopinavir-ritonavir (%)	NR	NR	
Glucocorticoids (%)	NR	NR	
Tocilizumab (%)	NR	NR	
Azithromycin (%)	NR	NR	
Remdesivir (%)	NR	NR	
Antivirals, any (%)	NR	NR	
Antibiotics, any (%)	6	6	
Comorbidities			
Cardiovascular disease (%)	NR	NR	NR
Hypertension (%)	21	26	NR
Diabetes (%)	8	11	NR
Obesity (%)	NR	NR	NR
Asthma (%)	6	8	NR
Outcomes			
Critical			
Mortality, n (%)	4 (1.6)	3 (1.2)	0.70
Hospitalisation, n (%)	14 (5.6)	21 (8.4)	0.227
IMV, n (%)	4 (1.6)	3 (1.2)	0.70
Serious adverse events n	0	0	NR
Adverse events, n (%)	45 (18)	53 (21.1)	0.6
Discontinued due to adverse events n	0	0	
Important			
Negative nasal swab day 3, n (%)	113 (47.1)	120 (49.8)	0.55
Negative nasal swab day 12, n (%)	212 (89.1)	221 (92.5)	0.29

Appendix E: Risk of bias

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

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Low risk	"randomised using a computer random number generator to select random permuted blocks with a block size of eight and an equal allocation ratio" Measures taken to ensure concealment " opaque, sealed envelopes"
Risk of bias due to deviations from the intended interventions	Unclear risk	Open-label (unblinded study). ITT (intention to treat) used. Use of co-intervention unclear although mentioned in standard care (antibiotics, hydrocortisone)
Missing outcome data	Low risk	Data available for all participants from randomisation.
Risk of bias in measurement of the outcome	Unclear risk	Outcome measures likely appropriate. Unblinded study.
Risk of bias in selection of the reported result	Unclear risk	Outcomes not clearly pre-specified.
Overall risk of bias	High risk	Open-label study. Some concerns surrounding changes of outcomes.

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

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	No information on randomisation and allocation concealment procedures. No protocol or trial registry available. Few baseline characteristics reported.
Risk of bias due to deviations from	Low risk	No information re co-interventions, possible deviations, although double-blinded study (no details

the intended interventions		provided). Modified intention to treat analysis used (excluding those who withdrew consent following randomisation).
Missing outcome data	Unclear risk	Mortality not reported, although listed as a secondary outcome in Methods. Unable to determine if all outcome data available for duration of hospitalisation.
Risk of bias in measurement of the outcome	Low risk	Double-blinded study --> discharge likely not influenced by knowledge of intervention.
Risk of bias in selection of the reported result	Unclear risk	Mortality not reported. Adverse events not reported. Unclear if all-cause serious adverse events. No protocol available. No clinical trial registry record available.
Overall risk of bias	Unclear risk	Very little methods information reported and no protocol/trial registry record available.

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

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Low risk	"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"
Risk of bias due to deviations from the intended interventions	Unclear risk	“The investigators and patients were blinded to the assignment.” Exclusion of positive RT-PCR test post randomisation (7 vs 14).
Missing outcome data	Unclear risk	Patients with missing data along the follow up were carried over from the last data available. No evidence that the result is not biased.
Risk of bias in measurement of the outcome	Low risk	Method of measuring the outcome probably appropriate. Blinded study (outcome assessor).

Risk of bias in selection of the reported result	Unclear risk	Retrospective registry. Unclear if analysed as pre-specified. AEs and SAEs
Overall risk of bias	Unclear risk	Blinded study, some concerns surrounding exclusion post randomisation and retrospective registry.

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

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	"The patients were randomised in a 1:1 ratio via a lottery method". No further information provided. Insufficient information provided on allocation concealment.
Risk of bias due to deviations from the intended interventions	High risk	There was no blinding, and patients in the intervention arm were provided with information about the drug, and their informed consent was taken"
Missing outcome data	High risk	14 of 100 patients were lost to follow up, as they "left [hospital] against medical advice"
Risk of bias in measurement of the outcome	High risk	The trial was unblinded.
Risk of bias in selection of the reported result	High risk	The clinicaltrials.gov entry lists two outcomes: negative PCR and need for mechanical ventilation. Only negative PCR outcomes were reported
Overall risk of bias	High risk	Insufficient information re: randomisation and allocation concealment, study was unblinded, significant number of patients lost to follow up and mechanical ventilation was not reported.

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.

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	Centralised computer system used for randomisation. However, some imbalances in baseline characteristics remain (e.g. % female, care settings, comorbidities etc) suggest some concerns.
Risk of bias due to deviations from the intended interventions	Low risk	Participants and investigators blinded. Analyses appeared appropriate.
Missing outcome data	Low risk	Flow chart provided to account for participants
Risk of bias in measurement of the outcome	Low risk	Method of measuring the outcome probably appropriate. Blinded study (outcome assessor).
Risk of bias in selection of the reported result	Low risk	No serious concerns about deviations from protocol.
Overall risk of bias	Unclear risk	Some imbalances in baseline characteristics noted

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

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	"The randomization sequence was computer-generated by the trial statistician using blocks of four to ensure balance. Allocation was made by the attending investigator using opaque envelopes. 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)."
Risk of bias due to deviations from the intended interventions	Unclear risk	Placebo-controlled; claims double-blinded study however details regarding blinding in patients are lacking. ITT analysis used.
Missing outcome data	Low risk	"All randomized patients received the corresponding study product and completed 28 days of follow-up (Figure 1)."
Risk of bias in measurement of the outcome	Low risk	RT-PCR, SAEs, progression to severe low risk of bias. Self-reported symptoms and AEs, however blinded study so at low risk of bias.
Risk of bias in selection of the reported result	Low risk	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 risk of bias	Unclear risk	Outcomes of interest: AEs, SAEs. Some concerns (rated as unclear risk for domains of randomisation process, and risk of bias due to intended interventions)

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

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	“Participants were allocated randomly to the groups by computer generated number”. “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.

