IVERMECTIN

RECOMMENDATION

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

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

We suggest against the use of ivermectin combined with doxycycline for the treatment of patients with COVID-19 *(Very low quality 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

EVIDENCE SUMMARY

Should ivermectin be used in the treatment of patients with COVID-19 infection?

Version: 3 (May 2021)

Evidence Reviewers:

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What's New in this Version (compared to the April 10 version):

1. Now includes 19 RCTs (added 3 RCTs – Chowdhury, Shahbaznejad, Babalola)
2. Inclusion criteria expanded to include studies which compared ivermectin against other active comparators.
3. Separate analyses for different comparisons: (a) ivermectin vs. placebo/standard of care, (b) ivermectin vs. hydroxychloroquine, (c) ivermectin vs. lopinavir/ritonavir, (d) ivermectin+doxycycline vs. placebo/standard of care, (e) ivermectin+doxycycline vs. hydroxychloroquine+azithromycin.
4. Updated data on review methods, risk of bias assessment, PRISMA Flow Diagram, GRADE Evidence Tables, and excluded studies.

Key Findings

Our search yielded 19 randomized controlled trials (RCTs). Ivermectin was compared to placebo or standard of care in 14 RCTs, lopinavir/ritonavir in 1 RCT, and hydroxychloroquine in 2 RCTs. Four RCTs investigated the effect of ivermectin in combination with doxycycline: 3 against placebo or standard of care and 1 against hydroxychloroquine with azithromycin.

No significant mortality benefit was found across all 5 comparisons. For RCTs that compared ivermectin against placebo/standard of care, a mortality reduction was noted only with the use of high dose ivermectin. Heterogeneity assessment revealed no effect of publication status, study quality, or disease severity on mortality.

Shorter time to viral clearance (3-5 days) was reported in studies that compared ivermectin with placebo/standard of care, hydroxychloroquine, and lopinavir/ritonavir. Clinical improvement on day 6-10 was also noted only in studies that used ivermectin combined with doxycycline. Significantly shorter time to symptom resolution was noted from 3 studies that used ivermectin-doxycycline versus placebo/standard of care; however, this combination was also found to result in significantly more adverse events.

Ivermectin did not have any significant effect on clinical deterioration, need for mechanical ventilation, proportion of patients attaining virologic clearance on day 7-14, duration of hospitalization, hospital discharge. The risk of serious and non-serious adverse events were not significantly higher among patients who received ivermectin.

These results must be interpreted in the context of very low certainty of evidence. The quality of evidence was downgraded due to varying degrees of risk of bias in most studies, serious imprecision due to a small number of events and sample sizes as well as wide confidence intervals in the estimates.

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.

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. Currently, it is unknown whether ivermectin can also reduce severity and prevent mortality of COVID-19 when used as therapy.[2]

Although several systematic reviews have already been completed on ivermectin[3–10], with varying eligibility criteria. However, it remains controversial whether ivermectin is indeed effective as a treatment for patients with COVID-19 due to the uncertainty from the results of existing reviews. This systematic review aims to synthesize available literature on the topic.

Review Methods

Eligibility Criteria

The inclusion criteria for this review were as follows:

- **Population:** patients with COVID-19 without restrictions to severity, age, gender
- **Intervention:** ivermectin or ivermectin combined with doxycycline or other drugs, used as a treatment or an adjunct to standard treatment
- **Comparator:** placebo, any active control (standard of care), or no intervention
- **Outcomes:** mortality, clinical deterioration, need for mechanical ventilation, hospital length of stay, time to clinical improvement, radiologic improvement, virologic clearance by RT-PCR, adverse events
- **Study design:** randomized controlled trials (RCTs)

Observational studies or quasi-randomized trials were excluded. In the initial version of this review, the intention comparison was limited to ivermectin versus placebo/standard of care. However, we have expanded the inclusion criteria to include studies which compared ivermectin against other active comparators.

Information Sources and Search Strategies

We conducted an initial systematic search of various information sources up to 04 April 2021; this search was last updated on 15 May 2021. The full search strategy used for each source is detailed in **Appendix 1**. We included electronic databases (MEDLINE, Cochrane COVID-19 Study Register, COVID-19 LOVE Evidence/Epistemonikos), preprint databases (MedRxiv, BioRxiv, ChinaXiv), trial registries (Chinese Clinical Trial Registry

[http://www.chictr.org.cn/searchprojen.aspx], WHO International Clinical Trials Registry [https://ictrptest.azurewebsites.net/Default.aspx]. Included studies from other living guidelines/systematic reviews on COVID-19 were also checked (COVID-19 Open Living Evidence Synthesis to Inform Decision (https://covid-nma.com/), Australian National COVID-19 Clinical Evidence Taskforce Living Guidelines (https://covid19evidence.net.au/), WHO Covid-19 Living Guidelines (https://app.magicapp.org/#/guideline/nBkO1E).

Reference lists or related systematic reviews on ivermectin[3–10] and from websites including IVMMeta were considered and included in the current review as long as they provided sufficient information to allow critical appraisal. As appropriate, authors of potentially eligible studies for this review were contacted via email to obtain data.

Selection Process

Two researchers (MJ and JB) independently screened titles and abstracts of all records and discussed inconsistencies. Both researchers independently assessed full-text articles for inclusion. In case of disagreement, consensus on inclusion or exclusion was reached by discussion and consultation with a third reviewer (HB) to make the final decision.

Data collection process, Data items

At least two researchers independently extracted data from each included study. Values were reviewed by a third or fourth author to assess accuracy. We collected information regarding the study characteristics (peer-review status, author, country, setting), participants (COVID-19 severity level, age), and interventions (dose, schedule, standard of care type, other active interventions). Outcomes collected included the following:

- Mortality
- Adverse events
- Virologic clearance (PCR negativity)
- Clinical deterioration
- Need for mechanical ventilation
- Clinical improvement
- Hospital discharge
- Time to viral negative conversion (in days)
- Duration of Hospitalization (in days)
- Time to symptom resolution (in days)

Study risk of bias assessment

We assessed the overall risk of bias in the included studies using the tool from the Randomized Controlled Trials: Painless Evidence Based Medicine Questions. The following domains were assessed:

(1) Were patients randomly assigned to treatment groups?
(2) Was allocation concealed?
(3) Were baseline characteristics similar at the start of the trial?
(4) Were patients blinded to treatment assignment?

(5) Were caregivers blinded to treatment assignment?
(6) Were outcome assessors blinded to treatment assignment?
(7) Were all patients analyzed in the group to which they were originally randomized?
(8) Was follow-up rate adequate?

An additional domain on whether the study was published in a peer-reviewed journal was included because many COVID-19 studies are published as pre-prints while awaiting peer review in response to the pandemic.

Two review authors (MG and HB) independently applied the tool to each included study and recorded supporting information and justifications for judgements of risk of bias for each domain (Yes; No; Unclear). Any discrepancies in judgements of risk of bias or justifications for judgements were resolved by discussion to reach consensus between the two review authors, with a third review author (DT) acting as an arbiter if necessary. We derived an overall risk of bias judgment (very serious, serious, and not serious) for all the studies included for individual outcomes.

Effect measures

We estimated the risk ratio (RR) and its 95% confidence interval (CI) after treatment with Ivermectin or in combination with doxycycline compared with placebo or standard of care for the following dichotomous outcomes. For continuous outcomes, mean difference (MD) and its 95% confidence interval (CI) were used for the following.

Synthesis methods

In cases where the median and interquartile ranges (IQRs) were reported, but not the standard deviations, the medians were assumed to be equal to the mean and the IQRs were approximately 1.35 standard deviations, as specified in the Cochrane Handbook[11].

In some studies, we have combined two intervention arms that employed slightly different doses of ivermectin according to low dose or high dose intervention groups and compared that to the control for a given outcome (studies).

For studies that did not report their mortality outcomes as intention-to-treat, we assumed the best case scenario based on the sample size at randomization and performed a sensitivity analysis for this outcome.

For the outcome of clinical deterioration, some studies reported clinical deterioration and mortality as mutually exclusive events. We reported clinical deterioration as the number of patients who deteriorated including those who died.

All results are presented in summary tables and forest plots. We developed an 'Evidence Profile' table using GRADEpro GDT to summarize effect estimates per outcome and the corresponding certainty assessment based on the number of studies, study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations. Number of patients in both the treatment group and control group were also presented. Overall certainty of evidence and justifications for each outcome with effect size estimates based on relative risk ratio (RR), mean difference (MD),

and 95% confidence interval (CI) were also reported. Random-effects models were used for all meta-analyses.

Subgroup analyses were done according to ivermectin dose used and/or COVID-19 disease severity especially for mortality and adverse events. To assess evidence of heterogeneity among the study-level effects, forest plots were carefully examined and I^2 estimates were calculated. Separate analyses were done for each type of comparison (e.g. ivermectin vs. placebo/SOC, ivermectin vs. other active control) to better account for heterogeneity.[12–14] We also performed sensitivity analysis to assess the robustness of the results when studies with serious risk of bias concerns were excluded.

Certainty assessment

The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) Approach was used to assess the certainty of evidence for each of the study outcomes. GRADE Evidence Profiles for each PICO are included in **Appendix 7**. Certainty of evidence was downgraded when issues related to risk of bias, imprecision, indirectness, inconsistency, and publication bias were present.

Results

Study selection

The initial search (04 April 2021) yielded 365 records, which we collated and de-duplicated in MS Excel. After de-duplication, 303 unique records remained. The updated search on 15 May 2021 yielded 92 additional records with no de-duplication done. **Appendix 4** shows the PRISMA flow diagram while **Appendix 3** tabulates all excluded studies with corresponding reasons for exclusion.

Study characteristics

As of 15 May 2021, we found 19 randomized controlled trials (RCTs)[15–33] (N=2226) that used ivermectin as treatment for adults with COVID-19. The trials were performed in Bangladesh[15,20,23,25], Spain[16], Pakistan[18,26], Egypt[27], Nigeria[21], Argentina[28], India[29,32], Iran[22,30], Turkey[31], Mexico[19], Brazil[33], Colombia[17], Iraq[24]. Sample sizes ranged from 20 to 473. Eight of the 19 studies[18,19,24,27–30,32] (42%) were still pre-prints and have not yet been peer-reviewed. Detailed characteristics of the included studies are summarized in **Appendix 2.**

Sixteen RCTs compared ivermectin against different comparison interventions: 14 used placebo or standard of care[15–20,22,26,28–33], 2 used hydroxychloroquine[19,27], and 1 used lopinavir/ritonavir[21]. Four RCTs investigated the effects of ivermectin combined with doxycycline: 3 against placebo or standard of care[15,23,24] and 1 against hydroxychloroquine with azithromycin[25]. Participants in the included studies had varying severity of COVID-19: 6 RCTs for mild, 5 RCTs for mild-to-moderate, 3 RCTs for severe, 6 RCTs for mixed non-severe and severe cases.

Seventeen RCTs compared ivermectin with placebo/standard of care. Different treatment regimens of ivermectin were used: 15 RCTs used low dose (200mcg/kg or 12mg and lower) while 7 RCTs used high dose ivermectin (400-600mcg/kg or 24 mg or higher). Duration of ivermectin

treatment ranged from 1-28 days. Nine studies were placebo-controlled while 9 used the existing standard of care in their country.

Risk of bias in studies

Risk of bias was rated very serious in 10/19 studies and serious in 6/19 studies. Only 3 trials (Mohan et al., 2020; Lopez-Medina et al., 2021; Babalola et al. 2021) were considered to have no serious risk of bias. At least 25% 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 5** provides details of the individual risk of bias ratings.

