Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the Department of Health

EVIDENCE SUMMARY

Among patients with COVID-19, should ivermectin be used for treatment?

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RECOMMENDATIONS

We recommend against the use of ivermectin for the treatment of patients with COVID-19 of any severity. *(Very low certainty of evidence; Strong recommendation)*

We suggest against the use of ivermectin combined with doxycycline for the treatment of patients with COVID-19. *(Very low certainty of evidence; Conditional recommendation)*

Consensus Issues

The review showed that ivermectin has no clear benefit for mortality and all other outcomes for patients with different disease severity, hence the panel made a general recommendation for all COVID-19 patients regardless of severity (mild, moderate, severe or critical).

This update provided additional evidence ivermectin did not differ significantly from placebo in terms of critical outcomes in the treatment of COVID-19. Hence, given the ongoing misuse and abuse of the drug, the panel unanimously voted for a strong recommendation against the use of ivermectin. Other considerations included issues on the pharmacologic property of the drug, given that the drug is registered for veterinary use, the need for higher doses, and concerns regarding adverse events. The panel also considered the issue on health equity wherein other medications for COVID-19 are available, hence resources should be allocated to these more effective and efficacious treatment with clear benefits. There are still a number of ongoing trials, including a local one, which will be considered once data is available.

There is no new evidence for ivermectin combined with doxycycline available, hence, no update was done and the previous recommendations were retained.

PREVIOUS RECOMMENDATIONS

We recommend against the use of ivermectin for the treatment of patients with severe and critical COVID-19. *(Very low certainty of evidence; Strong recommendation)*

We suggest against the use of ivermectin in the treatment of patients with mild-to-moderate COVID-19. *(Very low certainty of evidence; Conditional recommendation)*

We suggest against the use of ivermectin combined with doxycycline for the treatment of patients with COVID-19. *(Very low certainty of evidence; Conditional recommendation)*

Consensus Issues
The consensus panel noted that health equity may be decreased if budget will be allocated for ivermectin rather than efficacious medications and standard of care. The cost and availability of human grade ivermectin is another crucial consideration. The registered oral and parenteral preparations of ivermectin were registered for veterinary use only. Only the topical preparation of ivermectin is registered for human use. According to the Philippine Food and Drug Administration, drugs that were registered for veterinary use should not be utilized for human consumption.

In this update, the consensus panel made a conditional recommendation against the use of ivermectin as a treatment for mild and moderate COVID-19 cases since the current available evidence shows no clear benefit in terms of mortality reduction and clinical outcomes. Studies that showed a potential mortality benefit had significant methodological limitations and had results that are inconsistent with those reported in other trials. For severe and critical COVID-19 cases, the consensus panel made a strong recommendation against the use of ivermectin as there are currently other treatments with established effectiveness. The panel also recognized that while the current data showed no statistical difference between ivermectin and control in terms of adverse events, there is still limited data regarding the adverse effects that may be observed when ivermectin is administered in high doses or in doses similar to those given in in vitro studies. Results from the ongoing randomized clinical trials are still needed to establish whether ivermectin is a safe and effective treatment for COVID-19.

NOTE: The Consensus Panel agreed to make separate recommendations for patients with different disease severity. These recommendations were made without considering the dose of ivermectin.

What's new in this version?

This version includes four (4) new randomized controlled trials (total of 16 RCTs; Abd-Elsalam, Biber, Kishoria, and Vallejos). Four studies were excluded from the current analysis (2 RCTs were retracted from preprint publication - Elgazzar and Samaha; 2 RCTs included COVID-19 unconfirmed patients - Niaee and Shabaznejad). Separate analyses for trials evaluating ivermectin alone and those evaluating ivermectin combination treatment were done.

Key Findings

There are 16 randomized controlled trials (RCTs) that investigated the effects of ivermectin as treatment for patients with COVID-19. No significant over-all mortality benefit was found. Subgroup analysis by disease severity also showed no significant benefit for low dose ivermectin.

We cannot estimate the risk of benefit or harm associated with high dose ivermectin because no deaths were reported among the three included RCTs. Sensitivity analysis revealed that publication status and study quality did not influence our estimates.

Treatment with ivermectin was not significantly associated with clinical deterioration, need for mechanical ventilation, clinical improvement, reduction in hospital length of stay, time to symptom resolution, and virologic clearance. The risk for serious and non-serious adverse events was not significantly different among patients who received ivermectin. Our results agree with a recent Cochrane systematic review done in May 2021.

These results must be interpreted in the context of very low certainty of evidence. The certainty of evidence was downgraded due to varying degrees of risk of bias in most studies, inconsistency, and imprecision in several critical outcomes.

Introduction

Ivermectin is an anti-helminthic drug repurposed as a potential therapy for COVID-19 because of its anti-viral properties and immunomodulatory effects. In-vitro studies show that ivermectin limits viral infection from SARS-CoV-2 by preventing viruses from suppressing the host's antiviral response. This action is through the inhibition of the importin alpha/beta-1 nuclear transport proteins that are utilized by viruses to promote infection.[1] As an immunomodulator, ivermectin may reduce cytokine secretion by inhibiting the translocation of nuclear transcription factor K-B and phosphorylation of mitogen activated protein (MAP) kinases. Ivermectin also prevents the entry of SARS-CoV-2 into the cell by disrupting the interaction between spike receptor binding domain and ACE2 cellular receptors.[2] Among mice exposed to lethal doses of lipopolysaccharide endotoxin, ivermectin was shown to improve survival and was associated with lower levels of tumor necrosis factor alpha, IL-1, and IL-6 inflammatory markers. Finally, an in-vitro experiment by Caly et al., showed that ivermectin may inhibit the replication of SARS-CoV-2 infected Vero/hSLAM cells with the addition of 5 μM ivermectin.[3] They found a 5000-fold reduction in viral RNA counts. These findings taken together sparked interest in the compassionate use of ivermectin ahead or outside of clinical trials.

Several systematic reviews have already been completed on ivermectin, with varying eligibility criteria and conflicting conclusions.[4-17] A recent Cochrane systematic review published in May 2021 found insufficient evidence to recommend ivermectin as prophylaxis or treatment for COVID-19.[7] However, to date, completed trials on ivermectin continue to be published and a number of trials are still ongoing.

Review Methods

A systematic search was done from the date of the last search May 3, 2021 until September 10, 2021. We included electronic databases (MEDLINE, Cochrane COVID-19 Study Register, and COVID-19 LOVE Evidence/Epistemonikos), preprint databases (MedRxiv, BioRxiv, and ChinaXiv), and trial registries (Chinese Clinical Trial Registry and WHO International Clinical Trials Registry). We also checked the included studies from other living guidelines and systematic reviews on COVID-19. References of published systematic reviews were also hand searched for studies. Reference lists from websites including IVMMeta were considered and included in the current review as long as they provided sufficient information to allow critical appraisal.[4-17] As appropriate, authors of potentially eligible studies for this review were contacted via email to obtain additional data. The full search strategy used for each source is detailed in Appendix 2.

Only randomized controlled trials that compared ivermectin against placebo or standard of care (SOC) among COVID confirmed patients were included in this review. Outcomes of interest included mortality, clinical deterioration or improvement, development of acute respiratory syndrome, need for mechanical ventilation, need for hospitalization, duration of hospitalization, time to clinical recovery, improvement of radiographic findings, virologic clearance, or adverse events. No limits were placed on age, COVID-19 severity, hospitalization status, and dosing strategy of ivermectin. Subgroup analysis by dose and disease severity was planned. For the outcome of clinical deterioration, subgroup analysis by admission to ICU, deterioration in WHO ordinal scale, progression in O2 support, and need for hospitalization were also planned. We performed sensitivity analysis to assess the robustness of the results when studies with serious risk of bias concerns were excluded. We excluded studies that included patients who were diagnosed with COVID-19 based on radiographic evidence but were negative for COVID-19 RT-PCR or COVID-19 antigen test.

Results

The search yielded 574 records, of which 16 RCTs (N = 2,063) were included in this review. The trials were performed in Bangladesh [18,19], Spain [20], Pakistan [21,22], Egypt [23], Argentina [24,25], India [26-28], Turkey [29], Mexico [30], Brazil [31], Colombia [32], and Israel.[33] Sample sizes ranged from 24 to 501. Three of the 16 studies (16%) were still pre-prints.[21,30,33] Participants in the included studies had varying severity of COVID-19: 6 RCTs for mild [18,20,22,24,27,31], 7 RCTs for mild-to-moderate [19,21,23,25,26,28,33], 2 RCTs for severe [29,30], 1 RCTs for mixed non-severe and severe cases.[31] Different treatment regimens of ivermectin were used: 12 RCTs used low dose (200 mcg/kg or 12mg and lower) [18,19,21-24,27-30,32,33], 2 RCTs used high dose ivermectin (400-600 mcg/kg or 24mg or higher) [20,25], and 2 RCTs used mixed doses.[26,31] Eight studies were placebo-controlled [18,20,24,26,28,30,32,33], while 8 used the existing standard of care [19,21-23,25,27,29,31] in their country. The detailed characteristics of the included studies are summarized in Appendix 3.

The overall certainty of evidence was rated very low due to varying degrees of risk of bias in most studies, serious imprecision, and/or serious inconsistency in several outcomes. Risk of bias was rated very serious in 7/16 studies and serious in 5/16 studies, due to concerns with randomization, allocation concealment, and blinding of patients and outcome assessors. Only 4 trials [23,24,26,32] were appraised to have no serious risk of bias. At least 75% of all included studies had high risk for detection bias from unblinded assessors, performance bias from unblinded patients and investigators, and attrition bias from having incomplete outcome data. Appendix 4 provides details of the individual risk of bias ratings. Assessments of certainty of evidence per comparison are detailed in Appendix 5.