Risk of bias due to deviations from the intended interventions	Unclear risk	Participants and personal were not blinded.
Missing outcome data	Unclear risk	Outcomes were not blinded.
Risk of bias in measurement of the outcome	Unclear risk	All participants and their data after randomisation were included.
Risk of bias in selection of the reported result	High risk	“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 risk of bias	High risk	Concerns about outcome reporting and potential differences in baseline characteristics between groups

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

Bias	**Authors' judgement**	**Support for judgement**
Risk of bias arising from the randomization process	Unclear risk	"patients with an interval of >/= 500 ms were randomised to ivermectin or placebo, while those with an interval < 500 ms were randomised to ivermectin, hydroxychloroquine or placebo." - no further information provided on allocation.
Risk of bias due to deviations from the intended interventions	Unclear risk	"Blinding was assured with amber coloured vials. Each patient had a vial for the initial dose in order to blind the ivermectin and a second vial for subsequent doses. All patients received two vials, one with the initially prescribed dose and a second one, with the indication to take two tablets 12 hours after the initial dose followed by one tablet

		every 12 hours until all tablets were finished". Although all of the vials were 'amber coloured', there was no information regarding similarity of the pills contained within the vials.
Missing outcome data	Unclear risk	Insufficient information provided.
Risk of bias in measurement of the outcome	Low risk	Appears as though ITT population was analysed.
Risk of bias in selection of the reported result	High risk	Unclear due to absence of protocol or clinical trial entry.
Overall risk of bias	Unclear risk	Risk - unclear randomisation method and allocation concealment.

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

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Low risk	“The randomisation list was generated by a computerized system by a unit independent of the study team. The randomisation codes was kept in sealed sequentially numbered opaque envelopes.”
Risk of bias due to deviations from the intended interventions	Unclear risk	Open-label (unblinded). Unclear co-interventions outside of those included in standard care.
Missing outcome data	Unclear risk	Data available for all 32 participants.
Risk of bias in measurement of the outcome	Unclear risk	Open-label (unblinded).
Risk of bias in selection of the reported result	Unclear risk	Protocol and registry were not available. Unclear if conducted as pre-specified.
Overall risk of bias	Unclear risk	Unknown whether study was conducted in line with intended protocol.

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

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Low risk	Enrolled participants were randomly assigned (2:1) to either IVM group or untreated control group. Randomisation was stratified for each Centre. Randomisation 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.
Risk of bias due to deviations from the intended interventions	Unclear risk	"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 labelled with randomisation code and visit number." Only outcome assessors blinded. (single blinded) AES reported for all participant, no information on co-interventions (standard of care).
Missing outcome data	Low risk	SAEs & AEs information reported for all participants.
Risk of bias in measurement of the outcome	Unclear risk	Adverse events and serious adverse events may be affected by unblinding.
Risk of bias in selection of the reported result	Low risk	Outcomes reported as in the prespecified protocol. Unlikely that it affects the outcomes of interest.
Overall risk of bias	Unclear risk	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.

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

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Low risk	"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.
Risk of bias due to deviations from the intended interventions	Unclear risk	Unclear who/if anyone was blinded to outcomes. Labelling error also occurred for a period of the trial resulting in all participants receiving ivermectin and none receiving placebo during this time frame.
Missing outcome data	Unclear risk	476 participants randomised; 398 participants analysed. Reasons for missing data: error in labelling, which resulted in 38 placebo group participants receiving treatment.
Risk of bias in measurement of the outcome	Unclear risk	“The primary outcome was originally defined as the time from randomisation 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 randomisation to complete resolution of symptoms within the 21-day follow-up period”. Primary outcome measures were changed during the study.
Risk of bias in selection of the reported result	Unclear risk	Primary outcome measures unclear if reported as pre-specified.
Overall risk of bias	High risk	Concerns around how the trial was conducted and number of people receiving placebo.

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

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Low risk	"A variable block randomisation stratified based on disease severity (mild or moderate illness) was done using a centralised telephone-based system" "Patients, investigators, caregivers, and statisticians were blinded to the allocation".
Risk of bias due to deviations from the intended interventions	Unclear risk	Withdrawn consent of 5. A further 20 vs 7 participants were excluded from the analysis of clinical improvement and viral negative.
Missing outcome data	Unclear risk	Some exclusion.
Risk of bias in measurement of the outcome	Low risk	"Patients, investigators, caregivers, and statisticians were blinded to the allocation"
Risk of bias in selection of the reported result	Low risk	Outcomes listed in trial registry have been reported.
Overall risk of bias	Unclear risk	Low risk for some domains but some issues identified with reporting of outcome data.

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

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	High risk	Randomisation was done using an odd-even methodology applied to registration numbers, in a consecutive fashion of 1:1 ratio.
Risk of bias due to deviations from the intended interventions	Unclear risk	ITT used.

Missing outcome data	High risk	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).
Risk of bias in measurement of the outcome	High risk	Yes, 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.
Risk of bias in selection of the reported result	Unclear risk	Analysis plan / protocol not available.
Overall risk of bias	High risk	Issues with randomisation method used and outcome reporting.

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

Bias	**Authors' judgement**	**Support for judgement**
Risk of bias arising from the randomization process	Unclear risk	"randomisation list was developed according to a unique computer-generated number sequence. Randomisation was unbalanced in a 1:2:4:2 ratio, and processed in permuted blocks of sizes two, four and six, that were stored in sequentially numbered sealed opaque envelope"
Risk of bias due to deviations from the intended interventions	Unclear risk	"Investigators and patients were blinded to the viral load results during the study dosing period." Open-label, unblinded study. Co interventions unclear.

Missing outcome data	Unclear risk	One exclusion for protocol violation (from analysis).
Risk of bias in measurement of the outcome	Unclear risk	Unblinded study (outcome assessor). Outcome viral load unlikely influenced.
Risk of bias in selection of the reported result	High risk	The protocol and statistical analysis plan were not available. Secondary outcomes listed on trial registry not reported. Dosages for intervention group changed during study.
Overall risk of bias	Unclear risk	Unclear how methodological factors could have contributed to validity of results.

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

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Low risk	"Block randomisation (4, 6, 8)". the person doing the randomisation was not part of the investigation team" Measures were taken to conceal allocation (e.g. after confirmation of the treatment group, the investigation team doctor used to indent 2 tablets designated for that particular group. Both these treatment groups received 2 tablets similar in size, shape, colour, odour, and packaging on subsequent days).
Risk of bias due to deviations from the intended interventions	Low risk	Blinding occurred for all except pharmacist dispensing the tablets.
Missing outcome data	High risk	Reasons for missing data clarified as: discharged before 6th day; sample not sent for unknown reason; sample lost; died; report inconclusive.
Risk of bias in measurement of the outcome	Low risk	Method of measuring the outcome probably appropriate.