Certainty of evidence

Assessments of certainty of evidence per comparison are detailed in the **Appendix 7 (GRADE Evidence Tables).** The overall certainty of evidence was rated very low for most of the outcomes including mortality and adverse events; low for hospital discharge at day 10-14, number of symptomatic days, and virologic clearance/negative PCR at day 6-10; moderate for clinical improvement at day 6-10 and mean days to symptom resolution. The quality of evidence was downgraded due to varying degrees of risk of bias in most studies, serious imprecision due to a small number of events and sample sizes as well as wide confidence intervals in the estimates, and/or serious inconsistency in results due to moderate heterogeneity.

Comparison 1: Ivermectin vs. placebo or standard of care

Mortality

Based on 10 RCTs, ivermectin was reported to reduce overall mortality among COVID-19 patients compared to placebo or standard of care (16/640 (2.5%) for ivermectin vs 31/518 (6.0%) for control) (RR 0.48 [95% CI 0.23, 0.99], n=1,158). The certainty of this estimate for this outcome is affected by risk of bias concerns in most (8/10) of the studies and imprecision (i.e., using intention-to-treat data resulted in 95% CI of 0.23 to 1.00).

Of all the 10 RCTs included for this comparison, only the trial by Niaee et al.[30] reported a reduction in mortality (3.3 vs. 18.3%; RR 0.18 [95% 0.06, 0.55]), n=180). This study had serious risk of bias due to possible non-blinding of patients and caregivers, differences in baseline characteristics in the experimental versus placebo group (i.e., more patients with negative RT-PCR results in placebo). Due to these concerns related to risk of bias as well as serious imprecision, the quality of evidence was downgraded to very low.

High dose ivermectin was associated with significant mortality reduction (0.7% vs. 10.1%, RR 0.05 [95% CI 0.01, 0.34] I^2=0%, n=262) based on 4 RCTs. Only the RCT by Niaee et al. contributed to this finding as the other 3 RCTs reported no deaths for all participants. Statistical analysis for heterogeneity showed that the effect estimates for mortality were significantly influenced only by dose (P = 0.04) and not by publication status (P = 0.33), study quality (P = 0.89), or disease severity (P = 0.63).

Clinical outcomes

The effects of ivermectin were not different from placebo/SOC with regard to clinical improvement on day 6-10 (51 vs 50%; RR 1.01 [95% CI 0.87, 1.16], n=620), clinical deterioration (5 vs 7.5%; RR 0.74 [95% CI 0.45, 1.23], n=871), need for mechanical ventilation (2 vs 3.7%; RR 0.67 [95% CI 0.19, 2.39], n=407), hospital discharge at day 10-14 (88 vs 79.4%; RR 1.08 [95% CI 0.97,

1.21], n=237), and duration of hospitalization (mean difference (MD) -1.01[95% CI -2.36, 0.34] I^2=74%).

Viral clearance

Very low certainty evidence from 9 RCTs showed that the proportion of patients showing virologic clearance on day 6 to 10 (60 vs. 48%; RR 1.22 [95% CI 0.90, 1.65] I^2=84%; n=476) did not differ between the ivermectin and control groups. Disease severity did not affect these results (*P* = 0.33). Only the study by Ahmed et al. documented an advantage for low dose ivermectin over placebo for viral clearance (RR 3.83 [95% 1.23, 11.93]). This study also concluded a shorter time to PCR negativity for ivermectin (9.7 vs 12.7 days; MD -3.0 days [95% CI -4.71, -1.29]. This study, however, had a small sample size (n=24 for each arm) and unclear allocation concealment methods and data on baseline characteristics.

Table 1. Summary of results.

Outcome	Ivermectin vs. placebo/SOC	Ivermectin vs. hydroxychloroquine	Ivermectin vs. lopinavir/ritonavir	Ivermectin+doxycycline vs. placebo/SOC	Ivermectin+doxycycline vs. HCQ+AZT
Mortality (overall)	2.5% vs. 6.0% RR 0.48 [0.23, 0.99]	3.0% vs 11.2% RR 0.32 [0.03, 3.25]	0/42 vs 0/20 Not estimable	0.7% vs 3.3% RR 0.28 [0.07, 1.10]	0/60 vs 0/56 Not estimable
Mortality (mild)	0% vs 0.4% RR 0.33 [0.01, 8.05]				
Mortality (mild-to-moderate)	0% vs. 3.2% RR 0.12 [0.01, 2.09]	0% vs 4% RR 0.11 [0.01, 2.04]		0% vs 1.1% RR 0.14 [0.01, 2.75]	
Mortality (severe)	16.7% vs. 22.4% RR 0.74 [0.37, 1.48]	5.1% vs 11.2% RR 0.47 [0.02, 10.69]		9.1% vs. 27.3% RR 0.33 [0.08, 1.47]	
Clinical improvement (D6-10)	51% vs 50% RR 1.01 [0.87, 1.16]			60.7% vs. 44.4% RR 1.36 [1.12, 1.67]	45% vs. 25% RR 1.80 [1.06, 3.07][a]
Time to symptom resolution (days)	4.3-10.1 vs 4.6-11.5 days MD -0.83 [-1.49, -0.17] 10 vs 12[d] HR 1.07 [0.87, 1.32]			10.6 vs 17.9 days MD -7.3 [-9.31, -5.27][b] 7 vs. 9 days HR 0.73 [0.60, 0.90][c]	5.93 vs. 6.99 MD -1.06 [-2.21, 0.09]
Clinical deterioration	5% vs. 7.5% RR 0.74 [0.45, 1.23]	6.4% vs. 35.2% RR 0.20 [0.03, 1.47]		6.9% vs. 14.3% RR 0.48 [0.29, 0.81]	
Need for mechanical ventilation	2% vs 3.7% RR 0.67 [0.19, 2.39]				
Virologic clearance (D7-14)	59.8 vs 48% RR 1.22 [0.90, 1.65]			85.4% vs. 72.4% RR 0.57 [0.23, 1.43]	100% vs 96% RR 1.04 [0.98, 1.10]
Time to PCR negativity (days)	9.7 vs 12.7 days MD -3.0 [-4.71, -1.29]	5 vs 10 days (mild-to-mod); 6 vs 4 (severe) MD -5.50 [-6.48, -4.52]	5.33 vs. 9.15 days MD -3.82 [-7.21, -0.43]	11.5 vs. 12.7 days MD -1.20 [-2.55, 0.15]	
Duration of hospitalization (days)	5-9.6 vs 5-9.7 days MD -1.01 [-2.36, 0.34]	6 vs. 7 days MD -1.0 [-3.27, 1.27]		10.1 vs. 9.7 days MD 0.40 [-1.71, 2.51]	
Hospital discharge	88% vs. 79.4% RR 1.08 [0.97, 1.21]	88.8% vs. 90.9%[e] RR 0.98 [0.83, 1.15]			
Serious adverse events	1.1% vs. 6.9% RR 0.91 [0.23, 3.58]			0.97% vs 0% RR 4.92 [0.24, 101.74]	
Any adverse events	39.3% vs. 41.4% RR 1.05 [0.75, 1.47]		0/42 vs 0/20 Not estimable	4.4% vs. 0% RR 18.69 [1.10, 318.65]	31.7% vs. 46.4% RR 0.68 [0.43, 1.09]

[a] Symptom resolution on D5; [b] Hashim 2021; [c] Mahmud 2021; [d] Lopez-Medina 2021; [e] Unspecified follow-up period

Time to symptom resolution, number of symptomatic days

Although pooled results from 3 RCTs[20,22,29] showed a shorter time to symptom resolution associated with ivermectin (MD -0.83 days [95% CI -1.49, -0.17]), this effect remains uncertain. One of these RCTs (Mohan et al.) with high methodological quality reported no significant benefit (MD -0.32 [95% CI -1.51, 0.87]). Another RCT with a larger sample size (Lopez-Medina et al., 2021) reported an absolute difference of 2 days, with a non-significant hazard ratio (HR 1.07 [95% CI 0.87, 1.32]).

Low quality evidence from 1 RCT[16] suggested that ivermectin may significantly reduce the number of symptomatic days in mild-moderate cases by 30% (RR 0.70, 95% CI [0.63 to 0.78]; n=577). This study had unclear blinding of participants and investigators as well as allocation concealment.

Comparison 2: Ivermectin vs. hydroxychloroquine

Two RCTs used ivermectin and compared its effects against hydroxychloroquine (400 mg 2x/day on day 1, 200 mg 2x/day for 4-5 days). Beltran-Gonzalez et al. used low dose ivermectin on 69 patients with severe COVID-19 while Elgazzar et al. used high dose ivermectin on patients with mild-moderate and severe illness (n=100 each). Both RCTs had very serious risk of bias issues due to unclear randomization or allocation concealment methods, dissimilar baseline characteristics (i.e., enrolling more patients with ischemic heart disease in the control group--2% vs. 6% for mild-to-moderate, 5% vs. 12% in severe group), and absence of blinding for assessors, investigators, and patients.

Although pooled results showed fewer deaths among patients who received ivermectin compared to hydroxychloroquine (3 vs 11.2%), this was not found to be statistically significant (RR 0.32 [95% CI 0.03, 3.25]). Subgroup analysis by disease severity showed no significant mortality benefit for patients with non-severe (RR 0.11 [95% CI 0.01, 2.04] and severe COVID-19 (RR 0.47 [95% CI 0.02, 10.69], I^2=88%). Inconsistent findings were noted from both trials that enrolled severe cases, with mortality benefit being reported only in the study Elgazzar et al. that used high doses of ivermectin (2 vs. 20%; RR 0.01 [95% CI 0.02, 0.42]).

Elgazzar et al. also reported results favoring ivermectin in terms of clinical deterioration for both mild-to-moderate (1 vs. 26%, RR 0.04 [95% CI 0.01, 0.28]) and severe cases (6 vs. 50%, RR 0.12 [95% CI 0.05, 0.27]). Conflicting findings were again noted by Gonzalez et al. which concluded no significant benefit associated with ivermectin for severe patients (22 vs 18%; RR 0.38 [0.04,3.90]). Shorter viral clearance time with ivermectin was noted by Elgazzar et al. with a mean difference of 5.5 days between groups (MD -5.50 [95% CI -6.48, -4.52]).

Ivermectin did not significantly affect duration of hospitalization (6 vs 7 days; MD -1.0 [95% CI -3.27, 1.27]) and hospital discharge (89 vs 91%; RR 0.98 [95% CI 0.83, 1.15]). None of the 2 RCTs reported data on adverse events.

Comparison 3: Ivermectin vs. lopinavir/ritonavir

An RCT from Nigeria that enrolled 62 patients with mild-to-moderate COVID-19 investigated the effect of two different IVM doses (6 mg and 12 mg given every 84 hrs for 2 wks) versus lopinavir/ritonavir (daily for 2 weeks). This study had no serious risk of bias issues.

No deaths nor adverse events were documented in all patients. Ivermectin was associated with significantly shorter time to SARS-CoV-2 negativity compared to LPV/r (5.3 vs. 9.2 days; MD -3.82 [95% CI -7.21, -0.43]. Ivermectin was 3.45 more likely (95% CI 1.12, 10.63; *P* = 0.0271) to induce negativity by day 5 compared to LPV/r.

Comparison 4: Ivermectin+doxycycline vs. placebo/standard of care

Mortality, duration of hospitalization, virologic clearance

Based on very low certainty evidence from 3 RCTs, the mortality rate in the ivermectin+doxycycline group did not significantly differ with the control group (2/276 (0.7%) vs. 6/273 (2.2%); RR 0.28 [95% CI 0.07, 1.10] I^2=0%, n=549). This effect was observed for both patients with mild-to-moderate (RR 0.14 [95% CI 0.01, 2.75) I^2=0%, 3 RCTs, n=508) and severe illness [19] (RR 0.33 [95% CI 0.08, 1.47], n=44) (Figure 2.2). No significant benefit was also noted for the following outcomes: duration of hospitalization (MD 0.40 days [-1.71, 2.51], virologic clearance on D7-14 (RR 0.57 [95% CI 0.23, 1.43]) and time to PCR negativity (MD -1.20 [95% CI -2.55, 0.15]).