Mortality

Pooled analysis of 10 RCTs (N = 1,658) showed that ivermectin had no significant reduction in overall mortality among COVID-19 patients compared to placebo or standard of care (RR 0.73, 95% CI 0.42, 1.28; I^2 = 0%, for intention-to-treat analysis and for per-protocol analysis). Subgroup analysis by disease severity showed no significant reduction in mortality among those with mild (RR 1.05, 95% CI 0.27, 4.02, I^2 = 0%), mild to moderate (RR 0.43, 95% CI 0.08, 2.48, I^2 = 29%), and severe (RR 0.74, 95% CI 0.37, 1.48, I^2 = 0%).

Subgroup analysis by dose showed no significant difference in mortality among those given low-dose ivermectin compared to control (RR 0.73, 95% CI 0.42, 1.28, I^2 = 0%). For high dose ivermectin, we cannot estimate the risk of benefit or harm associated with treatment because no deaths were reported among the three included RCTs.

Sensitivity analysis by removing preprint studies from the analysis and excluding studies with serious risk of bias showed these had no significant influence on mortality (publication status, RR 0.69, 95% CI 0.36, 1.33; study quality, RR 0.90, 95% CI 0.33, 2.42).

Critical Clinical Outcomes

The effects of ivermectin were not significantly different from control for the following critical outcomes: clinical deterioration (RR 0.69, 95% CI 0.44, 1.09, I^2 = 0%), need for mechanical ventilation (RR 0.82, 95% CI 0.34, 1.99, I^2 = 0%), and clinical improvement (RR 1.05, 95% CI 0.94, 1.18, I^2 = 0%). Hospital length of stay was not significantly different from the control (MD -0.48 days, 95% CI -2.48 to 1.52) with significant heterogeneity (I^2 = 72%; p=0.03).

Subgroup analysis for clinical deterioration showed no significant difference in the proportion of patients requiring admission to ICU (RR 0.85, 95% CI 0.27, 2.62), deterioration in WHO ordinal scale (RR 0.59, 95% CI 0.26, 1.30), and need for hospitalization (RR 0.72, 95% CI 0.39, 1.36). Based on one study (Ahmed), no events were reported for the outcome of progression in oxygen support.

Pooled results from 2 RCTs [19,26] showed that treatment with ivermectin was not significantly associated with a shorter time to symptom resolution (MD -0.53 days, 95% CI -1.50 to 0.44, I^2 = 0%). One larger study by Lopez-Medina (N = 398) also similarly reported no significant difference in time to symptom resolution (Hazard Ratio 1.07, 95% CI 0.87, 1.32).

Other Outcomes

Virologic clearance

Very low certainty of evidence from 11 RCTs showed no significant difference in virologic clearance from days 3 to 10 (RR 1.30, 95% CI 0.95, 1.79; I^2 = 89%; N = 621) between the ivermectin and control groups, but with significant heterogeneity. Subgroup analysis showed that regardless of disease severity (mild: RR 1.43, 95% CI 0.53, 3.83, I^2 = 96%; mild-moderate RR 1.14, 95% CI 0.86, 1.50, I^2 = 64%, and severe: RR 2.33, 95% CI 0.94, 5.82), ivermectin treatment had no significant influence on virologic clearance, however, still with significant heterogeneity.

Adverse events

Ivermectin was not significantly associated with an overall increased risk of any adverse events compared to control (RR 0.96, 95% CI 0.81, 1.15, I^2 = 8%; 12 RCTs). Subgroup analysis per dose showed no significant difference in adverse events with the use of high dose ivermectin (RR 1.03, 95% CI 0.61, 1.73, I^2 = 0%), and low-dose ivermectin (RR 0.97, 95% CI 0.75, 1.24, I^2 = 22%). Gastrointestinal symptoms such as epigastric pain, diarrhea and nausea, neurologic symptoms such as headache, agitation, confusion, and dizziness, were the most common side effects reported across studies.

There was no significant difference in serious adverse events (RR 0.78, 95% CI 0.24, 2.53, I^2 = 0%). Six serious adverse events related to ivermectin were reported: hyponatremia (N = 1; low dose, mild-moderate COVID) [25], multiorgan failure (N = 2; low dose, mild-moderate COVID) [32], and need for ventilatory support (N = 1; low and high dose, mild-moderate COVID).[31] Delirium-like behavior (N = 2; low dose, severe COVID) [29] was reported among patients who were tested to have mutations of either the MDR-1/ABCB1 or CYP3A4 genes affecting ivermectin metabolism.

Recommendations from Other Groups

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
US-NIH (as of September 15, 2021) [34]	There are insufficient data for the Panel to recommend either for or against the use of ivermectin for the treatment of COVID-19.
Infectious Diseases Society of America (IDSA) (as of September 6, 2021) [36]	Does not recommend the use of ivermectin outside of trials.
WHO Living Guideline on COVID-19 Therapeutics (as of September 24, 2021) [37]	Does not recommend using ivermectin in patients with COVID-19 except in the context of a clinical trial.
India COVID-19 Guidelines (as of May 15, 2021) [38]	Recommends against using ivermectin for treatment of patients with any severity of COVID-19 (non-severe, severe, critical). The group further stated that “its use may distract from use of other therapies for which there is better evidence, and that indiscriminate use might also reduce its availability for other conditions where its benefit is established, such as parasitic infections”.

The Cochrane systematic review published last May 2021 similarly reported no significant difference in the following the critical outcomes: mortality, adverse events, clinical deterioration, and need for mechanical ventilation.

Research Gaps

As of September 2021, there are at 81 ongoing clinical trials investigating the efficacy of ivermectin as treatment for COVID-19 that are listed in COVID-19 NMA database.

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Appendix 1: Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 8)

FACTORS	JUDGEMENT (N=8)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (8)					
Benefits	Large	Moderate (1)	Small (2)	Uncertain (5)			No significant benefit for over-all mortality (RR 0.73, 95% CI 0.42-1.28), clinical deterioration (RR 0.69, 95% CI 0.44, 1.09), need for mechanical ventilation (RR 0.82, 95% CI 0.34, 1.99), clinical improvement (RR 1.05, 95% CI 0.94, 1.18), and hospital length of stay (mean difference (MD -0.48 days, 95% CI -2.48, 1.52).
Harm	Large	Small (3)	Uncertain (5)				There are no significant differences in adverse events (RR 0.96, 95% CI 0.81, 1.15) and serious adverse events (RR 0.78, 95% CI 0.24, 2.53) between patients receiving ivermectin and placebo
Certainty of Evidence	High	Moderate	Low (2)	Very low (6)			The overall certainty of evidence was rated very low, downgraded due to varying degrees of risk of bias in most studies, inconsistency, and imprecision in several critical outcomes.
Balance of effects	Favors drug	Does not favor drug (5)	Uncertain (3)				Ivermectin showed no significant difference in over-all mortality, clinical deterioration, need for mechanical ventilation, clinical improvement, hospital length of stay, time to symptom resolution and virologic clearance, no difference with Aes and SAEs
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (6)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain (2)	Large cost	Moderate cost (4)	Negligible cost (2)	Moderate savings	Large savings	Cost is around P20-27 per tablet depending on concentration.
Certainty of evidence of required resources	No included studies (1)	Very low (2)	Low (1)	Moderate (3)	High (1)		Pricing information is taken from the website of Dr. Zen's Research, Inc. is a subsidiary of InnoGen Pharmaceuticals, Inc.
Cost effectiveness	No included studies (6)	Favors the comparison (2)	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (4)	Reduced (2)	Probably no impact (2)	Increased			
Acceptability	Uncertain (6)	No (1)	Yes (1)				
Feasibility	Uncertain (4)	No (1)	Yes (3)				

Appendix 2: Search Strategy (as of 10 Sept 2021)

Database	Search Strategy	Yield	Eligible
MEDLINE (PubMed)	"((("COVID-19" [Supplementary Concept] OR "COVID-19 Testing" OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [Supplementary Concept] OR "COVID-19 vaccines" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR "2019-nCoV" OR "2019nCoV" OR "cov 2" OR "Covid-19" OR "sars coronavirus 2" OR "sars cov 2" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus 2" OR "COVID 19" OR "COVID-19" OR "2019 ncov" OR "2019nCoV" OR "corona virus disease 2019" OR "cov2" OR "COVID-19" OR "COVID19" OR "nCov 2019" OR "nCoV" OR "new corona virus" OR "new coronaviruses" OR "novel corona virus" OR "novel coronaviruses" OR "SARS Coronavirus 2" OR "SARS2" OR "SARS-COV-2" OR "Severe Acute Respiratory Syndrome Coronavirus 2") OR ((19[tiab] OR 2019[tiab] OR "2019-nCoV" OR "Beijing" OR "China" OR "Covid-19" OR epidem*[tiab] OR epidemic* OR epidemy OR new[tiab] OR "novel"[tiab] OR "outbreak" OR pandem* OR "SARS-CoV-2" OR "Shanghai" OR "Wuhan") AND ("Coronavirus Infections"[Mesh] OR "coronavirus"[MeSH Terms] OR coronavirus*[all] OR corona-virus*[all] OR cov[tiab] OR pneumonia-virus*[tiab]))) AND 2019/12/1:3000/12/31[PDAT]) AND ((ivermectin OR ivermectin[MeSH Terms])"	Sept 10: +270	34
Cochrane COVID-19 Study Register	"Ivermectin"	Sept 10: +70	23
MedRxiv	Advanced search: "Ivermectin AND COVID" with "match all" parameters	Sept 10: +142	14
BioRxiv	Advanced search: "Ivermectin AND COVID" with "match all" parameters	Sept 10: +51	0
ChinaXiv	Advanced search: "Ivermectin AND COVID" with "all fields" parameters	Sept 10: 0	0
Chinese Clinical Trial Registry	Under trial search (with more option), the search syntax "Ivermectin", under intervention and "COVID-19", under target disease was used	Sept 10: +1	0
WHO ICTRP	The search syntax "Ivermectin" was used. Results were filtered to "Restrict to COVID-19"	Sept 10: +7	6
Living Guidelines	Records were selected from three living guidelines (WHO Living Guidelines, Australian CPG, COVID-19 NMA)	Sept 10: +33	27

Appendix 3: Characteristics of Included Studies

Table 1. Ivermectin versus placebo or standard care (16 RCTs)