Risk of bias in selection of the reported result	Low risk	All initial measures were reported on.
Overall risk of bias	Unclear risk	Some issues around missing outcome data.

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

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	High risk	"The patients were randomly divided into 2 groups (ivermectin and control) by a simple randomisation method using a table of random numbers. Neither the participants nor the evaluators were aware of the randomisation process or group allocation." Methods/measures of randomisation and allocation unclear. Imbalance in severity of disease as a higher proportion of control group had severe disease in comparison to intervention group.
Risk of bias due to deviations from the intended interventions	Low risk	Double blinded. ITT
Missing outcome data	Unclear risk	Some missing data from 4 withdrawals. No evidence that bias did not occur.
Risk of bias in measurement of the outcome	Low risk	Double blinded, Outcome measures likely appropriate.
Risk of bias in selection of the reported result	Unclear risk	The protocol and statistical analysis plan were not available, the registry was retrospective.
Overall risk of bias	Unclear risk	Some missing data with unclear allocation and randomising methods.

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

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	Unclear how allocation concealment was ensured "Eligible patients were randomly allocated to either the standard, Placebo and the ivermectin arms. Randomisation according to the severity of the disease was as follows: mild, moderate, and sever [sic]. The transposed block randomisation sequence, including stratification, was prepared by a statistician not involved in the trial using Random Allocation Software."
Risk of bias due to deviations from the intended interventions	Unclear risk	No information provided.
Missing outcome data	High risk	Compared to trial registry information they do not report predefined outcomes besides hospital stay and CT scan, unclear how many participants were included in the final analysis.
Risk of bias in measurement of the outcome	Low risk	Investigator and patients were masked.
Risk of bias in selection of the reported result	High risk	Authors do not report predefined outcomes, instead they are reporting clinical outcomes (length of hospital stay, fever, tachypnea, duration of oxygen desaturation and mortality). Although mortality is not likely to be affected, it is not clear how the other variables were measured and they were not prespecified in the protocol.
Overall risk of bias	High risk	Most reported outcomes not predefined in protocol. No information on adverse events.

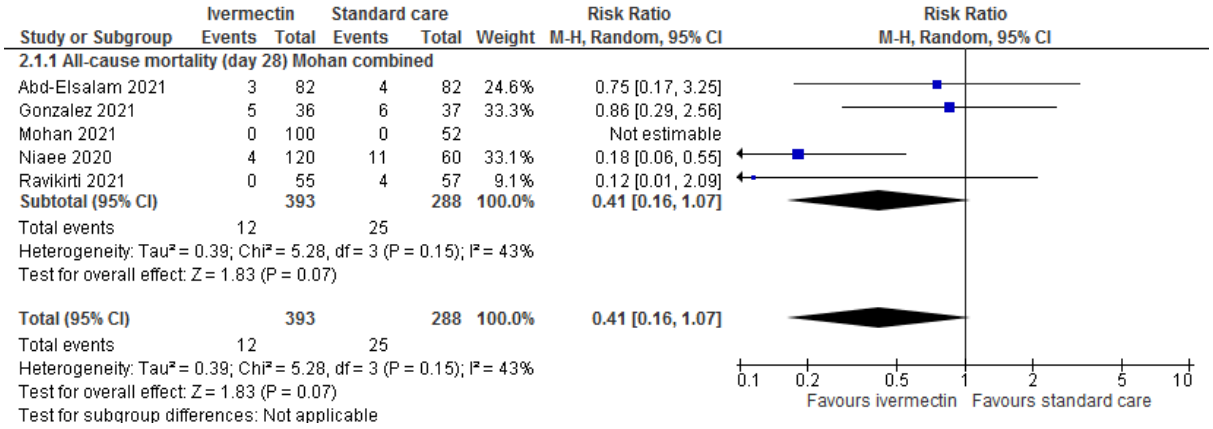
Vallejos, Julio, Zoni, Rodrigo, Bangher, Maria et al. (2021) Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial. BMC infectious diseases 21(1): 635

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Low risk	"Randomisation was performed by one of the investigators through the web-based system using randomly per- muted blocks in a 1:1 ratio (Supplementary Appendix). The investigator who performed the randomisation was not involved in the dispensing of the medication, inclusion, and follow-up of the patients. The rest of the investigators were blinded to the treatment received, as were the patients. Patients were consecutively assigned to the treatment kit in ascending order at inclusion."
Risk of bias due to deviations from the intended interventions	Low risk	"double-blind, placebo-controlled". ITT
Missing outcome data	Low risk	Data available for all 501 post randomisation.
Risk of bias in measurement of the outcome	Low risk	Method of measuring the outcome probably appropriate. double-blind.
Risk of bias in selection of the reported result	Low risk	Trial analysed as pre-specified.
Overall risk of bias	Low risk	No major concerns.

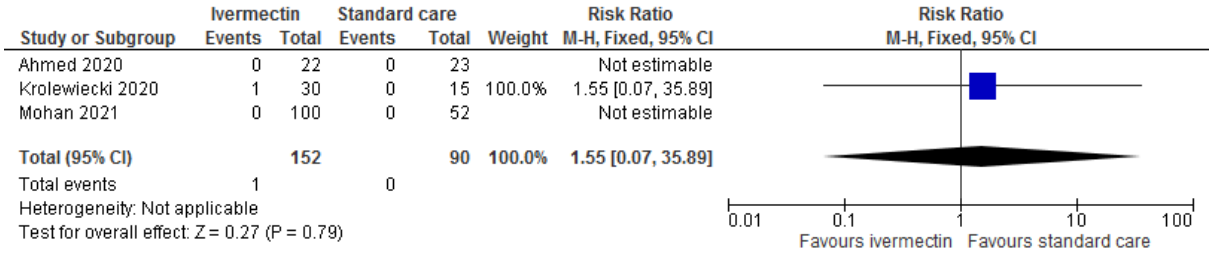
Appendix F: Forest plots

Ivermectin vs standard care (hospital setting)