Clinical recovery, clinical deterioration, time to symptom resolution

The RCT by Mahmud et al. reported a significantly higher proportion of patients showing clinical recovery on day 6-10 compared to placebo (111/183 (60.7%) vs. 80/180 (44.4%); RR 1.36 [95% CI 1.12, 1.67], n=363). Both groups had comparable recovery rates on day 12 (77% in IVM+DOX vs. 80% in placebo group). Ivermectin+doxycycline also showed benefit in terms of preventing clinical deterioration (6.9 vs 14.3%; RR 0.48 [95% CI 0.29, 0.81], n=549, 3 RCTs), and shortening time to symptom resolution by 7.3 days [95% CI -9.31, -5.27] in Hashim et al. and 2 days (HR 0.73 [95% CI 0.60, 0.90]) in Mahmud et al.

Comparison 5: Ivermectin+doxycycline vs. hydroxychloroquine (HCQ) +azithromycin (AZT)

One RCT from Bangladesh (Chowdhury et al. 2021) compared the effect of ivermectin plus doxycycline against HCQ plus AZT among 125 adult out-patients with mild or asymptomatic COVID-19. The experimental group received low dose ivermectin (200 mcg/kg, single dose) combined with doxycycline (100 mg twice daily for 10 days), while the comparison group received HCQ (400 mg on day 1, then 200 mg twice daily for 9 days) plus AZT (500 mg daily for 5 days). All patients were also given symptomatic treatment for fever, headache, cough, myalgia, etc. This study had a very serious risk of bias due to issues related to randomization techniques used (i.e. odd-even date), unblinded assessors, and unclear blinding of patients and investigators as well as allocation concealment methods.

Mortality, clinical resolution

No deaths were reported in all study participants. A significantly higher proportion of patients exhibited resolved symptoms on day 5 in the ivermectin-doxycycline group compared to the HCQ+AZT group (27/60 (45%) vs.14/56 (25%); RR 1.80 [95% CI 1.06, 3.07]).

No statistically significant differences were noted for other outcomes: time to symptom resolution (5.9 vs. 7.0 days; *P* = 0.07), viral negativity on day 7 (100% vs. 96.4%; *P* = 0.23), and adverse effects (19/60 (31.7%) vs. 26/56 (46.4%); *P* = 0.11).

Safety outcomes / Adverse events

Ivermectin
Based on 10 studies, the ivermectin was not associated with an overall increased risk of any adverse events compared to placebo or standard of care (36.4% vs. 39.7%; RR 1.05 [95% CI 0.75, 1.47] I^2=26, n=1025). Studies which compared ivermectin with LPV/r reported no adverse events for all patients, while studies on ivermectin versus HCQ have not included adverse events data in their results.

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. Serious adverse events related to ivermectin were hyponatremia (n=1; low dose, mild-moderate COVID) (Krolewiecki et al. 2020) and delirium-like behavior (n=2; low dose, severe COVID) (Okumus et al., 2021) in patients who were tested to have mutations affecting ivermectin metabolism.

Subgroup analysis for adverse events according to dose showed no significant difference between high (25% vs. 21.7%; RR 1.03 [95% CI 0.61, 1.73], I^2=0%, n=183) and low dose ivermectin (38.8% vs. 39.8%; RR 1.15 [95% 0.65, 2.06], I^2=46%, n=898).

Ivermectin with doxycycline
Significant harm was noted from low dose ivermectin+doxycycline in 2 RCTs (4.4% vs. 0%; RR 18.7 [95% CI 1.10, 318.75], n=409). Two serious adverse events (erosive esophagitis) and 7 other adverse events (non-ulcer dyspepsia) only occurred in the ivermectin+doxycycline group, although evidence is insufficient to conclude whether the drug combination is indeed associated with serious adverse events (RR 4.92 [95% CI 0.24, 101.74]).

Recommendations from Other Groups

The **US NIH** (11 Feb 2021) currently states: *"There are **insufficient data** for the Panel to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19."* Key limitations identified in studies included a small sample size, varying doses and schedules of ivermectin, potential confounding effect of concomitant medications given to patients, and incomplete description of outcomes and patient characteristics. The NIH guideline has not been updated since 11 February 2021.

The **Infectious Diseases Society of America (IDSA)** (13 Feb 2021)[34] suggests ***against*** the use of ivermectin for both outpatient/mild-to-moderate and hospitalized/severe COVID-19 cases unless in the context of a clinical trial (very low certainty of evidence, conditional recommendation). This IDSA recommendation was based on 7 RCTs and 2 non-randomized trials. This recommendation has not changed since 18 March 2021.

Other living guidelines / evidence syntheses do not recommend the use of ivermectin for treatment of COVID-19.

The **Australian COVID-19 Living CPG** (20 May 2021) ***does not recommend*** the use of ivermectin outside of trials[35]. This recommendation was based on very low certainty evidence from 13 RCTs. Ivermectin is not recommended to be used for special populations, including

children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care, unless further trials become available.

The **WHO living guideline on COVID-19 therapeutics** (31 March 2021) ***does not recommend*** using ivermectin in patients with COVID-19 except in the context of a clinical trial.[36] This recommendation applies to patients with any disease severity, any duration of symptoms. Seven RCTs informed this recommendation. The guideline further states that the current evidence has a high degree of uncertainty, with included trials having enrolled substantially fewer patients with far fewer events compared to other drug trials (e.g., corticosteroids, hydroxychloroquine, lopinavir/ritonavir).

Covid Guidelines India (15 May 2021) recommends ***against*** using ivermectin for treatment of patients with any severity of COVID-19 (non-severe, severe, critical).[37] This was a conditional recommendation based on very low certainty evidence from 12 RCTs. Further trials were deemed necessary to ensure its efficacy and safety as its effects are very uncertain with regard to mortality, progression to mechanical ventilation, time to achieving negative PCR for SARS-CoV-2 and adverse events. 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"*.

Research Gaps

As of 25 May 2021, there are at 97 ongoing clinical trials investigating the efficacy of ivermectin as treatment for COVID-19 that are listed in COVID-19 NMA database.[38]

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Appendix 1: Search Strategy (as of 15 May 2021)

Information Source	Search Strategy	Results
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])"	April 4: 166 May 15: +23
Cochrane COVID-19 Study Register	"Ivermectin"	April 4: 33 May 15: +4
MedRxiv	Advanced search: "Ivermectin AND COVID" with "match all" parameters	April 4: 96 May 15: +12
BioRxiv	Advanced search: "Ivermectin AND COVID" with "match all" parameters	April 4: 32 May 15: +3
ChinaXiv	Advanced search: "Ivermectin AND COVID" with "all fields" parameters	April 4: 0 May 15: 0
COVID-19 LOVE / Epistemonikos	Under "By PICO", the search syntax "Ivermectin" was used within "prevention or treatment" category. Results filtered to "RCT" and "Reporting data"	May 15: 50
Chinese Clinical Trial Registry	Under trial search (with more option), the search syntax "Ivermectin", under intervention and "COVID-19", under target disease was used	April 4: 1 May 15: +0
WHO ICTRP	The search syntax "Ivermectin" was used. Results were filtered to "Restrict to COVID-19"	April 4: 6 May 15: +0
Living Guidelines	Records were selected from three living guidelines (WHO Living Guidelines, Australian CPG, COVID-19 NMA)	April 4: 31 May 15: +0

Appendix 2: Characteristics of Included Studies

Table 1.1. Ivermectin versus placebo or standard of care (14 RCTs).

No.	Clinical Trial ID/ Title	Country	Study design	Population	Intervention	Comparator	Outcomes
1	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) Treatment	Mild COVID-19 Age 18 to 65 years Hospitalized w/in the last 7 days; w/ either fever (≥37.5C); cough or sore throat; and diagnosed positive for SARS-CoV-2 by rRT-PCR.	Oral ivermectin, 12 mg once daily 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 *Follow up 14 days*
2	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) Treatment	Mild COVID-19 Age 18 to 59 years Outpatient setting. Without comorbidities considered as risk factors to develop severe disease or COVID-19.	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 *Follow up 28 days*
3	Chachar 2020 Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients	Pakistan	Open-label RCT (N=50) Treatment	Mild COVID-19 Age 18 to 75 years excluded severe COVID-19, with malignancy, chronic kidney disease, and liver cirrhosis	3 dose regimen of oral ivermectin 12mg, 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 *Follow up 7 days*
4	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) Adjunct	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) for 5 days Co-Intervention: Standard care [n=30] High dose ivermectin	Standard care [n=15] Standard care: uncertain	1. Mortality 2. Clinical deterioration 3. Adverse effects *Follow up 30 days*

5	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 *Follow up 14 days*
6	Niaee 2020 Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial	Iran	Double blind RCT (N=180) Adjunct	Mild-Severe COVID-19 Age 18 years and older excluded patients who are immunocompromised, pregnant women; have chronic kidney disease; malignancy	Single 1 day low dose oral ivermectin (200mcg/kg) OD Co-intervention: Standard care [n=30] 3 day low dose oral ivermectin (200mcg/kg) OD on D1, D3, and D5 Co-intervention: Standard care [n=30] Single 1 day high dose ivermectin (400mcg/kg) OD Co-intervention: Standard care [n=30] 3 day high dose ivermectin (400, 200, 200mcg/kg), 4 pills in D1, D3, and D5 Co-intervention: Standard care [n=30] Low dose and high dose ivermectin	Placebo [n=30] Standard care [n=30] Standard care: oral hydroxychloroquine (HCQ) 200 mg/kg twice per day as standard regimen and a heparin prophylaxis in combination with supplemental oxygen.	1. Mortality 2. Duration of hospitalization 3. Clinical improvement *Follow up 45 days*

7	Okumuş 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 for 5 days [n=30] Co-intervention: Standard care Low dose ivermectin	Standard care [n=30] Standard care: Hydroxychloroquine, favipiravir and azithromycin (HFA) HCQine (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) (HFA),	1. Mortality 2. Clinical improvement 3. Viral clearance D10 4. Adverse effects *Follow up 90 days*
8	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) Adjunct	Mild-Moderate COVID-19 Age 18 years and older	Oral ivermectin 12mg on D1 and D2 Co-intervention: standard care [n=57] 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 *Follow up 10 days*
9	Pott-Junior 2021 Use of ivermectin in the treatment of COVID-19: a pilot trial	Brazil	Open-label RCT (N=32)	Mild-severe Age 18 years and older	SOC + Ivermectin a. 100mcg/kg (n=6) b. 200mcg/kg (n=14) c. 400mcg/kg (n=7)	SOC (n=4)	1. Viral clearance (% patients with 2 negative PCR tests w/in 7 days) 2. Adverse events
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 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. Deaths
11	Bukhari 2021 Efficacy of ivermectin in COVID-19 patients with mild to moderate disease	Pakistan	Open-label RCT (N=100)	Mild-moderate COVID-19 15-65 yo	Ivermectin 12 mg single dose at admission (n=50) Low dose Ivermectin	SOC (n=50) SOC includes Vit C 500mg OD, Vit D3 200k IU once weekly, paracetamol 500mg SOS	1. Viral clearance (days to RT-PCR negativity) 2. Adverse effects
12	Podder 2020	Bangladesh	Open-label RCT (N=62)	Mild-moderate COVID-19	single dose of ivermectin 200 micrograms/kg on	symptomatic treatment which included antipyretics, cough suppressants, and capsule	1. time needed for resolution of fever,

	Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study			Age more than 18 years old	the day 1 of randomisation Low dose Ivermectin	doxycycline (100 mg every 12 hours for seven days)	cough, shortness of breath 2. time needed for full recovery from all symptoms 3. Viral clearance (repeat RT-PCR on day 10)
13	Shahbaznejad 2021 Effect of ivermectin on COVID-19: A multicenter double-blind randomized controlled clinical trial	Iran	RCT (N=73)	Hospitalized COVID-19 confirmed or probable (age>5 yrs; wt >15kg – range 5-86 yrs) Moderate to Critical COVID-19	Low dose IVM + SOC Intervention: single (200mcg/kg) oral dose of IVM on day of admission Standard of care: HQC and/or lopinavir/ritonavir	Control: SOC Standard of care: HQC and/or lopinavir/ritonavir	1. Time to Clinical improvement (defined as resolution of baseline coughing that interferes with daily activity and tachypnea) 2. Duration of symptoms 3. Length of hospitalization 4. Need for mechanical ventilation 5. Need for supplemental oxygen 6. Mortality 7. Adverse events
14	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	Ivermectin 12 or 18 mg accdg to weight (n=36)	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(%)

Table 1.2. Ivermectin versus hydroxychloroquine (2 RCTs).