No.	Clinical Trial ID/ Title	Country	Study design	Population	Intervention	Comparator	Outcomes
1	Abd-Elsalam 2021 Clinical study evaluating the efficacy of Ivermectin in COVID-19 treatment: A randomized controlled study	Egypt	Open-label RCT (N=164)	Mild-moderate COVID-19 Age 20 to 65 years old	Oral Ivermectin, 12 mg once a day for 3 days. (n=82) Low dose Ivermectin	Standard care (n=82) Standard care: paracetamol, empiric antibiotics, oseltamivir if needed.	1. Mortality 2. Need for mechanical ventilation 3. Safety
2	Ahmed 2020 A five day course of Ivermectin for the treatment of COVID-19 may reduce the duration of illness.	Bangladesh	Double-blind RCT (N=76)	Mild COVID-19 Age 18 to 65 years hospitalized within the last 7 days; with either fever (≥37.5C); cough or sore throat; and diagnosed positive for SARS-CoV-2 by RT-PCR.	Oral Ivermectin, 12 mg once a day for 5 days. (n=22) Low dose Ivermectin	Placebo (n=22)	1. Mortality 2. Clinical deterioration 3. Duration of hospitalization 4. Remission of symptoms 5. Time to PCR negativity 6. Adverse effects
3	Beltran-Gonzalez 2021 Efficacy and safety of Ivermectin and hydroxychloroquine in patients with severe COVID-19	Mexico	Double-blind RCT (N=106)	Severe COVID-19 Mean age 53	Oral Ivermectin 12 or 18 mg according to weight (n=36) Low dose Ivermectin	Placebo (n=37)	1. Duration of hospitalization 2. Hospital discharge, n(%) 3. Discharged without respiratory deterioration or death, n(%) 4. Respiratory deterioration or death, n(%)
4	Biber 2021 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.	Israel	Double-blind RCT (N=89)	Mild-moderate COVID-19 Age 18 years and older	Oral Ivermectin, 12 or 15 mg according to weight (n=47) Low dose Ivermectin	Placebo (n=42)	1. Viral clearance (repeat RT-PCR on D4,6,8,10)
5	Bukhari 2021 Efficacy of Ivermectin in COVID-19 patients with mild to moderate disease	Pakistan	Open-label RCT (N=100)	Mild-moderate COVID-19 Age 15 to 65 years	Oral Ivermectin 12 mg single dose at admission (n=50) Low dose Ivermectin	Standard care (n=50) Standard care: Vit C 500mg OD, Vit D3 200k IU once weekly, paracetamol 500mg	1. Viral clearance (days to RT-PCR negativity) 2. Adverse effects
6	Chaccour 2020 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.	Spain	Double-blind RCT (N=24)	Mild COVID-19 Age 18 to 59 years Outpatient setting. without comorbidities considered as risk factors to	Oral Ivermectin, 400 mcg/kg, single dose (n= 12) High dose Ivermectin	Placebo (n= 12)	1. Mortality 2. Clinical improvement 3. Virologic clearance: proportion of patients who become negative at day 7 and viral culture 4. Adverse effects

				develop severe disease or COVID-19.			
7	Chachar 2020 Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients	Pakistan	Open-label RCT (N=50)	Mild COVID-19 Age 18 to 75 years excluded severe COVID-19, with malignancy, chronic kidney disease, and liver cirrhosis	Oral Ivermectin, 12 mg on D0, then 12 mg after 12 hours, and 12 mg after 24 hours. (n=25) Low dose Ivermectin	Standard care (n=25) Standard care: conventional symptomatic treatment	1. Clinical improvement 2. Adverse effects
8	Kishoria 2020 Ivermectin as adjuvant to hydroxycholoroquine in patients resistant to standard treatment for sars-cov-2:results of an open-label randomized clinical study	India	Open-label RCT (N=32)	Mild COVID-19 Age 18 years and older Patients who remain positive after 6 days of standard care treatment.	Oral Ivermectin, 12 mg single dose on D1 (n=19) Standard care: HCQ 400 mg/tab twice a day for 5 days Paracetamol 500mg/tab prn, Vitamin C BID. Low dose Ivermectin	Standard care (n=13) Standard care: HCQ 400 mg/tab twice a day for 5 days Paracetamol 500mg/tab prn, Vitamin C BID.	1. Viral clearance D5 2. Hospital Discharge D5
9	Królewiecki 2020 Antiviral effect of high-dose Ivermectin in adults with COVID-19: a pilot randomised, controlled, open label, multicentre trial.	Argentina	Single-blind (outcome-assessor) RCT (N=45)	Mild-Moderate COVID-19 Age 18 to 69 years hospitalized patients not requiring ICU admission excluded patients with poorly controlled comorbidities	Oral Ivermectin, 600mcg/kg, once a day for 5 days (n=30) Co-Intervention: Standard care High dose Ivermectin	Standard care (n=15) Standard care: uncertain	1. Mortality 2. Clinical deterioration 3. Adverse effects
10	Lopez-Medina 2021 Effect of Ivermectin on time to resolution of symptoms among adults with mild COVID-19	Colombia	Double-blind RCT (N=476)	Mild COVID-19 Mean age 37 (range: 28-49)	Oral Ivermectin, 300 mcg/kg, once a day for 5 days (n=238) Low dose Ivermectin	Placebo (n=238)	1. Time to resolution of symptoms (D21); % patients with resolved symptoms 2. Clinical deterioration (% patient with clinical deterioration) 3. Fever since randomization 4. Escalation of care 5. Mortality
11	Mohan 2021 Ivermectin in mild and moderate COVID-19 (RIVETCOV): a randomized, placebo-controlled trial	India	Triple-blind RCT (N=157 mITT=125)	Mild-Moderate COVID-19 Age 18 years and older	Oral Ivermectin, 12 mg, single dose (n=40) Oral Ivermectin, 24 mg, single dose (n=40) Low dose and high dose Ivermectin	Placebo (n=45)	1. Mortality 2. Clinical deterioration 3. Progression to ventilation 4. Clinical improvement 5. Duration of hospitalization 6. Viral clearance 7. Adverse effects

12	Okumus 2021 The Effectiveness and Safety of Ivermectin as add-on Therapy in Severe COVID-19 Management	Turkey	Randomized open label (N=66)	Severe COVID-19 Age 18 years and older	Oral Ivermectin 200 mcg/kg, once a day for 5 days (n=30) Co-intervention: Standard care Low dose Ivermectin	Standard care (n=30) Standard care: Hydroxychloroquine, favipiravir and azithromycin (HFA) HCQ (2x400mg loading dose followed by 2x200mg, PO, 5 days), favipiravir (2x1600mg loading dose followed by 2x600mg maintenance dose, PO, total 5 days) and azithromycin (500mg 1st day loading dose, followed by 250mg/day, PO, total 5 days)	1. Mortality 2. Clinical improvement 3. Viral clearance D10 4. Adverse effects
13	Podder 2020 Outcome of Ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study	Bangladesh	Open-label RCT (N=62)	Mild-moderate COVID-19 Age 18 years and older	single dose of Ivermectin 200 mcg/kg on the day 1 of randomization (n=32) Low dose Ivermectin	Standard care (n=30) Standard care: symptomatic treatment which included antipyretics, cough suppressants, and capsule doxycycline (100 mg every 12 hours for seven days)	1. time needed for resolution of fever, cough, shortness of breath 2. time needed for full recovery from all symptoms 3. Viral clearance (repeat RT-PCR on day 10)
14	Pott-Junior 2021 Use of Ivermectin in the treatment of COVID-19: a pilot trial	Brazil	Open-label RCT (N=32)	Mild-severe COVID-19 Age 18 years and older	Ivermectin + SOC 100mcg/kg (n=6) 200mcg/kg (n=14) 400mcg/kg (n=7) Low and high dose Ivermectin	Standard care (n=4)	1. Viral clearance (% patients with 2 negative PCR tests w/in 7 days) 2. Adverse events
15	Ravikirti 2021 Ivermectin as a potential treatment for mild to moderate COVID-19 – A Double-blind randomized placebo-controlled trial	India	Double-blind RCT (N=115)	Mild-Moderate COVID-19 Age 18 years and older	Oral Ivermectin 12mg on D1 and D2 (n=57) Co-intervention: standard care Low dose Ivermectin	Placebo (n=58) Standard care: Hydroxychloroquine, steroids, enoxaparin, antibiotics, remdesivir, convalescent plasma, tocilizumab	1. Mortality 2. Clinical deterioration 3. Progression to Ventilation 4. Clinical improvement 5. Viral Clearance
16	Vallejos 2021 Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo controlled trial	Argentina	Double-blind RCT (N=501)	Mild COVID-19 Age 18 years and older	Oral Ivermectin, 150-200mcg/kg, once a day for 2 days (n=250) Low dose Ivermectin	Placebo (n=251)	1. Clinical deterioration (need for hospitalization) 2. Mortality 3. Need for mechanical ventilation 4. Safety

Appendix 4: Methodological Quality Assessment of Included Studies

Table 1. Methodological quality assessment: Ivermectin vs. placebo/standard of care (17 RCTs)

Studies	Risk of bias	Random assignment	Allocation concealment	Similar baseline characteristics	Patients blinded	Caregivers blinded	Assessors blinded[1]	Intention-to-treat analysis	Adequate follow-up rate	Peer-reviewed
1. Abd-Elsalam*	**Not serious**	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
2. Ahmed	**Serious**	Yes	Unclear	Unclear	Yes	Yes	Unclear	No	Yes	Yes
3. Beltran-Gonzalez	**Very serious**	Yes	Unclear	No	Yes	Unclear	Unclear	Yes	Yes	No
4. Biber*	**Serious**	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
5. Bukhari	**Very serious**	Yes	Unclear	Yes	No	No	No	Yes	No	No
6. Chaccour	**Serious**	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
7. Chachar	**Serious**	Yes	No	Yes	No	No	No	Yes	Yes	Yes
8. Kishoria*	**Very serious**	Yes	Yes	Unclear	No	No	No	Yes	Yes	Yes
9. Królewiecki	**Serious**	Yes	Yes	Yes	No	No	No	Yes	No	Yes
10. Lopez-Medina	**Not serious**	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
11. Mohan	**Not serious**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Okumuş	**Very serious**	Yes	Unclear	Yes	No	No	No	Yes	No	Yes
13. Podder	**Very serious**	Yes	No	Yes	No	No	No	No	No	Yes
14. Pott-Junior	**Very serious**	Yes	Unclear	Unclear	No	No	No	Yes	No	Yes
15. Ravikirti	**Very serious**	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
16. Vallejos*	**Not serious**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