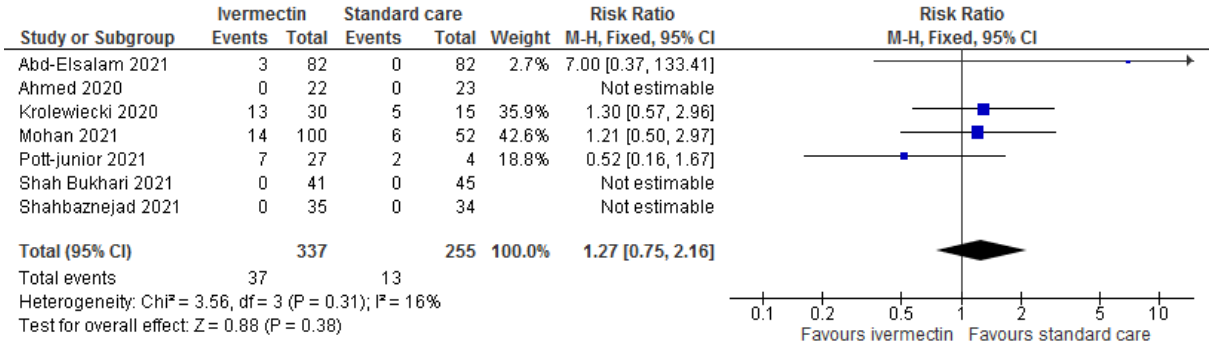
All-cause mortality (day 28)



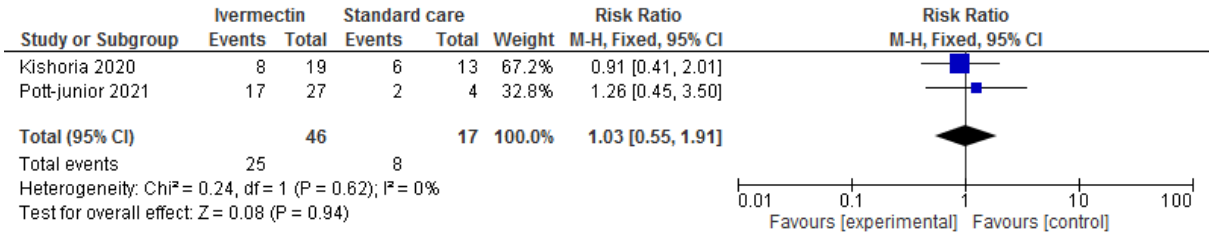
Serious adverse events (end of follow-up)



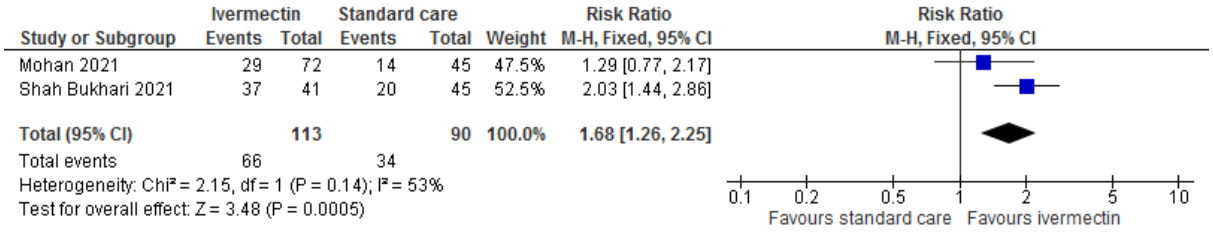
Adverse events (end of follow-up)



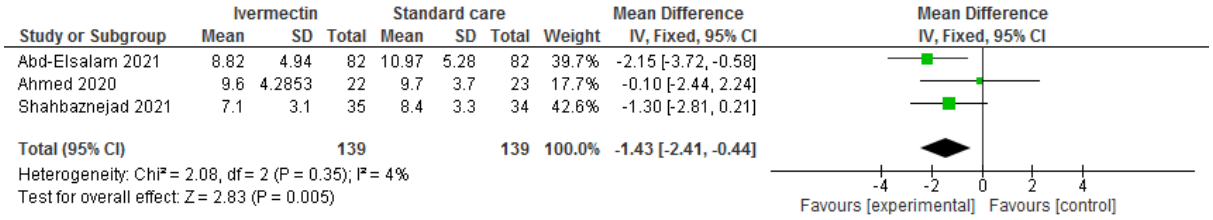
Viral clearance (1 – 7 days)



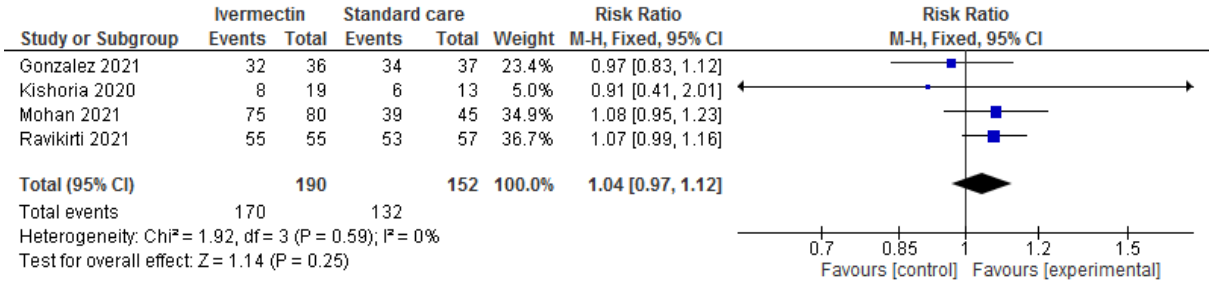
Viral clearance (7 -12 days)



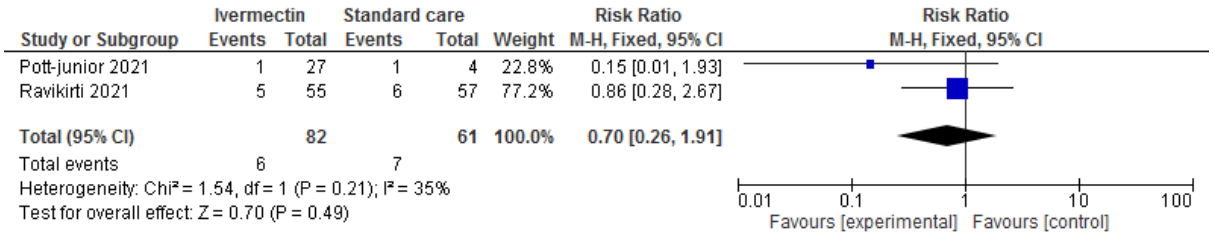
Duration of hospitalisation (days)