No.	Clinical Trial ID/ Title	Country	Study design	Population	Intervention	Comparator	Outcomes
1	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	Ivermectin 12 or 18 mg accdg to weight (n=36)	HCQ 400 mg BID on D1, 200 mg BID for 4 days (n=33)	1. Duration of hospitalization 2. Hospital discharge, n(%) 3. Discharged without respiratory deterioration or death, n(%) 4. Respiratory deterioration or death, n(%)

2	Elgazzar 2020 Efficacy and Safety of Ivermectin for Treatment and prophylaxis of COVID-19 Pandemic Follow up 25 days	Egypt	RCT (N=400) Treatment	Mild-Severe COVID-19 Age 14 to 80 years	Oral ivermectin 400 mcg/kg once daily for 4 days [n=200] High dose ivermectin Group I: mild-moderate COVID-19, IVM [n=100] Group II: severe COVID-19; IVM [n=100]	Hydroxychloroquine 400 mg on day 1, then 200 mg every 12 hours for 5 days plus standard of care [n=200] Standard care: Azithromycin, paracetamol,Vitamin C, Lactoferrin, Acetylcysteine Group III: mild-moderate COVID-19, SOC [n=100] Group IV: severe COVID-19; SOC [n=100]	1. Mortality 2. Clinical deterioration 3. Clinical improvement 4. Virologic clearance 5. Adverse events

Table 1.3. Ivermectin versus lopinavir/ritonavir (1 RCT).

No.	Clinical Trial ID/ Title	Country	Study design	Population	Intervention	Comparator	Outcomes
1	Babalola 2021 Ivermectin shows clinical benefits in mild to moderate COVID19: a randomised controlled double-blind, dose-response study in Lagos	Nigeria (May 2020-November 2020)	RCT (N=60)	PCR-confirmed COVID-19 (mean age 44 [20-82]; 43M19F) asymptomatic or with mild-to-moderate symptoms (Mild' = with signs and symptoms, but no clinical/imaging evidence of pneumonia. 'Moderate' = fever or respiratory tract symptoms, and imaging shows pneumonia)	A. Low dose IVM 6 mg (given every 84 hrs), 2x a week + SOC B. IVM 12 mg (given every 84 hrs) for 2 weeks	SOC + Lopinavir/ritonavir (daily for 2 weeks)	1. Days to PCR negativity 2. Mortality 3. Adverse effects 4. change in clinical status, SPO2, liver function tests, kidney function tests, rheological variables (platelet count, PTT)

Table 1.4. Ivermectin + doxycycline versus placebo / standard of care (3 RCT).

No.	Clinical Trial ID/ Title	Country	Study design	Population	Intervention	Comparator	Outcomes
1	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 rRT-PCR.	Oral single dose of ivermectin, 12 mg plus oral doxycycline loading dose of 200mg followed by 100 mg q12 for 4 days [n=23] Low dose ivermectin	Placebo [n=22]	Mortality Clinical deterioration Duration of hospitalization Remission of symptoms Virologic clearance Adverse effects *Follow up 14 days

2	Mahmud 2020 Ivermectin in combination with doxycycline for treating COVID-19 symptoms: a randomized trial	Bangladesh	Double blind RCT (N=400)	Mild-Moderate COVID-19 Age 18 years and older	Oral ivermectin 12 mg OD and Doxycycline 100mg/cap BID for 5 days. [n=200] Low dose ivermectin	Placebo [n=200]	Mortality Clinical improvement Clinical Deterioration Virologic Clearance Adverse Events * Follow up 30 days
3	Hashim 2020 Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq Follow up 56 days	Iraq	Single blind RCT (N=140)	Mild-Critical COVID-19	Ivermectin 200ug/kg OD for 2 days and another on D7 (if admitted) Doxycycline 100mg/cap BID for 5-10 days (based on clinical improvement) Low dose ivermectin	Standard care [n=70] Acetaminophen, Vitamin C 1000mg twice/ day, Zinc 75-125 mg/day, Vitamin D3 5000IU/day, Azithromycin 250mg/day x 5 days, Oxygen therapy/ C-Pap if needed, Dexamethasone 6 mg/day or Methylprednisolone 40mg twice per day, if needed , Mechanical ventilation, if needed	Mortality Clinical Deterioration Mean days to symptomatic resolution

Table 1.5. Ivermectin + doxycycline versus hydroxychloroquine + azithromycin (1 RCT).

No.	Clinical Trial ID/ Title	Country	Study design	Population	Intervention	Comparator	Outcomes
1	Chowdhury 2021 A Randomized Trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients.	Bangladesh	RCT (N=125)	Symptomatic and asymptomatic COVID-19 confirmed with RT-PCR (age >18 yrs, Out-patient setting) Mild COVID-19	Low dose IVM Group A (n=60): IVM 200 mcg/kg single dose + Doxycycline 100 mg BID for 10days Standard of care: symptomatic treatment	Group B (n=56): Hydroxychloroquine 400 mg 1st day then200mg BID for 9days + Azithromycin 500 mg daily for 5Days. Standard of care: symptomatic treatment	1. Mortality 2. Adverse Events 3. Duration to negative PCR 4. Proporation of patients symptomatic at D10

Appendix 3: Characteristics of Excluded Studies

1	Afsar 2020	Ivermectin use associated with reduced duration of COVID-19 febrile illness in a community setting	Case-control study (n = 95)	Non-RCT
2	Aguilar 2020	Current Understanding of COVID-19 Clinical Course and Investigational Treatments		Review article
3	Alam 2020	Ivermectin as Pre-exposure Prophylaxis for COVID-19 among Healthcare Providers in a Selected Tertiary Hospital in Dhaka – An Observational Study	Prospective cohort (n = 118)	Ivermectin as prophylaxis, non-RCT
4	Alexander 2021	Early Multidrug Outpatient Treatment of SARS-CoV-2 Infection (COVID-19) and Reduced Mortality Among Nursing Home Residents		Review article
5	Asghar 2020	Efficacy of Ivermectin in COVID-19	RCT (n = 100)	Unable to retrieve published data
6	Behera 2021	Role of ivermectin in the prevention of SARSCoV-2 infection among healthcare workers in India: A matched case-control study	Case-control study (n = 117)	Ivermectin as prophylaxis
7	Bernigaud 2020	Ivermectin benefit: from scabies to COVID-19, an example of serendipity	Retrospective cohort (n = 121)	Ivermectin as prophylaxis
8	Budhiraja 2020	Clinical Profile of First 1000 COVID-19 Cases Admitted at Tertiary Care Hospitals and the Correlates of their Mortality: An Indian Experience	Retrospective cohort (n = 1000)	Non-RCT
9	Cadegiani 2020	Early COVID-19 Therapy with Azithromycin Plus Nitazoxanide, Ivermectin or Hydroxychloroquine in Outpatient Settings Significantly Reduced Symptoms Compared to Known Outcomes in Untreated Patients.	Prospective Cohort (n = 585)	Non-RCT
10	Camprubi 2020	Lack of efficacy of standard doses of ivermectin in severe COVID-19 patients	Retrospective cohort (n - 26)	Non-RCT
11	Carvallo 2020	USEFULNESS of Topic Ivermectin and Carrageenan to Prevent Contagion of Covid 19 (IVERCAR)	Prospective cohort (n = 229)	Non-RCT
12	Castañeda-Sabogal 2021	Outcomes of Ivermectin in the treatment of COVID-19: a systematic review and meta-analysis		Review article
13	Chahla 2021	A randomized trial - intensive treatment based in ivermectin and iota-carrageenan as pre-exposure prophylaxis for COVID- 19 in healthcare agents	Randomized controlled trial (n = 234)	Ivermectin as pre-exposure prophylaxis
14	Chahla 2021	Ivermectin repurposing for COVID-19 treatment outpatients in mild stage in primary health care centers	Cluster-RCT	Non-RCT
15	Debela 2021	Comparing the efficacy of anti□infectious drugs for the treatment of mild to severe COVID-19 patients: a protocol for a systematic review and network meta-analysis of randomized clinical trials		Study Protocol
16	DiNicolantonio 2020	Ivermectin may be a clinically useful anti-inflammatory agent for late-stage COVID-19		Review article
17	Elalfy 2021	Effect of a combination of nitazoxanide, ribavirin, and ivermectin plus zinc supplement (MANS.NRIZ study) on the clearance of mild COVID-19	Phase I clinical trial (n = 113)	Non-RCT
18	Elsawah 2021	Ivermectin Role in Covid-19 Clinical Trial (IRICT)	RCT (n = 300)	Unable to retrieve published data
19	Espitia-Hernandez 2021	A Comparative Study on Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin Therapy on COVID-19 Patients	Proof-of-concept study (n = 35)	Non-RCT
20	Fonseca 2020	Risk of hospitalization for Covid-19 outpatients treated with various drug regimens in Brazil: Comparative analysis	Prospective cohort (n = 717)	Non-RCT