* New RCTs
Green: not serious; Yellow: serious; Red: very serious

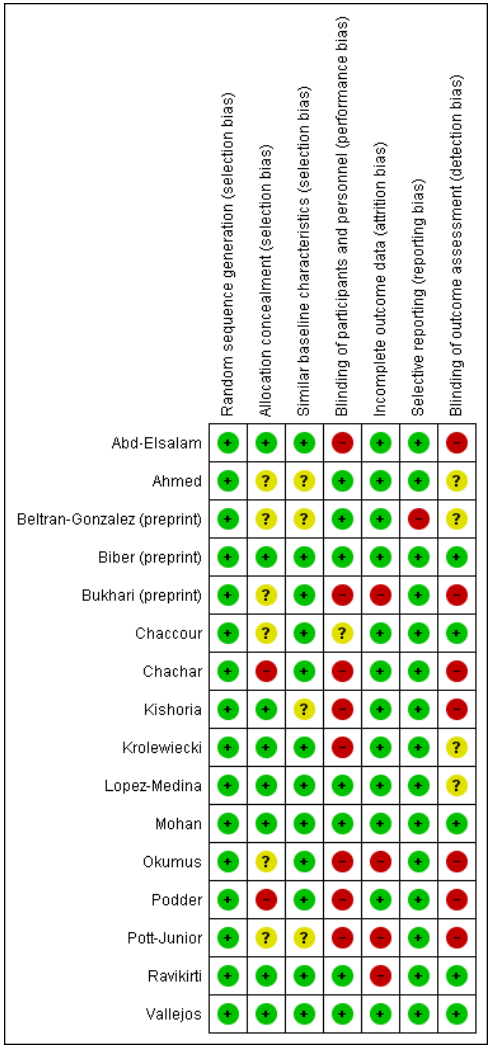


Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Appendix 5: Grade Evidence Profile

Author(s): MVASGJoson, HHGBayona, JJVBesa, DLROTating, MGCCruz

Question: Ivermectin compared to standard of care or placebo as treatment for COVID-19

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ivermectin	Standard of care or placebo as treatment	Relative (95% CI)	Absolute (95% CI)		
Mortality												
10[a]	randomised trials	serious[b]	not serious	not serious	serious[c]	none	18/859 (2.1%)	27/799 (3.4%)	**RR 0.73** (0.42 to 1.28)	**9 fewer per 1,000** (from 20 fewer to 9 more)	⨁⨁◯◯ LOW	CRITICAL
Clinical deterioration												
7	randomised trials	not serious	not serious	not serious	serious[c]	none	32/756 (4.2%)	41/697 (5.9%)	**RR 0.69** (0.44 to 1.09)	**18 fewer per 1,000** (from 33 fewer to 5 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Need for mechanical ventilation												
6	randomised trials	not serious	serious[d]	not serious	serious[e]	none	10/547 (1.8%)	11/462 (2.4%)	**RR 0.82** (0.34 to 1.99)	**4 fewer per 1,000** (from 16 fewer to 24 more)	⨁⨁◯◯ LOW	CRITICAL
Clinical improvement (follow-up: 6-14 days)												
6	randomised trials	serious[f]	not serious	not serious	not serious	none	239/469 (51.0%)	191/416 (45.9%)	**RR 1.05** (0.94 to 1.18)	**23 more per 1,000** (from 28 fewer to 83 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Hospital length of stay (days)												
3	randomised trials	serious[g]	serious[h]	not serious	serious[i]	none	142	143	-	MD **0.48 days lower** (2.48 lower to 1.52 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Time to symptom resolution (in days)												
3	randomised trials	very serious[j]	serious[d]	not serious	not serious	none	**Pooled mean difference for Mohan 2020, Podder 2020:** MD -0.53 [-1.50, 0.44] days. **Lopez-Medina:** 10 days (IQR, 9-13) ivermectin group compared with 12 days (IQR, 9-13) placebo group. Hazard Ratio 1.07 [95%CI, 0.87 to 1.32]; *p* = .53 by log-rank test.			⨁◯◯◯ VERY LOW	IMPORTANT
Virologic clearance (negative RT-PCR) (follow-up: 3-10 days)												
11	randomised trials	very serious[k]	serious[l]	not serious	serious[c]	none	215/341 (63.0%)	135/280 (48.2%)	**RR 1.30** (0.95 to 1.79)	**145 more per 1,000** (from 24 fewer to 381 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Adverse Events												
12	randomised trials	not serious[m]	serious[n]	not serious	not serious	none	256/926 (27.6%)	239/842 (28.4%)	**RR 0.96** (0.81 to 1.15)	**11 fewer per 1,000** (from 54 fewer to 43 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Serious Adverse Events

10	randomised trials	not serious	very serious[o]	not serious	serious[p]	none	6/594 (1.0%)	4/509 (0.8%)	**RR 0.78** (0.24 to 2.53)	**2 fewer per 1,000** (from 6 fewer to 12 more)	⨁◯◯◯ Very low	CRITICAL

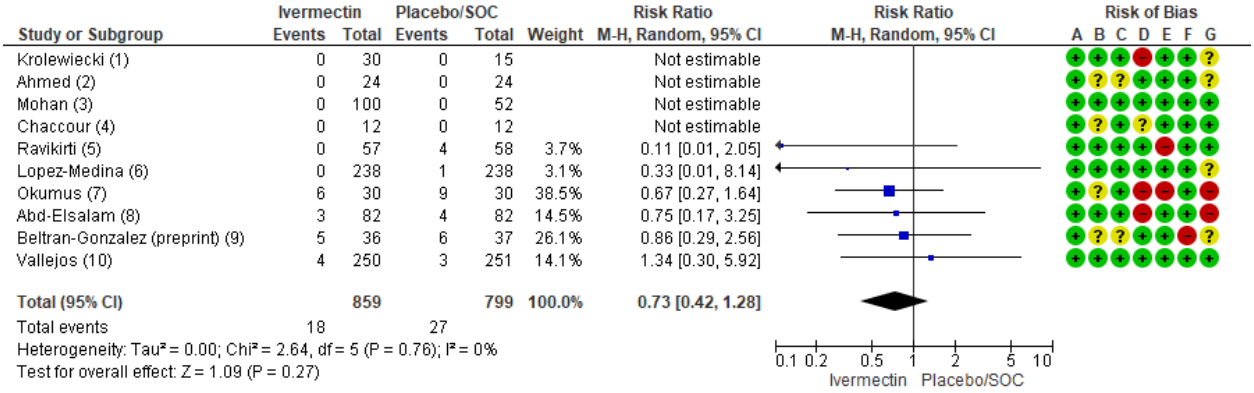
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Trials: Ahmed, Chaccour, Krolewiecki, Mohan, Ravikirti, Niaee, Lopez-Medina, Okumus, Abd-Elsalam, Beltran-Gonzalez, Vallejos, and Shahbaznejad; Okumus 2020 assessed mortality at D60
b. Risk of bias downgraded by 1 level: some concerns regarding adequate randomization and deviations from intended interventions.
c. Wide confidence interval containing 1.00
d. Serious inconsistency due to different direction of effect of the included studies
e. Wide confidence interval, few events
f. Serious concern for bias over the clinical outcome measured since the study of Chachar, Kishoria, and Okmus are open-label in design.
g. Very serious risk of bias in one study (Beltran-Gonzales)
h. Results varied across 3 studies; High heterogeneity (I2 = 71%)
i. wide confidence interval
j. very serious risk of bias for Podder et al., 2020 - open-label in design
k. Risk of bias downgraded by 2 levels: high risk of bias due to inadequate randomization and missing data, some concerns regarding deviations from intended interventions and selection of reported results. Serious concern for risk of bias due to high drop out in the study of Ravikirti.
l. Some concern for inconsistency. I2 = 89%.
m. Two studies with low risk of bias (Lopez-Medina and Vallejos) contributed to 83.3% of the overall effect. Risk of bias: not serious
n. There is some concern with the difference in ADR reporting between the RCTs
o. Very serious inconsistency due to different direction of effect of the included studies.
p. imprecision due to small event rates

Appendix 6: Forest Plots

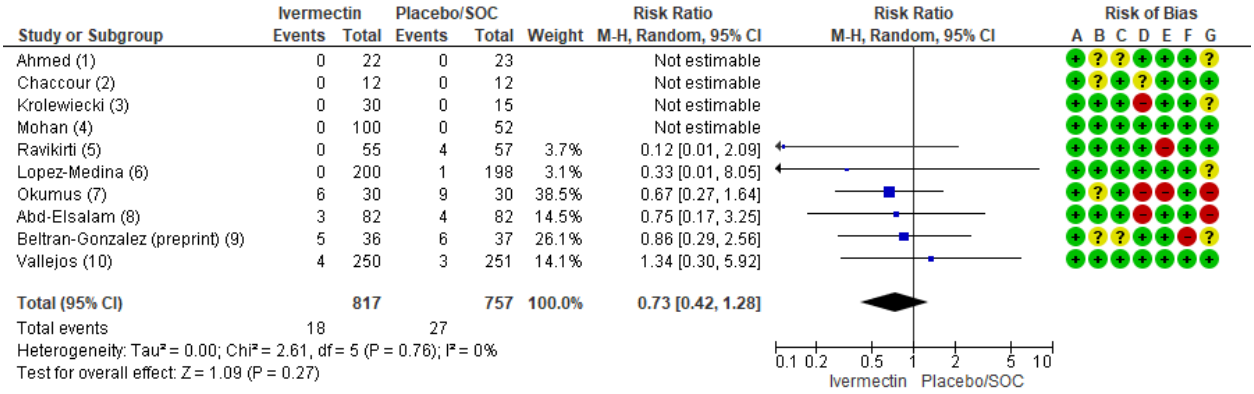
Comparison 1: Ivermectin vs. placebo or standard of care