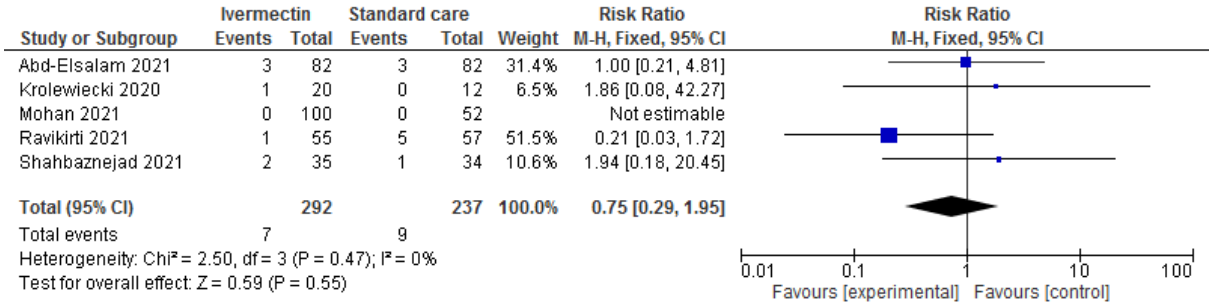
Discharge from hospital (end of follow-up)



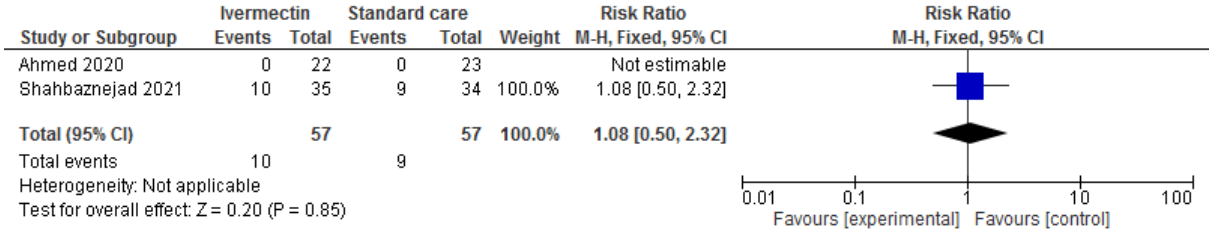
Admission to ICU



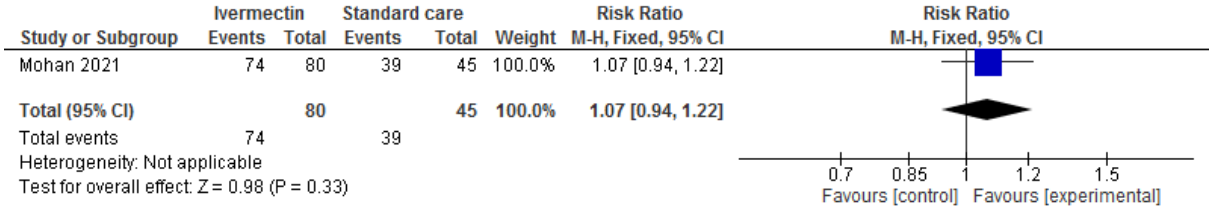
Invasive mechanical ventilation



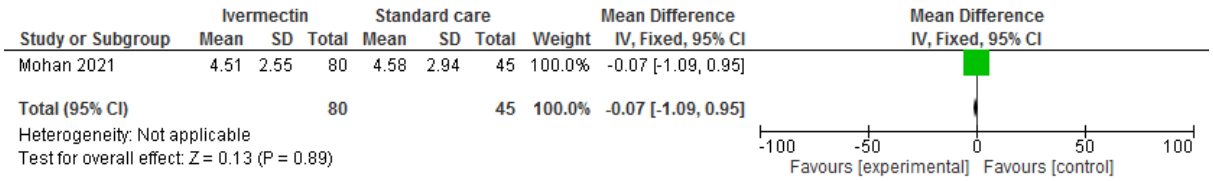
Number of patients requiring oxygen



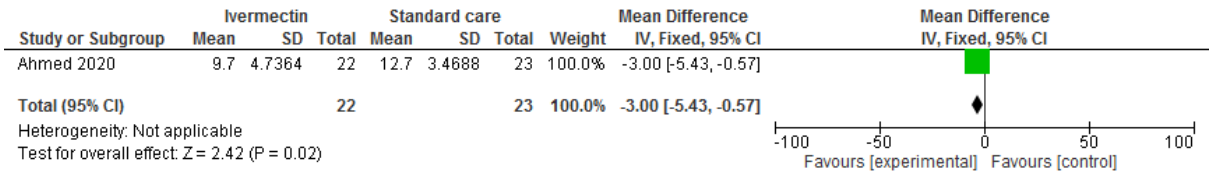
Clinical improvement (2 or more decrease WHO)



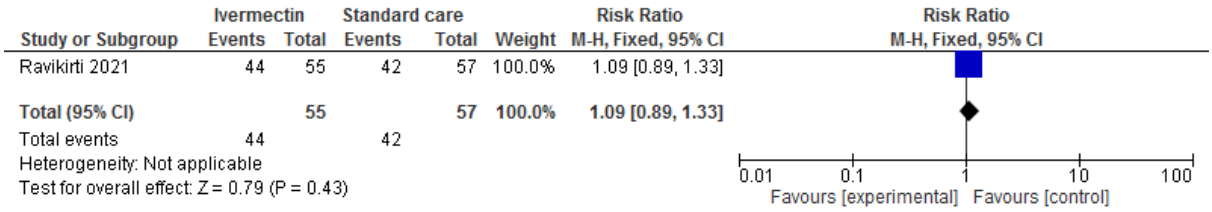
Time to recovery (resolution of symptoms)