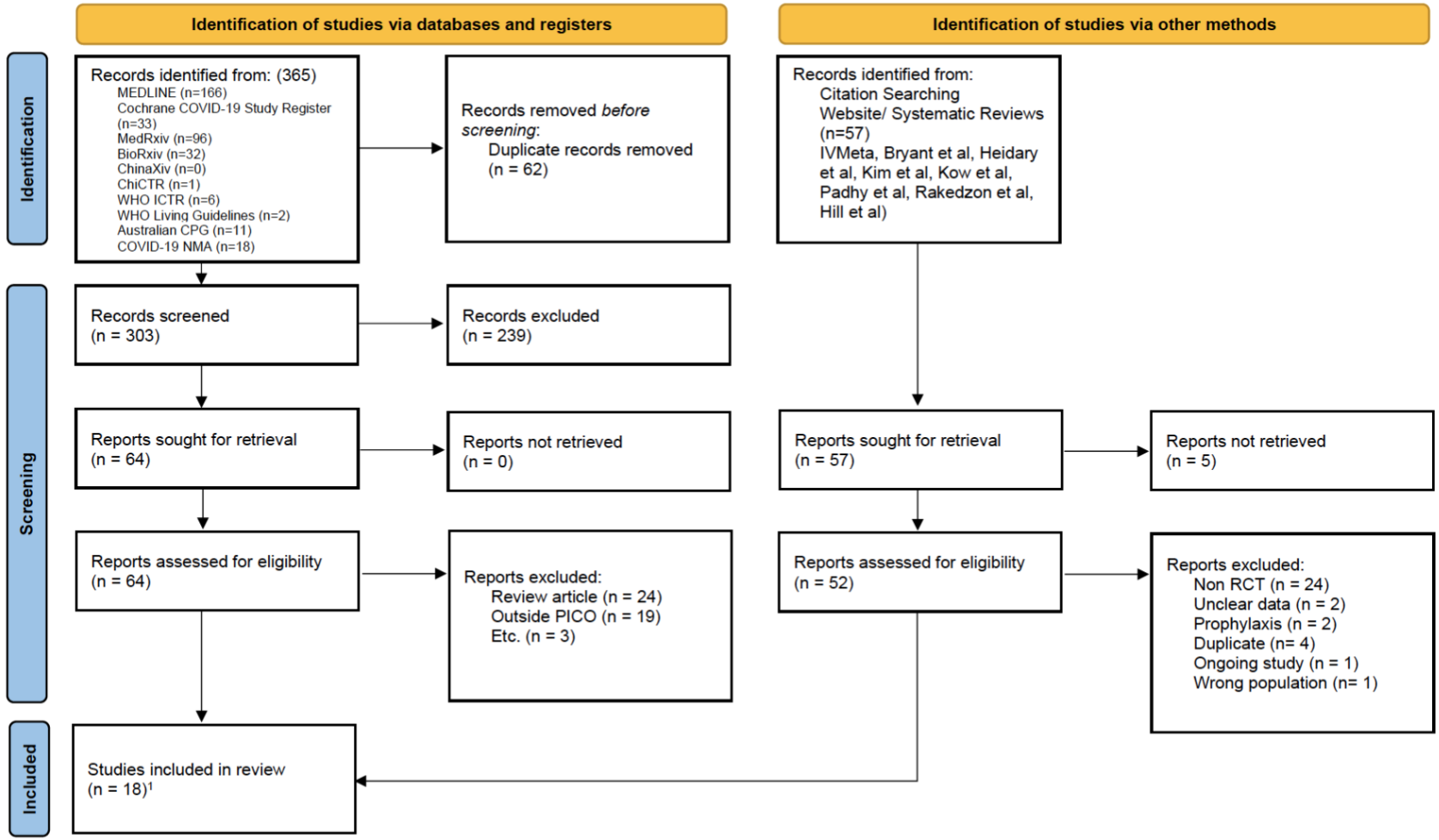
21	Galan 2021	Phase 2 randomized study on chloroquine, hydroxychloroquine or ivermectin in hospitalized patients with severe manifestations of SARS-CoV-2 infection	Randomized controlled trial (n = 168)	No placebo or standard of care as control group
22	Gorial 2020	Effectiveness of Ivermectin as add-on Therapy in COVID-19 Management (Pilot Trial)	Pilot trial with synthetic controlled arm (n = 87)	Non-RCT
23	Guerrero 2020	COVID-19: The Ivermectin African Enigma	Ecological study	Non-RCT
24	Gupta 2020	Ivermectin: potential candidate for the treatment of Covid 19		Review article
25	Hector 2020	Safety and Efficacy of the combined use of ivermectin, dexamethasone, enoxaparin and aspirin against COVID 19	Phase I clinical trial (n = 167)	Non-RCT
26	Heimfarth 2020	Ivermectin: Panacea or true promise for COVID-19		Review article
27	Hellwig 2020	A COVID-19 Prophylaxis? Lower incidence associated with prophylactic administration of Ivermectin	Ecological study	Ivermectin as prophylaxis, non-RCT
28	Hidalgo 2021	Pragmatic study "CORIVER": Ivermectin as antiviral treatment for patients infected by SARS-COV2 (COVID-19)		On going study
29	Kalfas 2020	THE THERAPEUTIC POTENTIAL OF IVERMECTIN FOR COVID-19: A SYSTEMATIC REVIEW OF MECHANISMS AND EVIDENCE		Review article
30	Khan 2020	Ivermectin treatment may improve the prognosis of patients with COVID-19	Retrospective cohort (n = 325)	Non-RCT
31	Khan 2020	Diagnostic approaches and potential therapeutic options for coronavirus disease 2019	Review article	Non-RCT
32	Kim 2020	Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: A systematic review and network meta-analysis		Review article
33	Kishoria 2021	Ivermectin as adjuvant to hydroxychloroquine in patients resistant to standard treatment for SARS-COV-2: results of an open-label randomized clinical study	RCT	Wrong population; persistent COVID-19
34	Kotecha 2020	Repurposing of drugs for Covid-19: a systematic review and meta-analysis		Review article
35	Kow 2021	The association between the use of ivermectin and mortality in patients with COVID-19: a meta-analysis		Review article
36	Lima-Morales 2021	Effectiveness of a multidrug therapy consisting of Ivermectin, Azithromycin, Montelukast, and Acetylsalicylic acid to prevent hospitalization and death among ambulatory COVID-19 cases in Tlaxcala, Mexico	Prospective cohort (n = 768)	Non-RCT
37	Malik 2020	Clinical Presentation, Management and In-Hospital Outcome of Healthcare Personnel With COVID-19 Disease	Cross sectional study (n = 1409)	Non-RCT
38	Marcolino 2020	What to expect from different drugs used in the treatment of COVID-19: A study on applications and in vivo and in vitro results		Review article
39	Misra 2020	Effect of various treatment modalities on the novel coronavirus (nCOV-2019) infection in humans: a systematic review & meta-analysis		Review article
40	Mondal 2020	Socio-demographic, clinical, hospital admission and oxygen requirement characteristics of COVID-19 patients of Bangladesh	Cross-sectional study (n = 305)	Non-RCT
41	Morgenstern 2020	The use of compassionate Ivermectin in the management of symptomatic outpatients and hospitalized patients with clinical diagnosis of COVID-19 at the Medical Center Bournigal and the Medical Center Punta Cana, Rescue Group, Dominican Republic, from may 1 to august 10, 2020	Retrospective cohort (n = 3,099)	Non-RCT

42	Muacevic 2020	Clinical Presentation, Management and In-Hospital Outcome of Healthcare Personnel With COVID-19 Disease	Cross-sectional study (n = 305)	non-RCT
43	Mucaevic 2020	The History of Methylprednisolone, Ascorbic Acid, Thiamine, and Heparin Protocol and I-MASK+ Ivermectin Protocol for COVID-19		Review article
44	Padhy 2020	Therapeutic potential of ivermectin as add on treatment in COVID 19: A systematic review and meta-analysis		Review article
45	Pandey 2020	Ivermectin in COVID-19: What do we know?		Review article
46	Petkov (Huvemek) 2021	Multicenter, randomized, double-blind, placebo-controlled study investigating efficacy, safety and tolerability of ivermectin HUVE-19 in patients with proven SARS-CoV-2 infection (COVID-19) and manifested clinical symptoms.	RCT (n = 120)	Unable to retrieve published data
47	Procter 2020	Clinical outcomes after early ambulatory multidrug therapy for high risk SARS-CoV-2 (COVID-19) infection	Prospective cohort (n = 922)	Non-RCT
48	Raad (Fawaz) 2020	. In vivo use of ivermectin (IVR) for treatment for corona virus infected patients (COVID-19): a randomized controlled trial	RCT (n = 30)	Unable to retrieve published data
49	Rajter 2020	Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019 The Ivermectin in COVID Nineteen Study	Retrospective cohort (n = 476)	Non-RCT
50	Rakedzon 2021	From hydroxychloroquine to ivermectin: what are the anti-viral properties of anti-parasitic drugs to combat SARS-CoV-2?		Review article
51	Rezai 2020	Effectiveness of Ivermectin in the Treatment of Coronavirus Infection in Patients admitted to Educational Hospitals of Mazandaran in 2020	RCT (n = 60)	Unable to retrieve published data
52	Rochwerg 2020	A living WHO guideline on drugs for covid-19		Review article
53	Roy 2021	Outcome of Different Therapeutic Interventions in Mild COVID-19 Patients in a Single OPD Clinic of West Bengal: A Retrospective study	Retrospective cohort (n = 56)	Non-RCT
54	Schwartz 2020	Ivermectin vs. Placebo for the Treatment of Patients With Mild to Moderate COVID-19	RCT (n = 100)	Unable to retrieve published data
55	Sharun 2020	Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19		Review article
56	Shouman 2021	Use of Ivermectin as a Potential Chemoprophylaxis for COVID-19 in Egypt: A Randomised Clinical Trial	RCT (n = 203)	Ivermectin as prophylaxis
57	Siddiqui 2020	Current status and strategic possibilities on potential use of combinational drug therapy against COVID-19 caused by SARS-CoV-2		Review article
58	Siordia 2020	Systematic and Statistical Review of Coronavirus Disease 19 Treatment Trials		Review article
59	Soto-Becerra 2020	Real-World Effectiveness of hydroxychloroquine, azithromycin, and ivermectin among hospitalized COVID-19 patients: Results of a target trial emulation using observational data from a nationwide Healthcare System in Peru	Retrospective cohort (n = 5683)	Non-RCT
60	Spoorthi 2021	Utility of Ivermectin and Doxycycline combination for the treatment of SARSCoV-2	Prospective cohort (n=122)	Non-RCT
61	Tanioka 2021	Why COVID-19 is not so spread in Africa: How does Ivermectin affect it?	Ecological study	Non-RCT
62	Vallejos 2021	Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19): a structured summary of a study protocol for a randomized controlled trial	Ongoing study	Study protocol only

63	Venkatesulu 2020	Mechanistic rationale of drugs, Primary endpoints, Geographical distribution of clinical trials against Severe acute respiratory syndrome-related coronavirus-2: A Systematic review		Review article
64	Wadvalla 2021	Covid-19: Ivermectin's politicisation is a warning sign for doctors turning to orphan treatments		Review article
65	Zhang 2020	A Systematic Review and Network Meta-Analysis for COVID-19 Treatments		Review article
66	Little 2021	A Narrative Review of Pharmacologic Treatments for COVID-19: Safety Considerations and Ototoxicity		Review article

Appendix 4: PRISMA Flow Diagram (n=19, Last updated May 15, 2021)

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources (April 4, 2021)



[1]Ahmed, Babalola, Beltran-Gonzalez, Bukhari, Chaccour, Chachar, Chowdhury, Elgazzar, Hashim, Kirti, Krolewiecki, Lopez-Medina, Mahmud, Mohan, Niaee, Okumus, Podder, Pott-Junior

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Appendix 5: Methodological Quality Assessment of Included Studies

Table 5.1. Methodological quality assessment: Ivermectin vs. placebo/standard of care (14 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. Ahmed	**Serious**	Yes	Unclear	Unclear	Yes	Yes	Unclear	No[3]	Yes	Yes
2. Beltran-Gonzalez	**Very serious**	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
3. Bukhari	**Very serious**	Yes	Unclear	Yes	No	No	No	Yes	No	No
4. Chaccour	**Serious**	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
5. Chachar	**Serious**	Yes	No	Yes	No	No	No	Yes	Yes	Yes
6. Królewiecki	**Serious**	Yes	Yes	Yes	No	No	No	Yes	No	No
7. Lopez-Medina	**Not serious**	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
8. Mohan	**Not serious**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
9. Niaee	**Serious**	Yes	Yes	Unclear	No	No	Unclear	Yes	Yes	No
10. Okumuş	**Very serious**	Yes	Unclear	Yes	No	No	No	Yes	No	No
11. Podder	**Very serious**	Yes	No	Yes	No	No	No	No	No[2]	Yes
12. Pott-Junior	**Very serious**	Yes	Unclear	Unclear	No	No	No	Yes	No[4]	Yes
13. Ravikirti	**Very serious**	Yes	Yes	Yes	Yes	Yes	Yes	No[2]	Yes	No
14. Shahbaznejad	**Serious**	Unclear	Yes	Yes	Unclear	Unclear	Unclear	No	Yes	Yes

[1]For outcomes of mortality and viral clearance, risk of bias for assessor blinding was rated low as these objective outcomes.
[2]High rop-out rate for outcome of virologic clearance IVM 12/32 drop outs; Control 10/30 drop outs.
[3]Used non-ITT data for the Kaplan Meier analysis.
[4]only 4 samples included in the control; drop out rate of 1/4 (25%)

Table 5.2. Methodological quality assessment: Ivermectin vs.hydroxychloroquine (2 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. Elgazzar	**Very serious**	Unclear	Unclear	No	Unclear	Unclear	Unclear	Yes	Yes	No
2. Gonzalez	**Very serious**	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No

Table 5.3. Methodological quality assessment: Ivermectin vs. lopinavir/ritonavir (1 RCT).