Footnotes
(1) IVM 600 mcg/kg x 5 days + SOC vs. SOC (unspecified)
(2) IVM 12 mg once daily x 5 days vs. placebo
(3) IVM 24mg single dose (arm1) or 12 mg single dose (arm2) vs. placebo
(4) IVM 400 mcg/kg (single dose) vs placebo
(5) IVM 12mg x 2 days + SOC; vs. placebo + SOC (HCQ, steroids, enoxaparin, antibiotics, remdesivir,
(6) IVM 300 mcg/kg 1x/day for 5 days vs. placebo
(7) IVM 200mcg/kg x 5 days vs. SOC (HCQ, AZT, favipiravir)
(8) IVM 12 mg once daily x 3 days vs. SOC
(9) IVM 12-18 mg/kg (unspecified duration) vs. placebo
(10) IVM 150-200mcg/kg oral x 2 days + SOC vs. placebo + SOC

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Similar baseline characteristics (selection bias)
(D) Blinding of participants and personnel (performance...
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Blinding of outcome assessment (detection bias)

Figure 1.1. Mortality, overall (intention-to-treat)



Footnotes
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(2) IVM 400 mcg/kg (single dose) vs. placebo
(3) IVM 600 mcg/kg x 5 days + SOC vs. SOC (unspecified)
(4) IVM 24mg single dose (arm1) or 12 mg single dose (arm2) vs. placebo
(5) IVM 12mg x 2 days + SOC; vs. placebo + SOC (HCQ, steroids, enoxaparin, antibiotics, remdesivir,
(6) IVM 300 mcg/kg 1x/day for 5 days vs. placebo
(7) IVM 200mcg/kg x 5 days vs. SOC (HCQ, AZT, favipiravir)
(8) IVM 12 mg once daily x 3 days vs. SOC
(9) IVM 12-18 mg/kg (unspecified duration) vs. placebo
(10) IVM 150-200mcg/kg oral x 2 days + SOC vs. placebo + SOC

Risk of bias legend
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(F) Selective reporting (reporting bias)
(G) Blinding of outcome assessment (detection bias)

Figure 1.2. Mortality, overall (per protocol)

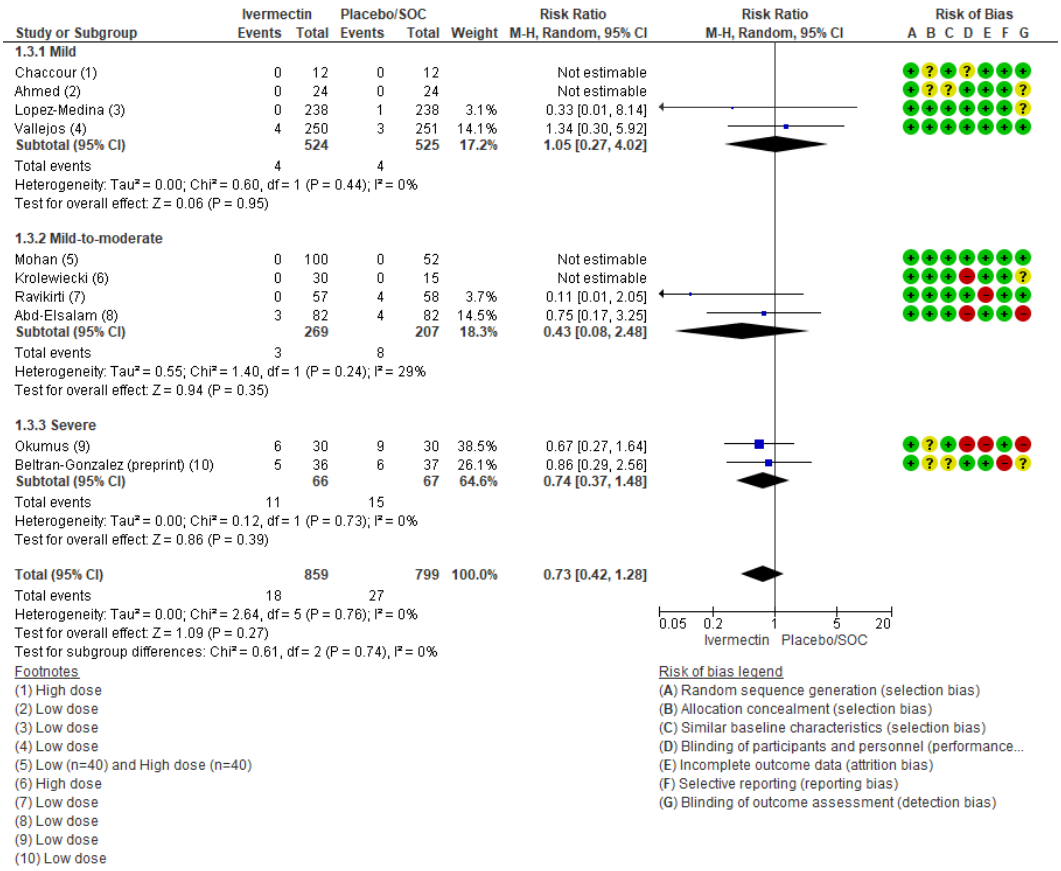


Figure 1.3. Mortality, by disease severity (ITT)

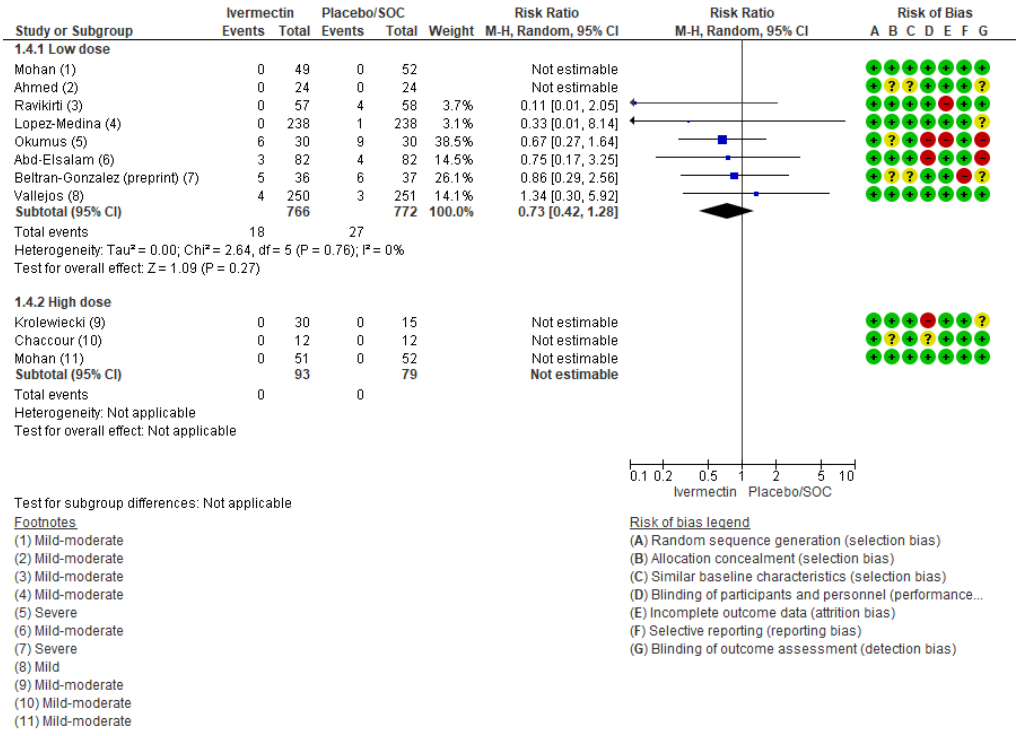
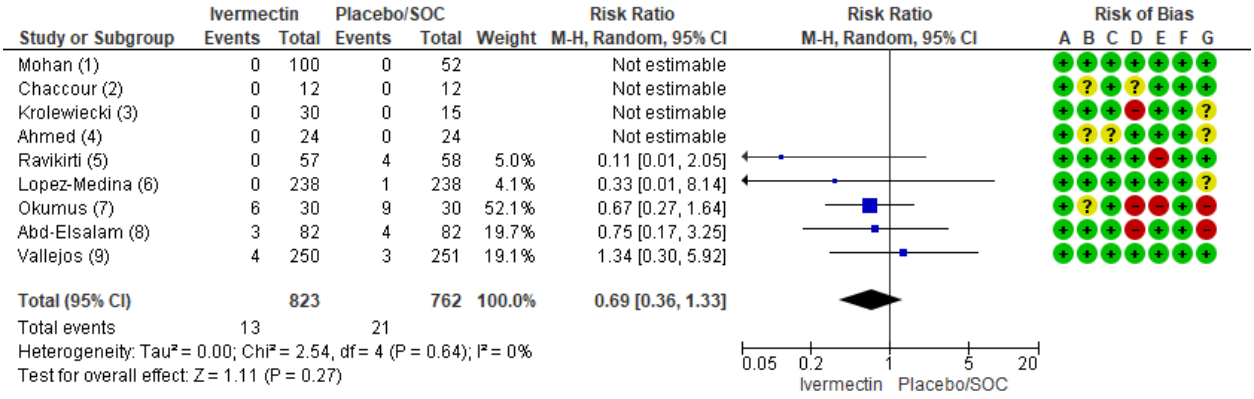