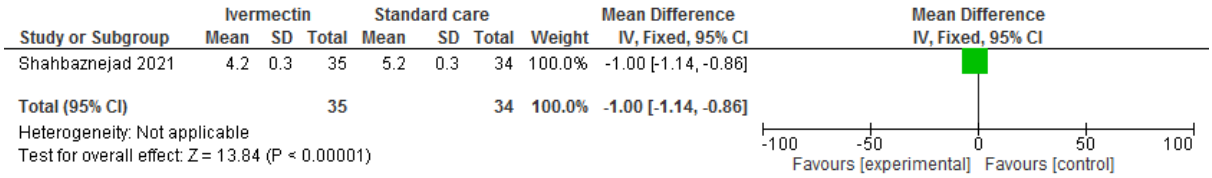
Duration to viral clearance



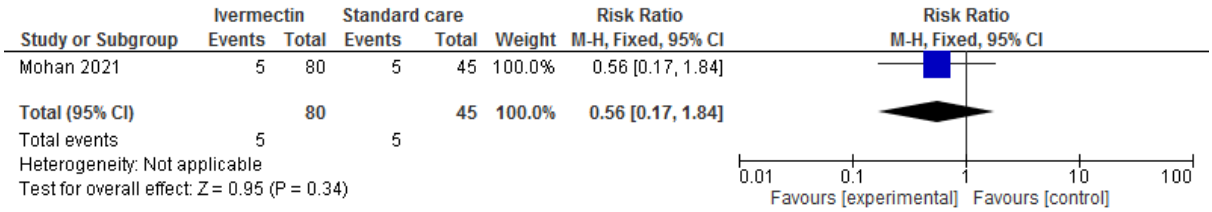
Discharge from hospital (by day 10)



Duration of symptoms

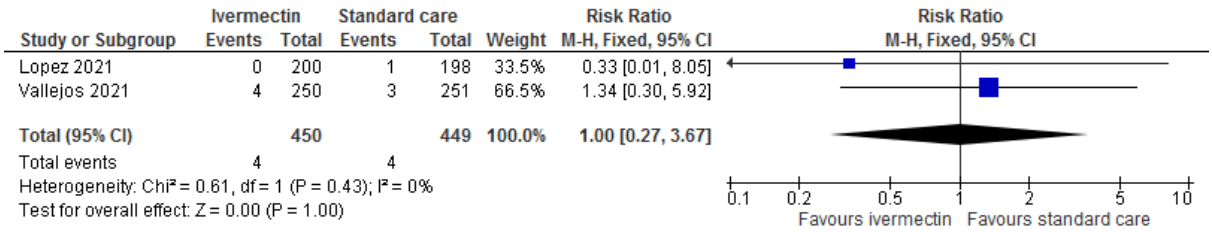


Clinical worsening

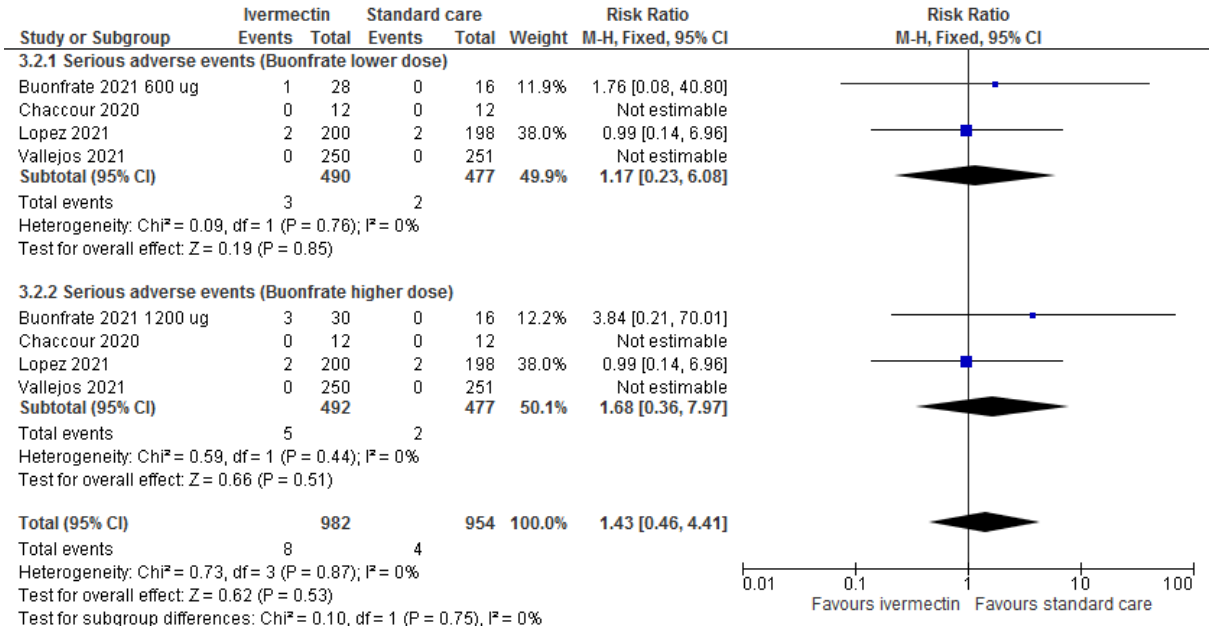


Ivermectin vs standard care (community setting)

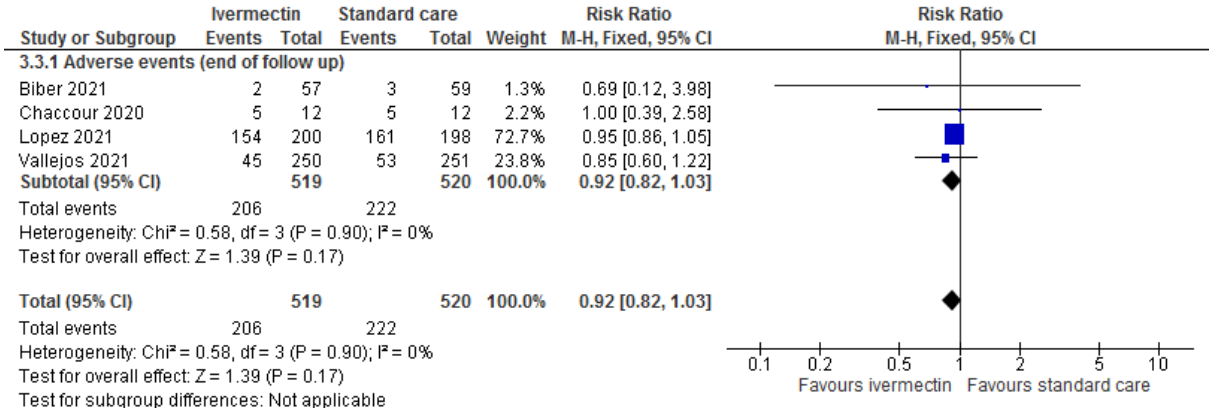
All-cause mortality (28 days)