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
2. Babalola	**Not serious**	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table 5.4. Ivermectin+doxycycline vs. placebo/standard of care (3 RCTs).

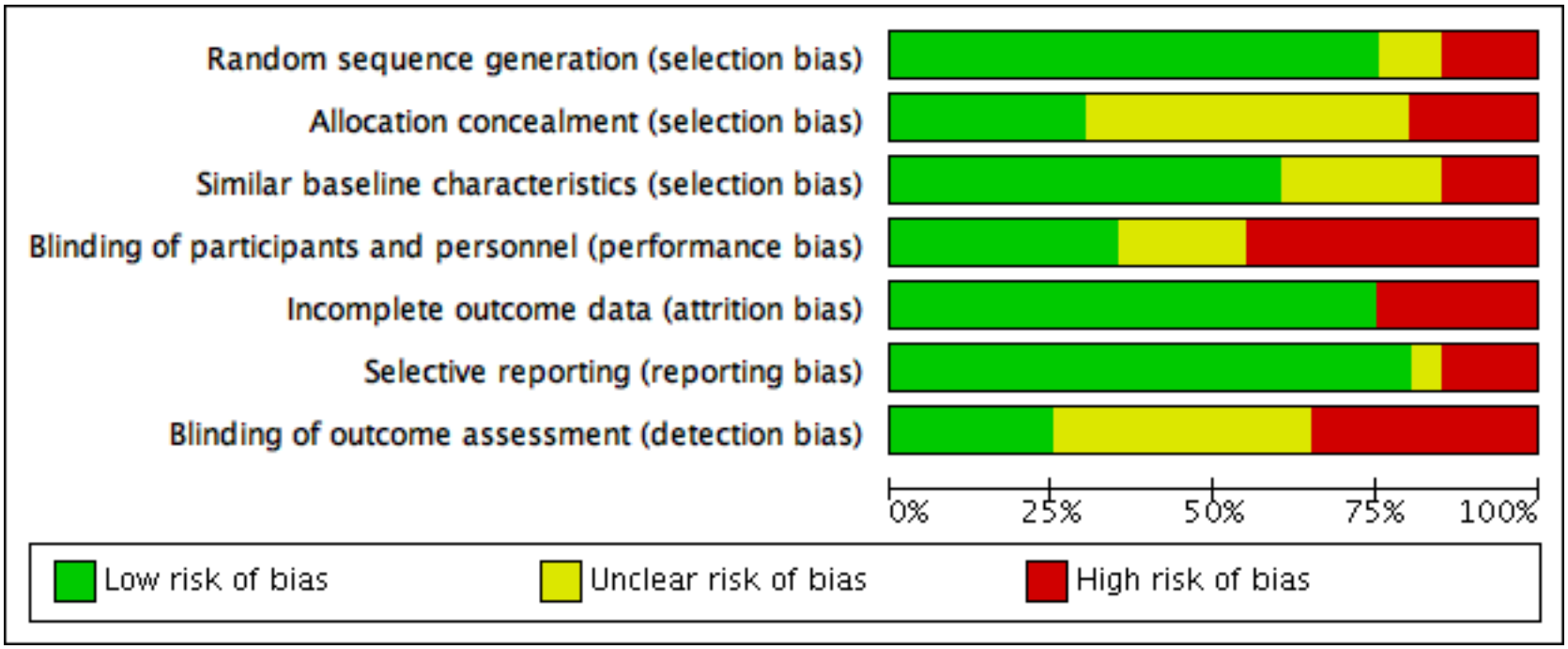
Studies	Risk of bias	Random assignment	Allocation concealment	Similar baseline characteristics	Patients blinded	Caregivers blinded	Assessors blinded	Intention-to-treat analysis	Adequate follow-up rate	Peer-reviewed
1. Ahmed	**Serious**	Yes	Unclear	Unclear	Yes	Yes	Unclear	No	Unclear	Yes
2. Mahmud	**Very Serious**[1]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No	Yes
3. Hashim	**Very Serious**	No[2]	No	Unclear	No	No	No	Yes	Yes	No
[1]Very serious due to dropout rate (considered high as event rates are low)										

Table 5.5. Ivermectin+doxycycline vs. hydroxychloroquine+azithromycin (1 RCT).

	Risk of bias	Random assignment	Allocation concealment	Similar baseline characteristics	Patients blinded	Caregivers blinded	Assessors blinded	Intention-to-treat analysis	Adequate follow-up rate	Peer-reviewed

1. Chowdhury	Very Serious[1]	No	Unclear	Yes	Unclear	Unclear	No	Yes	Yes	No

[1]Very serious due to some concern with randomization - odd even date methodology and poor methodological quality



Appendix 5. Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

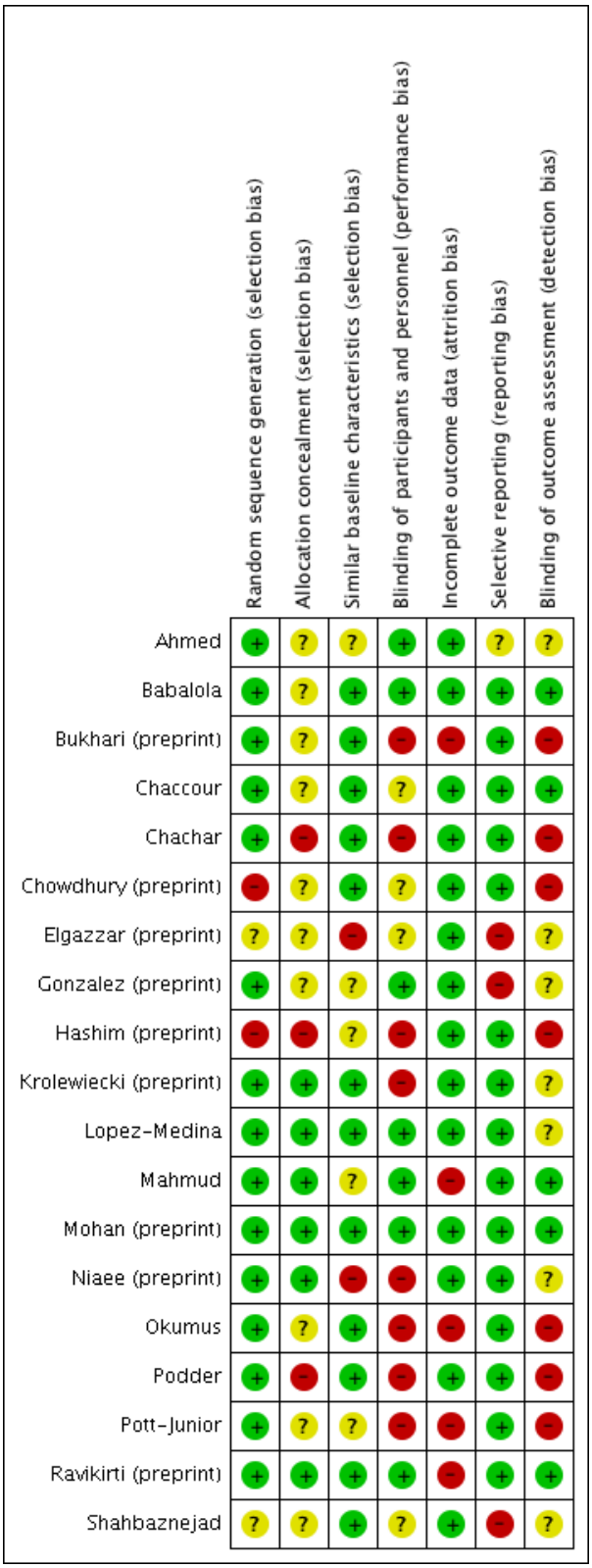
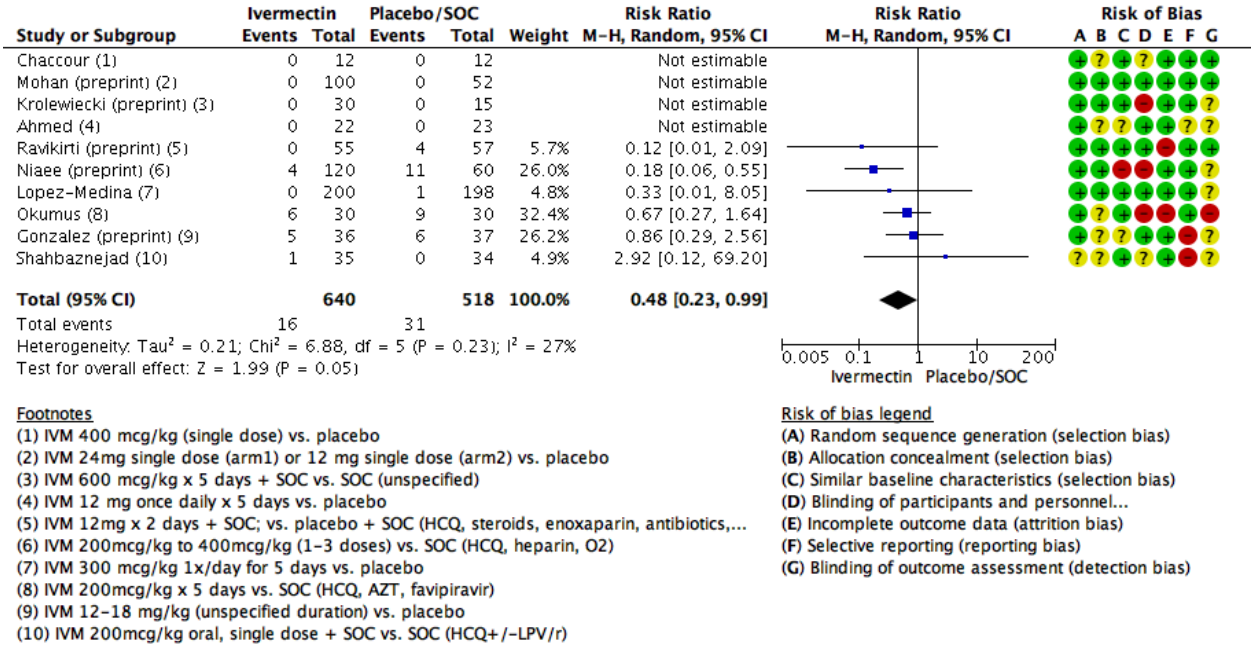


Figure 5.2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Appendix 6: Forest Plots

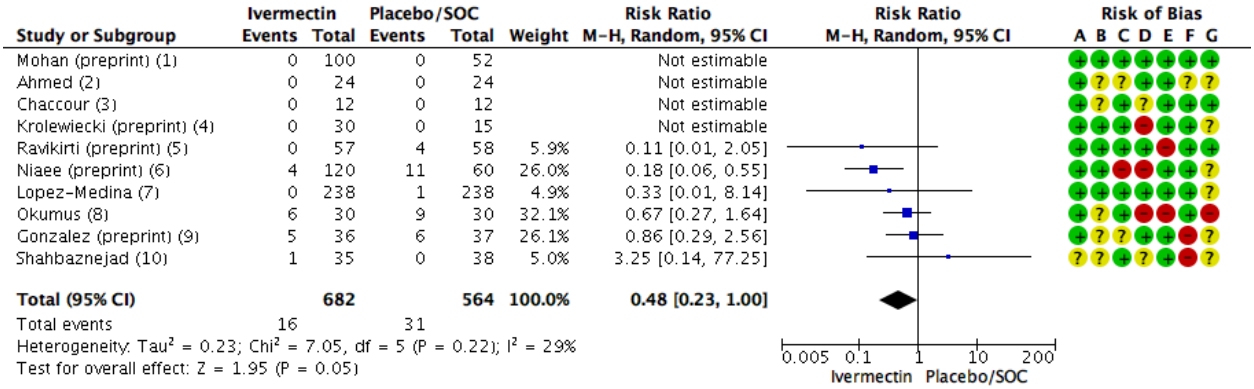
1. Ivermectin vs. placebo/standard of care



Footnotes
(1) IVM 400 mcg/kg (single dose) vs. placebo
(2) IVM 24mg single dose (arm1) or 12 mg single dose (arm2) 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 200mcg/kg to 400mcg/kg (1-3 doses) vs. SOC (HCQ, heparin, O2)
(7) IVM 300 mcg/kg 1x/day for 5 days vs. placebo
(8) IVM 200mcg/kg x 5 days vs. SOC (HCQ, AZT, favipiravir)
(9) IVM 12-18 mg/kg (unspecified duration) vs. placebo
(10) IVM 200mcg/kg oral, single dose + SOC vs. SOC (HCQ+/-LPV/r)

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...
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Blinding of outcome assessment (detection bias)

Figure 1.1. Mortality, overall (per protocol).