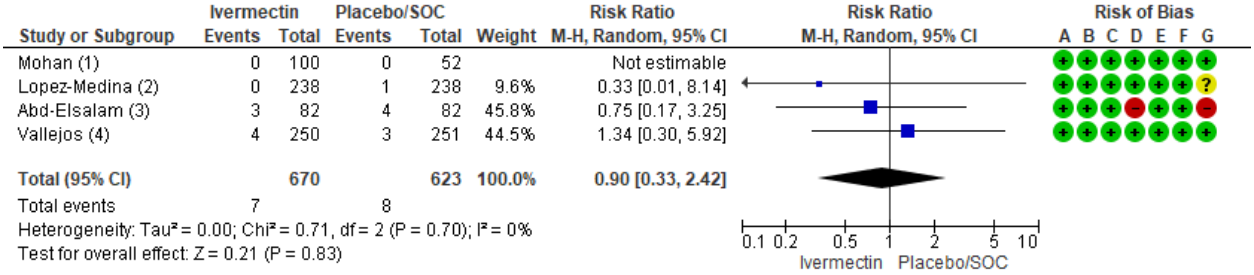
Figure 1.4. Mortality, by dose (ITT)



Footnotes
(1) IVM 24mg single dose (arm1) or 12 mg single dose (arm2) vs. placebo
(2) IVM 400 mcg/kg (single dose) vs placebo
(3) IVM 600 mcg/kg x 5 days + SOC vs. SOC (unspecified)
(4) IVM 12 mg once daily x 5 days vs. placebo
(5) IVM 12mg x 2 days + SOC; vs. placebo + SOC (HCQ, steroids, enoxaparin, antibiotics,..
(6) IVM 300 mcg/kg 1x/day for 5 days vs. placebo
(7) IVM 200mcg/kg x 5 days vs. SOC (HCQ, AZT, favipiravir)
(8) IVM 12 mg once daily x 3 days vs. SOC
(9) IVM 150-200mcg/kg oral x 2 days + SOC vs. placebo + SOC

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Similar baseline characteristics (selection bias)
(D) Blinding of participants and personnel (performance...
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Blinding of outcome assessment (detection bias)

Figure 1.5. Mortality, by publication status (ITT)



Footnotes
(1) IVM 24mg single dose (arm1) or 12 mg single dose (arm2) vs. placebo
(2) IVM 300 mcg/kg 1x/day for 5 days vs. placebo
(3) IVM 12 mg once daily x 3 days vs. SOC
(4) IVM 150-200mcg/kg oral x 2 days + SOC vs. placebo + SOC

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
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(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Blinding of outcome assessment (detection bias)

Figure 1.6. Mortality, by study quality (ITT)

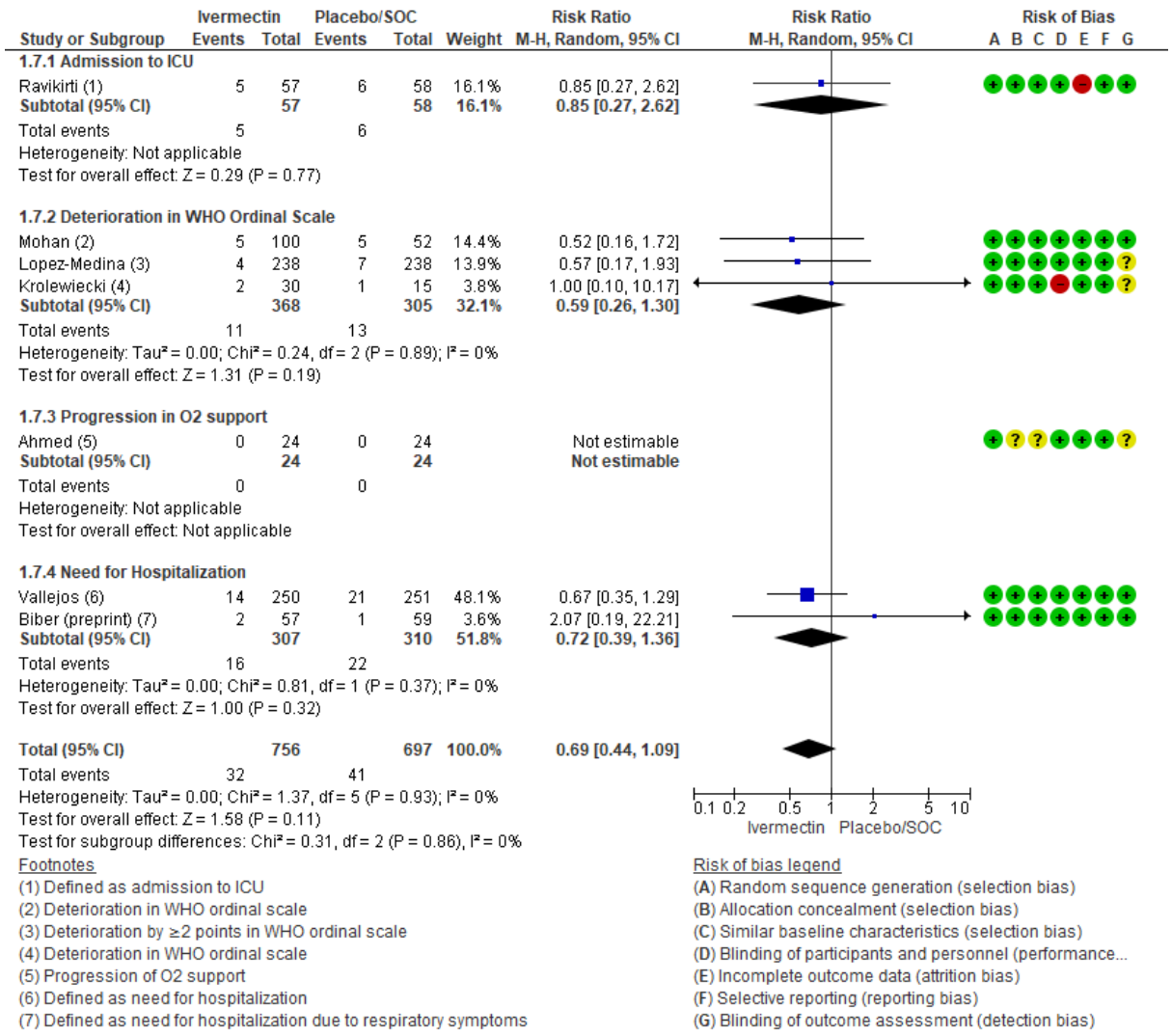


Figure 1.7. Clinical deterioration (ITT)

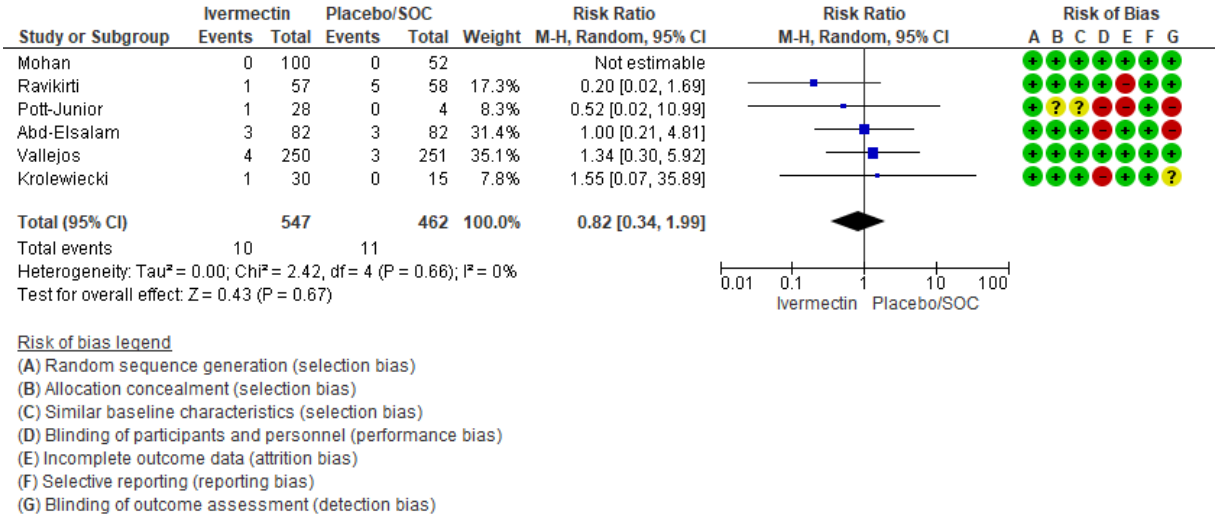


Figure 1.8. Need for mechanical ventilation (ITT)

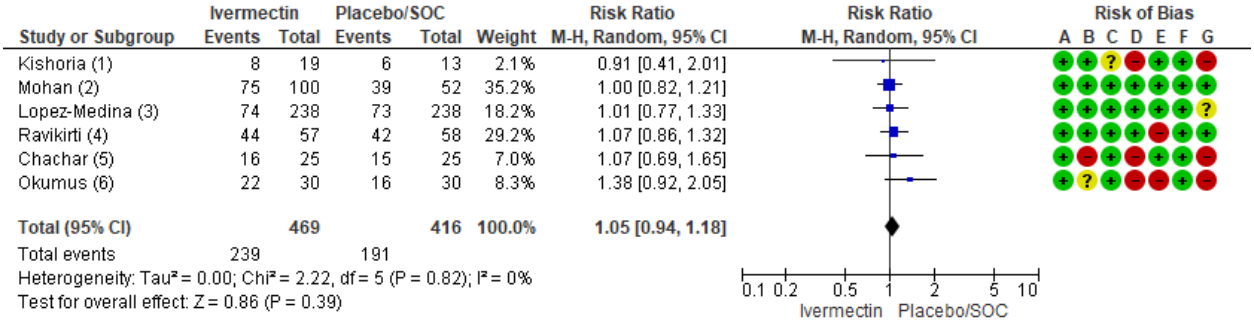


Figure 1.9. Clinical Improvement (ITT)