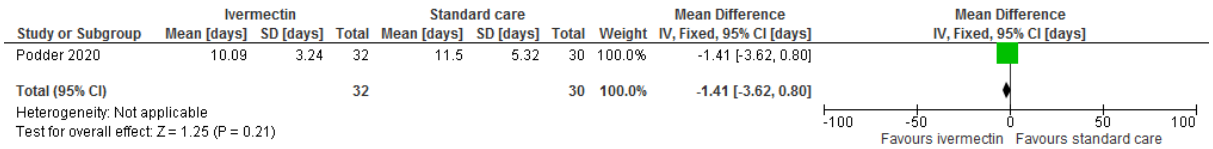
Serious adverse events (end of follow-up)



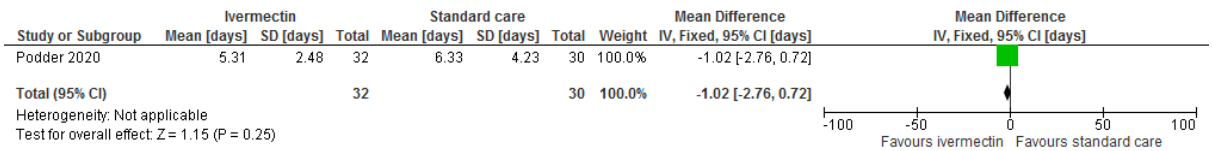
Adverse events (end of follow-up)



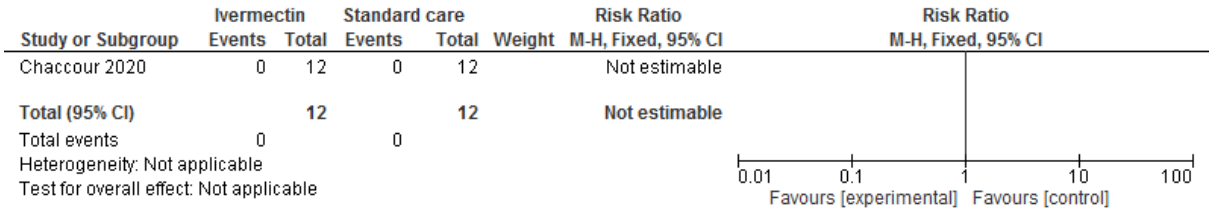
Recovery (from date of illness onset – days)



Recovery (from date of enrolment – days)

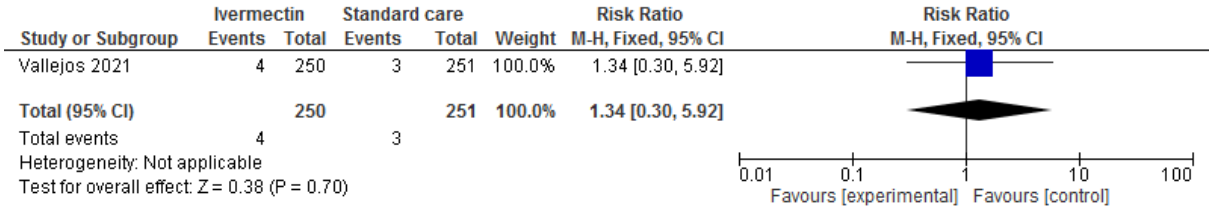


Viral clearance (1 – 7 days)

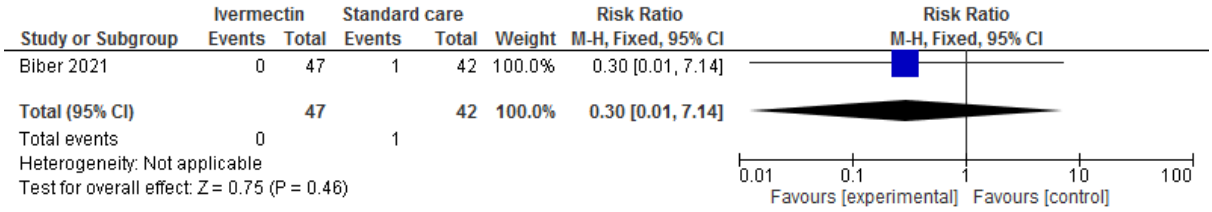


Viral clearance (7 – 12 days)