Footnotes
(1) IVM 24mg single dose (arm1) or 12 mg single dose (arm2) vs. placebo
(2) IVM 12 mg once daily x 5 days vs. placebo
(3) IVM 400 mcg/kg (single dose) vs placebo
(4) IVM 600 mcg/kg x 5 days + SOC vs. SOC (unspecified)
(5) IVM 12mg x 2 days + SOC; vs. placebo + SOC (HCQ, steroids, enoxaparin, antibiotics,...
(6) IVM 200mcg/kg to 400mcg/kg (1-3 doses) vs. SOC (HCQ, heparin, O2)
(7) IVM 300 mcg/kg 1x/day for 5 days vs. placebo
(8) IVM 200mcg/kg x 5 days vs. SOC (HCQ, AZT, favipiravir)
(9) IVM 12-18 mg/kg (unspecified duration) vs. placebo
(10) IVM 200mcg/kg oral, single dose + SOC vs. SOC (HCQ+/-LPV/r)

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...
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Blinding of outcome assessment (detection bias)

Figure 1.2. Mortality, overall (intention-to-treat).

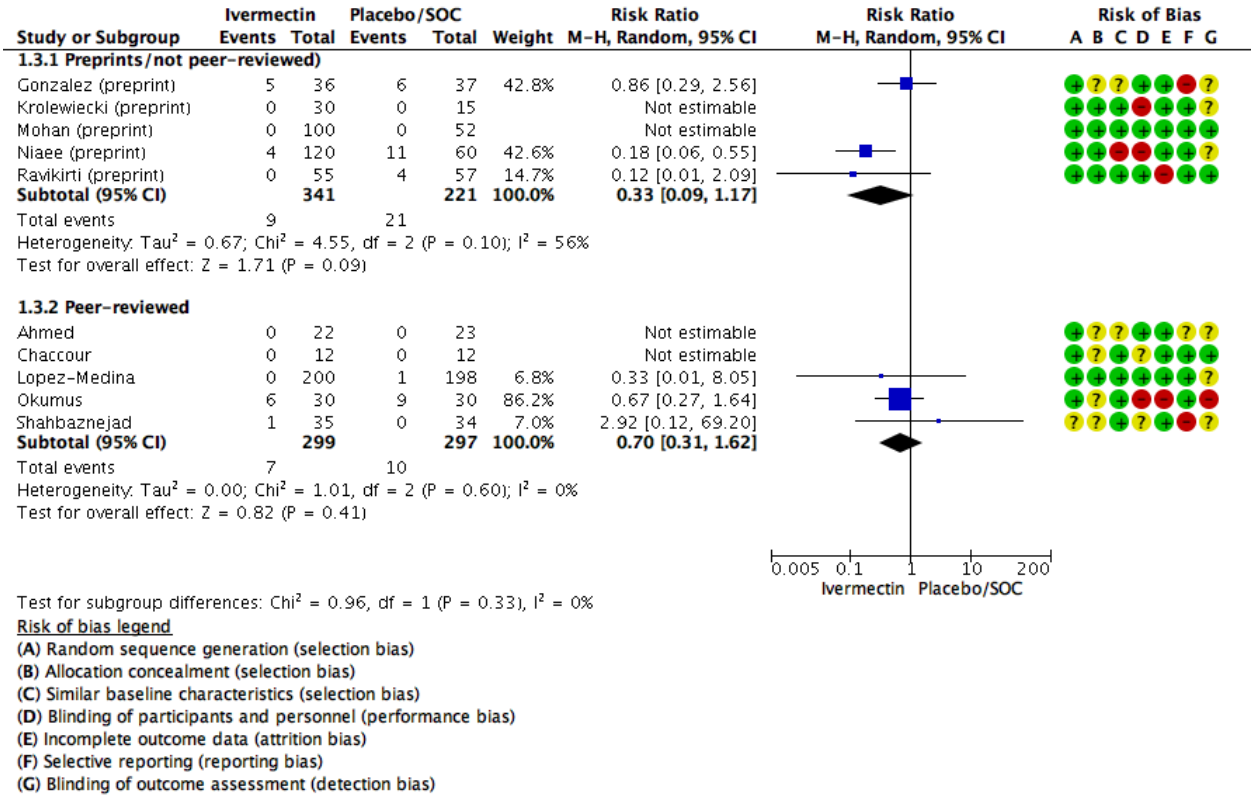


Figure 1.3. Mortality, by publication status (per protocol).

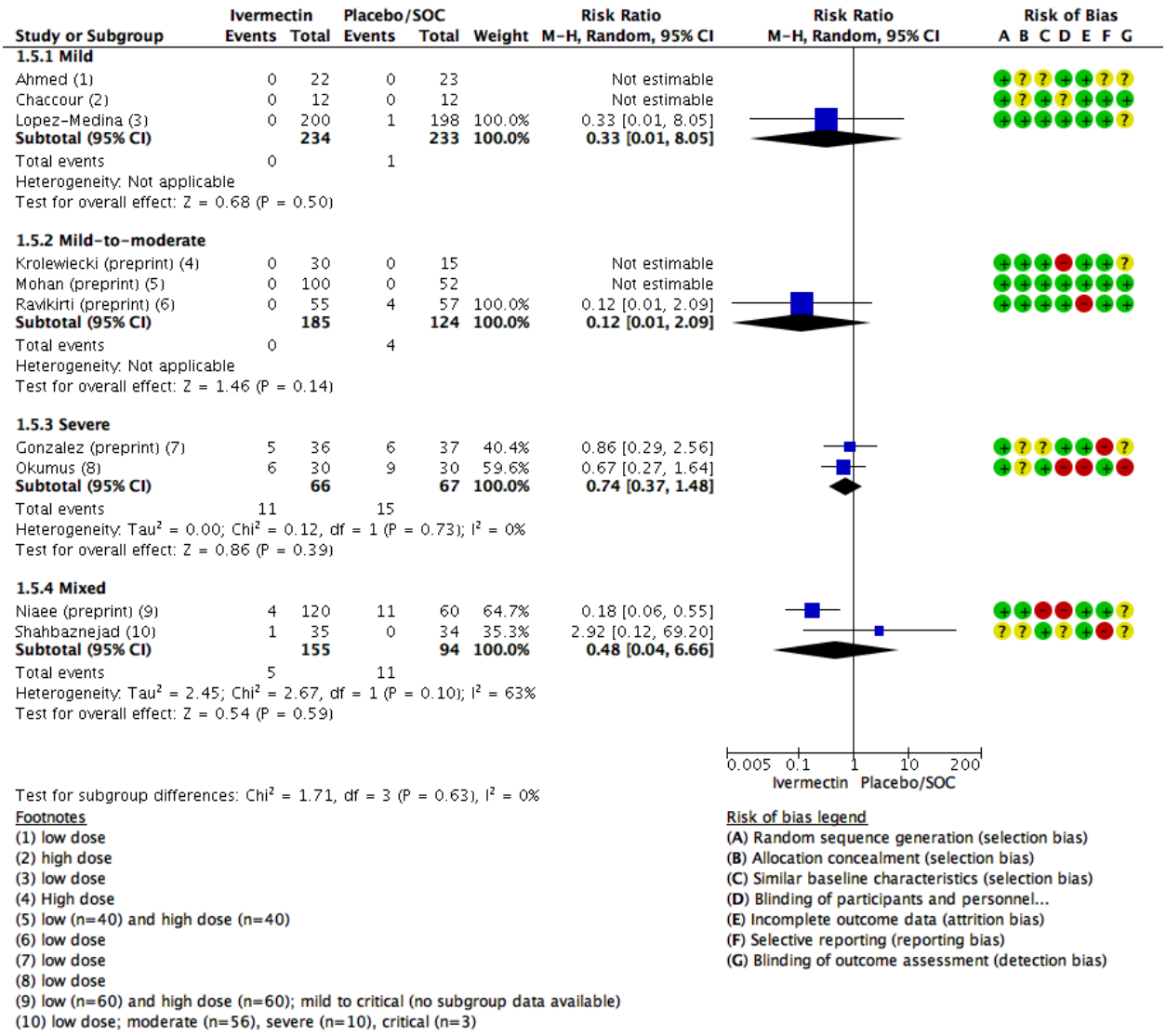


Figure 1.4. Mortality, by disease severity (per protocol).