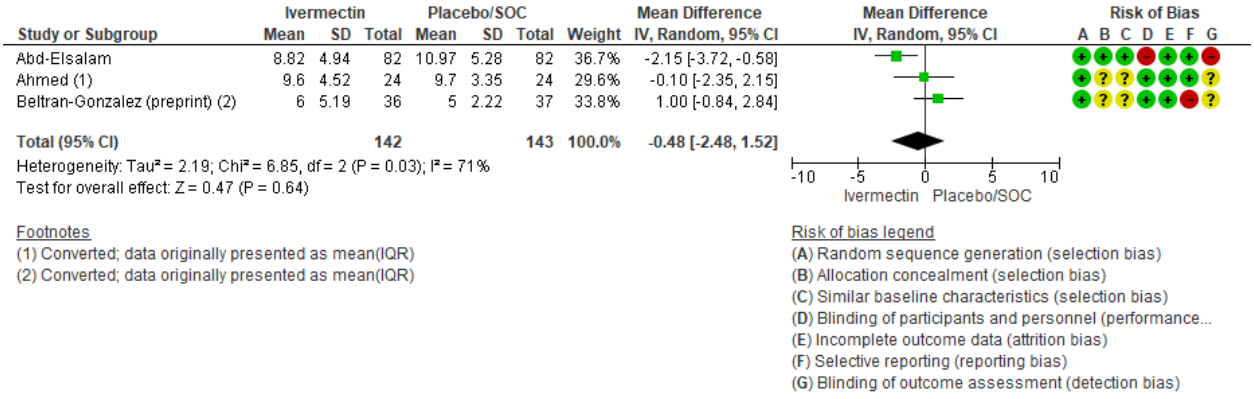


Figure 1.10. Hospital Length of stay (in days, ITT)

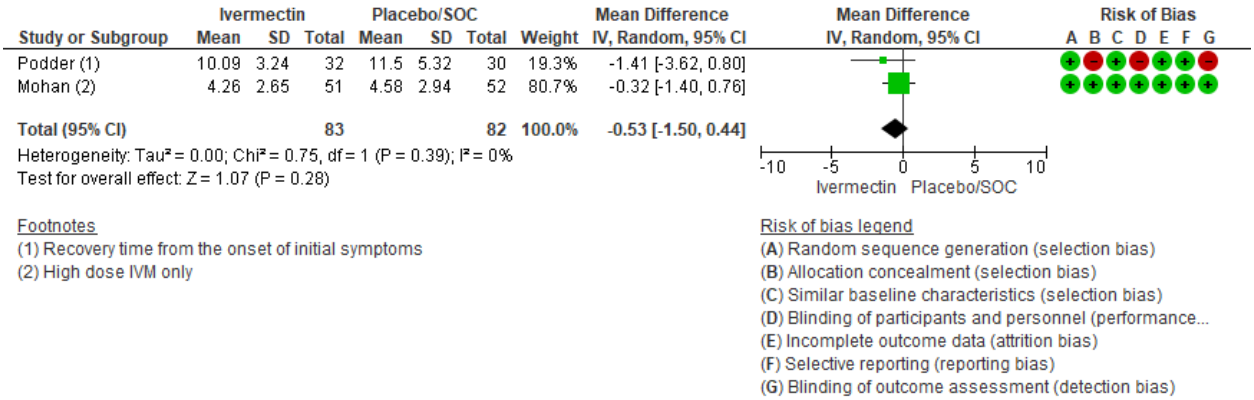


Figure 1.11. Time to symptom resolution (in days)

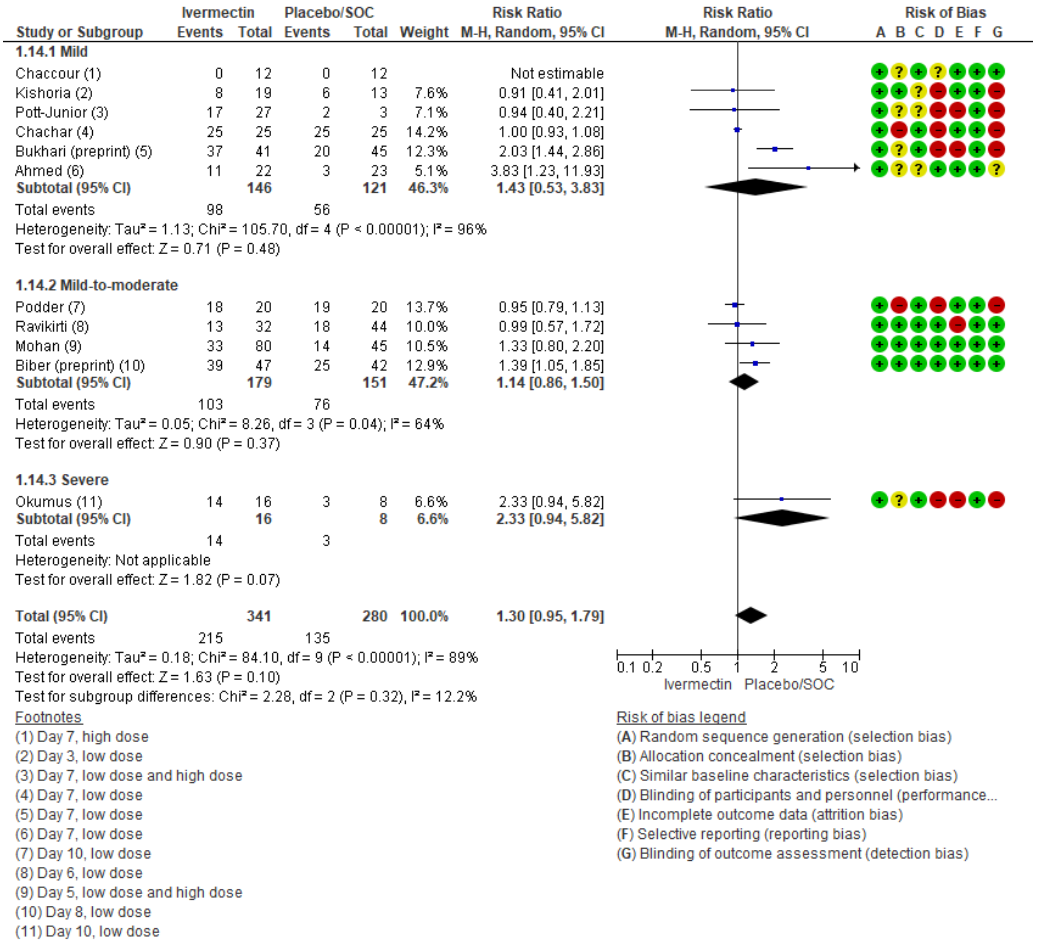


Figure 1.12. Virologic clearance

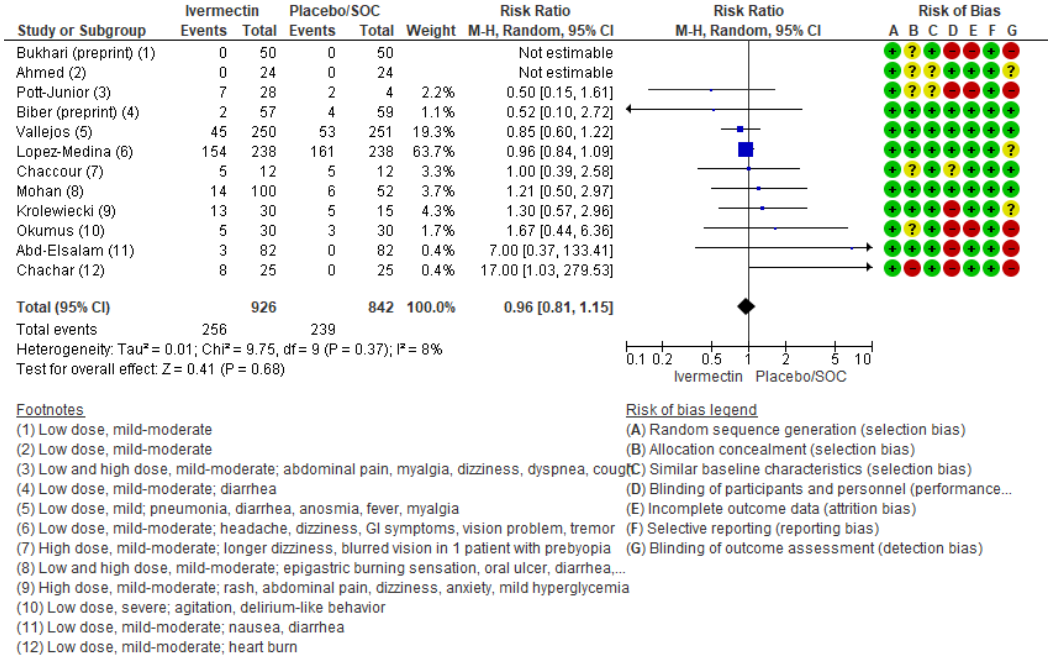
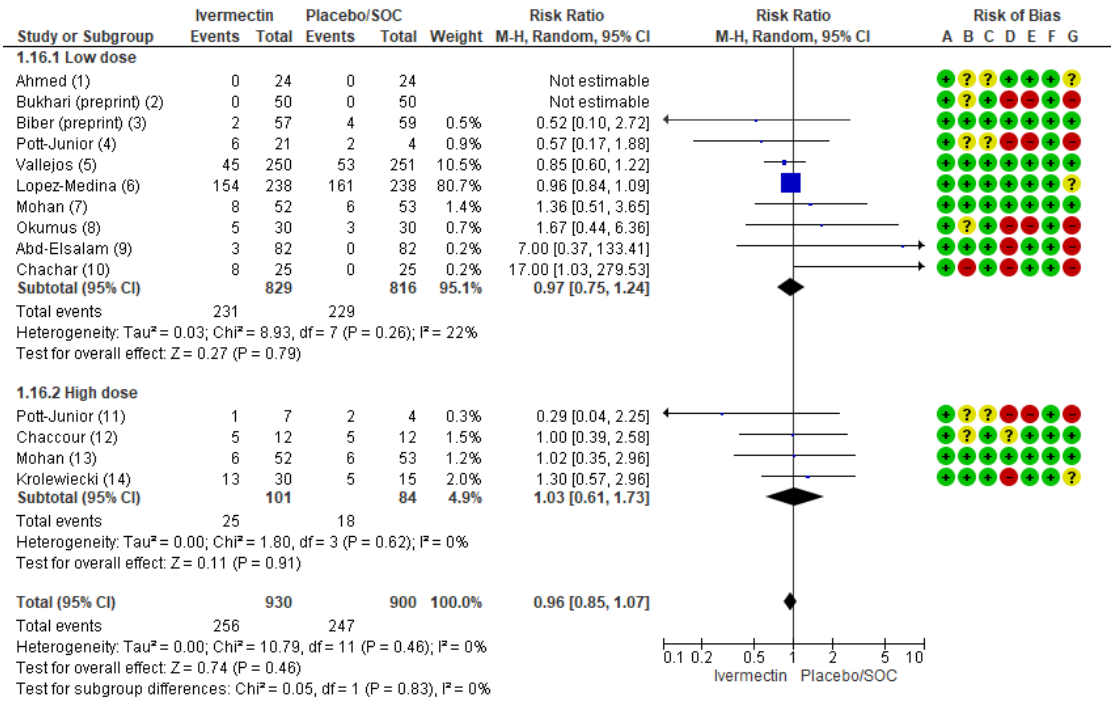