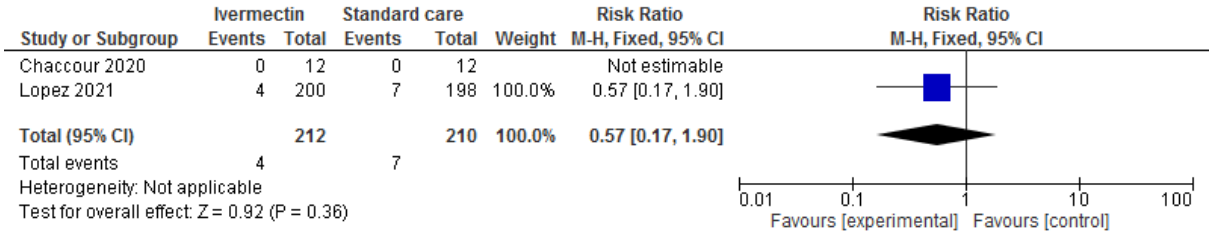
Invasive mechanical ventilation



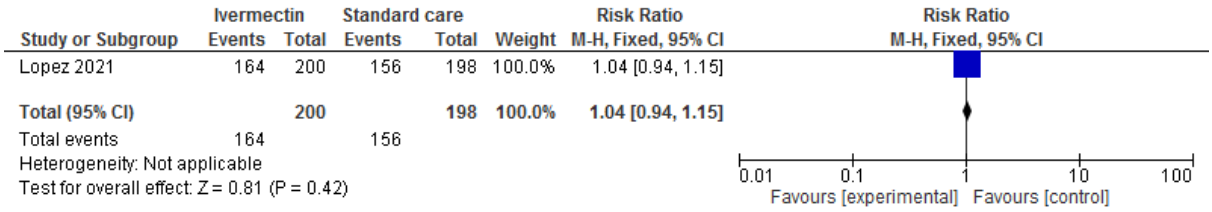
Number of patients requiring oxygen



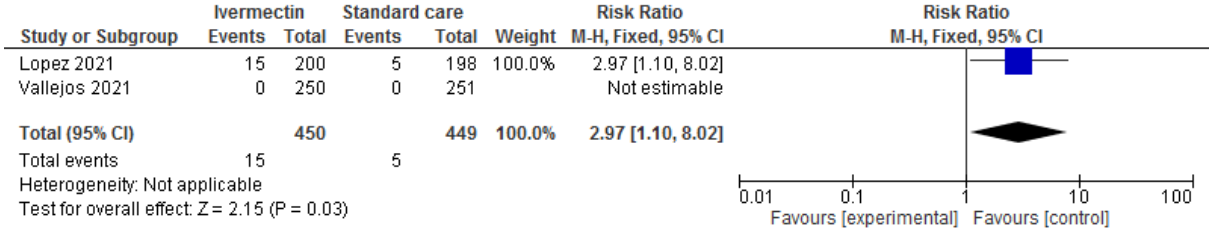
Clinical progression



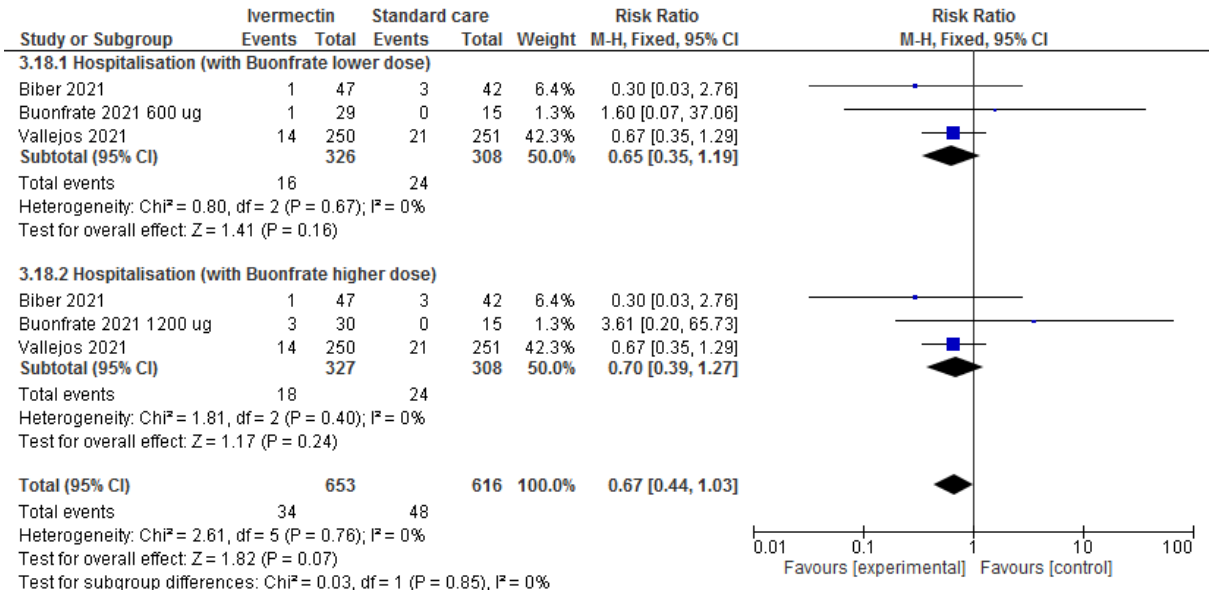
Clinical recovery (21 days)



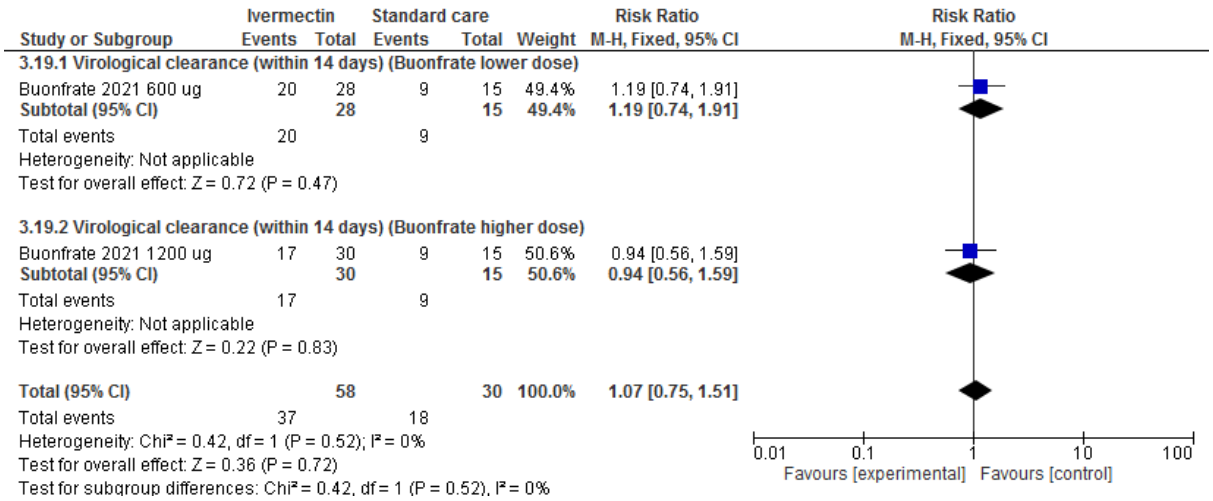
Discontinuation due to adverse event



Hospitalisation



Virological clearance (14 days)



Symptomatic at day 7