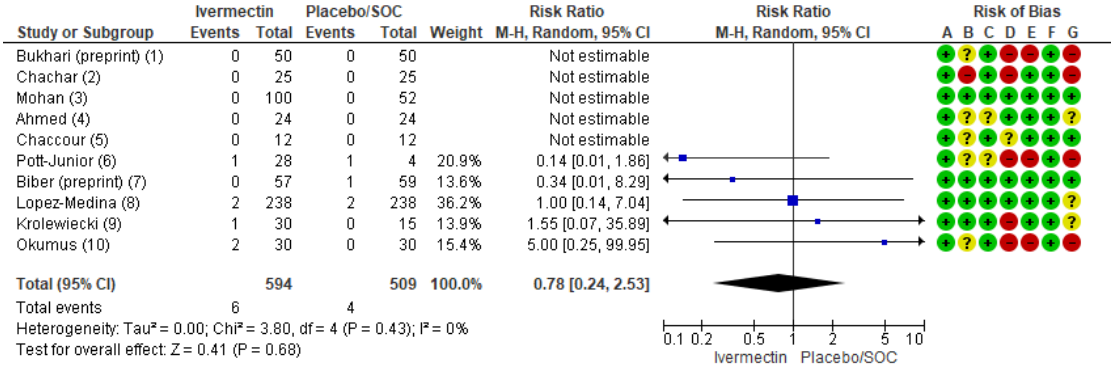
Figure 1.13. Any adverse events (ITT)



Footnotes
(1) Low dose, mild-moderate
(2) Low dose, mild-moderate
(3) Low dose, mild-moderate; diarrhea
(4) Low dose, mild-severe; abdominal pain, dizziness, myalgia, cough, dyspnea, ICU...
(5) Low dose, mild; pneumonia, diarrhea, anosmia, fever, myalgia
(6) Low dose, mild-moderate; headache, dizziness, GI symptoms, vision problem, tremor
(7) Low dose, mild-moderate; epigastric burning, dizziness
(8) Low dose, severe; agitation, delirium-like behavior
(9) Low dose, mild-moderate; nausea, diarrhea
(10) Low dose, mild-moderate; heart burn
(11) High dose, mild-moderate; dizziness
(12) High dose, mild-moderate; longer dizziness, blurred vision in 1 patient with prebyopia
(13) High dose, mild-moderate; epigastric burning sensation, oral ulcer, diarrhea, dizziness
(14) High dose, mild-moderate; rash, abdominal pain, dizziness, anxiety, mild hyperglycemia

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Similar baseline characteristics (selection bias)
(D) Blinding of participants and personnel (performance...
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Blinding of outcome assessment (detection bias)

Figure 1.14. Any adverse events (by dose, ITT)



Footnotes
(1) Low dose, mild-moderate
(2) Low dose, mild-moderate
(3) Low and high dose, mild-moderate
(4) Low dose, mild-moderate
(5) High dose, mild-moderate
(6) Low and high dose, mild-moderate; ICU admission for ventilatory support
(7) Low dose, mild-moderate; sinusitis requiring hospitalization
(8) Low dose, mild-moderate; multiorgan failure (both groups)
(9) High dose, mild-moderate; hyponatremia (unspecified level)
(10) Low dose, severe; agitation, delirium-like behavior requiring admission

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Similar baseline characteristics (selection bias)
(D) Blinding of participants and personnel (performance...
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Blinding of outcome assessment (detection bias)

Figure 1.15. Serious adverse events (ITT)

Appendix 7: Summary of Results of this Review

Outcome	RCTs	Ivermectin	Control	Ivermectin vs. placebo/SOC	Interpretation	Certainty of evidence
Mortality (overall, ITT)	10 RCTs (n=1,718)	2.1% (18/859)	3.4% (27/799)	RR 0.73 [0.42, 1.28]	Inconclusive	⊕⊕◯◯ Low
Mortality based on disease severity						
Mortality (mild, ITT)	4 RCTs (n=1,049)	0.8% (4/524)	0.8% (4/525)	RR 1.05 [0.27, 4.02]	Inconclusive	⊕⊕⊕◯ Moderate
Mortality (mild-to-moderate, ITT)	4 RCTs (n=476)	1.1% (3/269)	3.8% (8/207)	RR 0.43 [0.08, 2.48]	Inconclusive	⊕⊕⊕◯ Moderate
Mortality (severe, ITT)	2 RCTs (n=133)	16.7% (11/66)	22.4% (15/67)	RR 0.74 [0.37, 1.48]	Inconclusive	⊕⊕◯◯ Low
Mortality (low dose, ITT)	8 RCTs (n=1,538)	2.3% (18/766)	3.5% (27/772)	RR 0.73 [0.42, 1.28]	Inconclusive	⊕⊕◯◯ Low
Clinical deterioration (ITT)	7 RCTs (n=1,453)	4.2% (32/756)	5.9% (41/697)	RR 0.69 [0.44, 1.09]	Inconclusive	⊕⊕⊕◯ Moderate
Need for mechanical ventilation (ITT)	6 RCTs (n=1,009)	1.8% (10/547)	2.4% (11/462)	RR 0.82 [0.34, 1.99]	Inconclusive	⊕⊕◯◯ Low
Clinical improvement (ITT)	6 RCTs (n=885)	51.0% (239/469)	45.9% (191/416)	RR 1.05 [0.94, 1.18]	Inconclusive	⊕⊕⊕◯ Moderate
Hospital length of stay (days, ITT)	3 RCTs (n=285)	8.8-9.6 vs 3.4-5.3 MD -0.48 [-2.48, 1.52]			Inconclusive	⊕◯◯◯ Very low
Time to symptom resolution (days, ITT)	3 RCTs (n=165)	4.3-10.1 vs 4.6-11.5 [a] MD -0.53 [-1.50, 0.44] 10 vs 12[b] HR 1.07 [0.87, 1.32]			Inconclusive	⊕◯◯◯ Very low
Virologic clearance (D3-10)	11 RCTs (n=621)	63.0% (215/341)	48.2% (135/280)	RR 1.30 [0.95, 1.79]	Inconclusive	⊕◯◯◯ Very low
Any adverse events (ITT)	12 RCTs (n=1,768)	27.6% (256/926)	28.4% (239/842)	RR 0.96 [0.81, 1.15]	Inconclusive	⊕⊕⊕◯ Moderate
Any adverse events (low dose, ITT)	10 RCTs (n=1,645)	27.9% (231/829)	28.1% (229/816)	RR 0.97 [0.75, 1.24]	Inconclusive	⊕⊕⊕◯ Moderate
Any adverse events (high dose, ITT)	4 RCTs (n=185)	25% (25/101)	21.4% (18/84)	RR 1.03 [0.61, 1.73]	Inconclusive	⊕⊕⊕◯ Moderate
Serious adverse events (ITT)[c]	10 RCTs (n=1,103)	1.0% (6/594)	0.8% (4/509)	RR 0.78 [0.24, 2.53]	Inconclusive	⊕◯◯◯ Very low

[a] Mohan 2021, Podder 2020
[b] Lopez-Medina 2021
[c] six serious adverse events

Appendix 8: Summary of Results of the Cochrane Review

(*Popp et al, 2021*)

Mild (out-patient)	RCTs	Ivermectin vs. placebo/SOC	
All-cause mortality (28 days)	2 RCT Chaccour, Lopez-Medina	RR 0.33 [0.01, 8.05]	⊕◯◯◯ Very low
Need for invasive ventilation (14 days)	1 RCT Lopez-Medina	RR 2.97 [0.12, 72.47]	⊕◯◯◯ Very low
Symptom resolution (up to 14 days)	1 RCT Lopez-Medina	RR 1.04 [0.89, 1.21]	⊕⊕◯◯ Low
Adverse events (28 days)	2 RCT Chaccour, Lopez-Medina	RR 0.95 [0.86, 1.05]	⊕⊕◯◯ Low
Viral clearance at D7	1 RCT Chaccour	RR 3.00 [0.13, 67.06]	⊕⊕◯◯ Low
Moderate to Severe (in patient)	**RCTs**	**Ivermectin vs. placebo/SOC**	
All-cause mortality (28 days)	2 RCTs Beltran-Gonzalez, Ravikirti	RR 0.60 [0.14, 2.51]	⊕◯◯◯ Very low
Need for invasive ventilation (28 days)	2 RCTs Beltran-Gonzalez, Ravikirti	RR 0.55 [0.11, 2.59]	⊕◯◯◯ Very low
Clinical improvement (28 days)	1 RCT Beltran-Gonzalez	RR 1.03 [0.78, 1.35]	⊕⊕◯◯ Low
Adverse events (28 days)	1 RCT Mohan	RR 1.21 [0.50, 2.97]	⊕◯◯◯ Very low
Duration of hospitalization	1 RCT Ahmed	MD -0.10 [-2.43 to 2.23]	⊕⊕◯◯ Low
Viral clearance at D7	2 RCTs Ahmed, Mohan	RR 1.82 [0.51, 6.48]	⊕◯◯◯ Very low