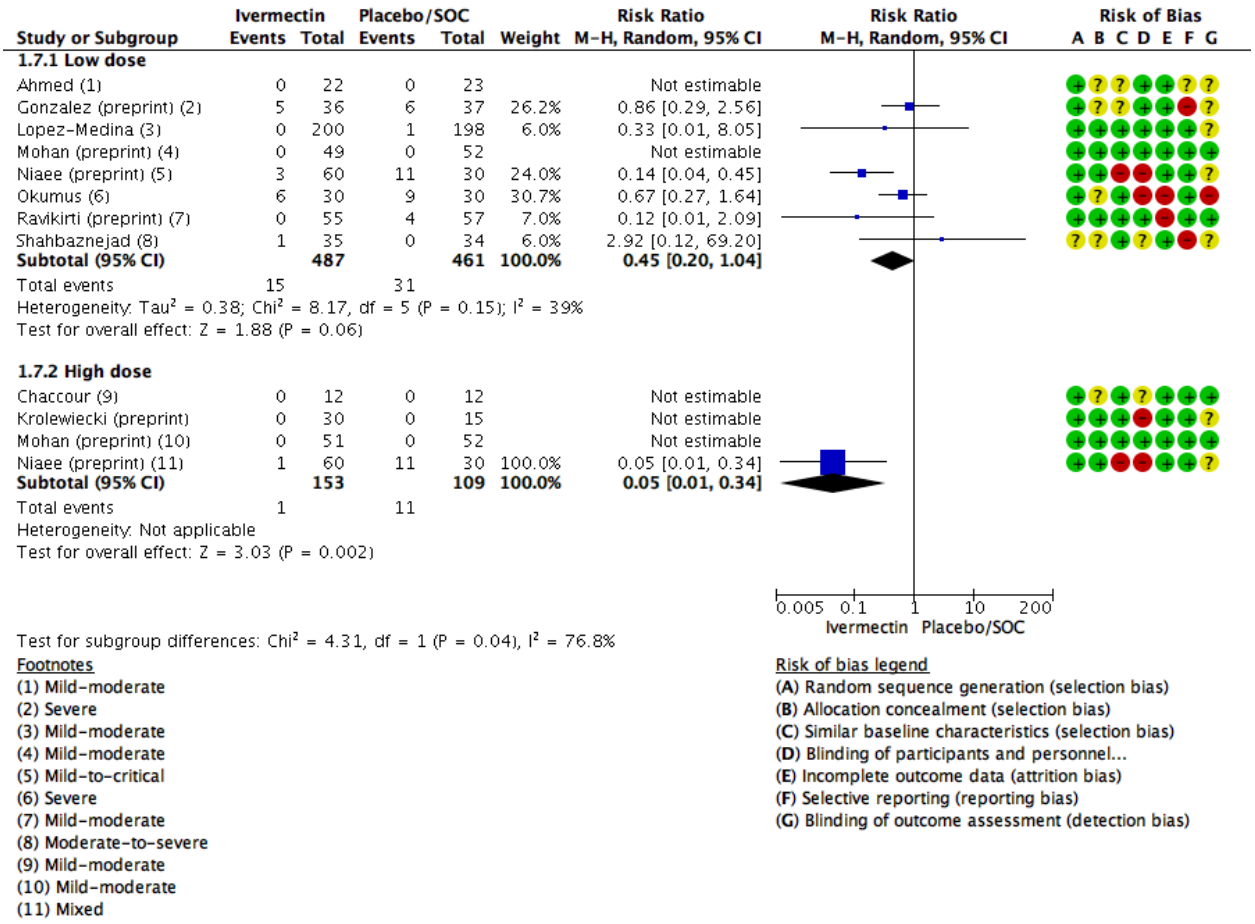
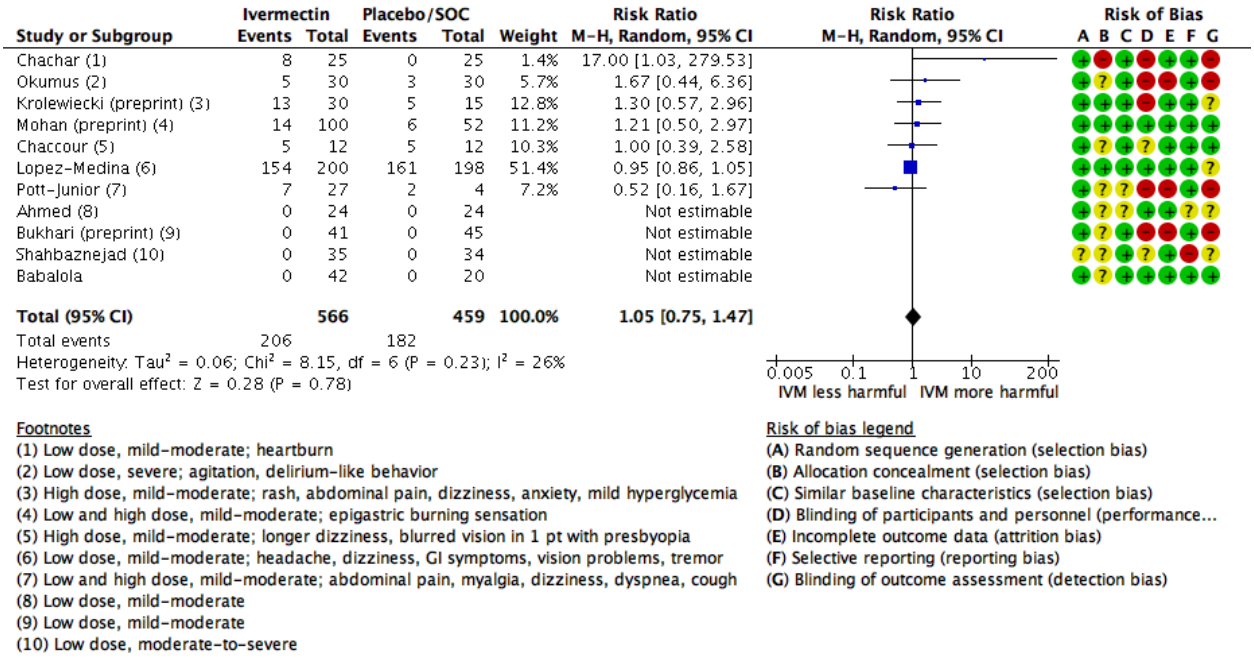


Figure 1.5. Mortality, by dose (per protocol).



Footnotes
(1) Low dose, mild-moderate; heartburn
(2) Low dose, severe; agitation, delirium-like behavior
(3) High dose, mild-moderate; rash, abdominal pain, dizziness, anxiety, mild hyperglycemia
(4) Low and high dose, mild-moderate; epigastric burning sensation
(5) High dose, mild-moderate; longer dizziness, blurred vision in 1 pt with presbyopia
(6) Low dose, mild-moderate; headache, dizziness, GI symptoms, vision problems, tremor
(7) Low and high dose, mild-moderate; abdominal pain, myalgia, dizziness, dyspnea, cough
(8) Low dose, mild-moderate
(9) Low dose, mild-moderate
(10) Low dose, moderate-to-severe

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 1.6. Any adverse events (includes ivermectin vs. lopinavir/ritonavir).

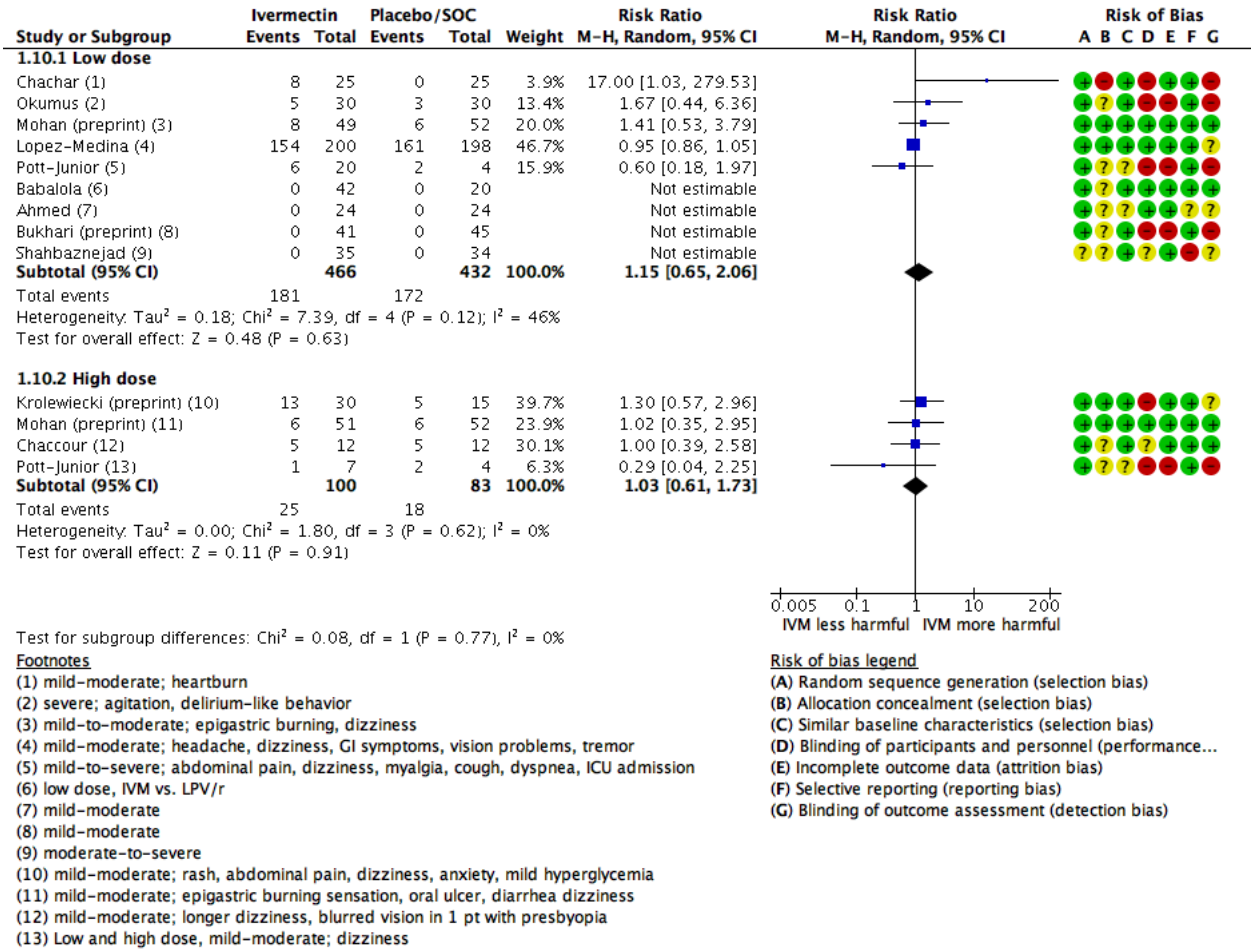
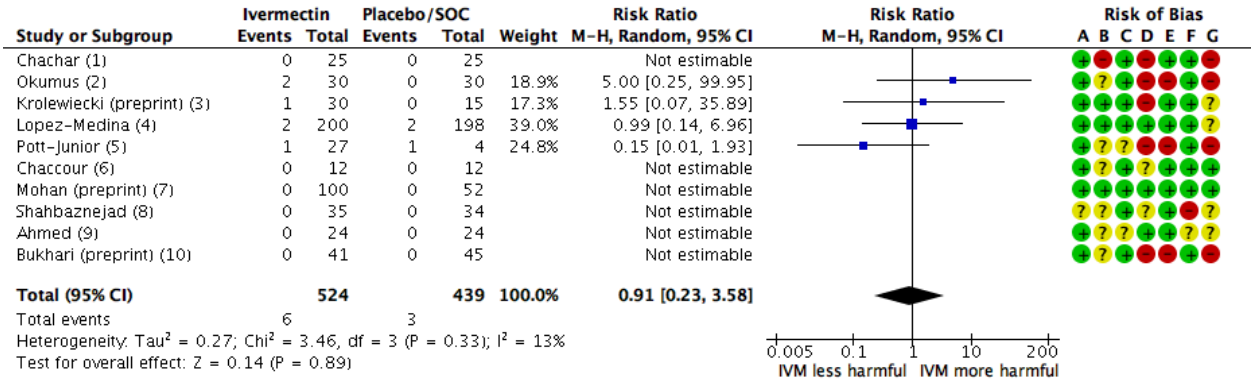


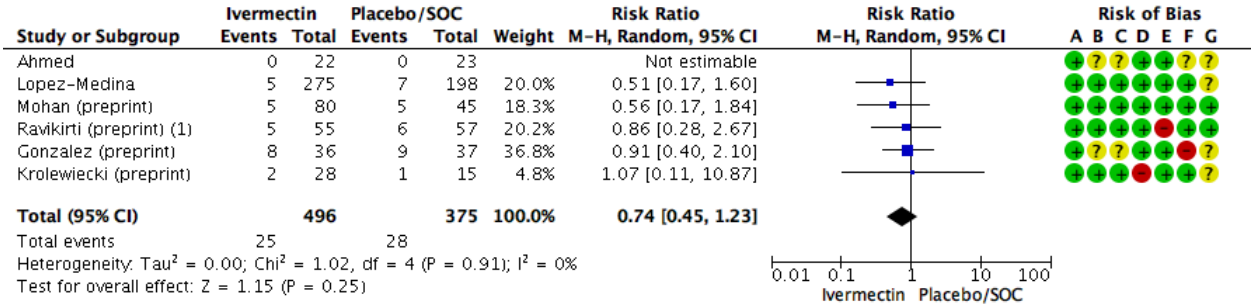
Figure 1.7. Any adverse events (by dose).



Footnotes
(1) Low dose, mild-moderate
(2) Low dose, severe; delirium-like behavior requiring admission
(3) High dose, mild-moderate; hyponatremia (unspecified level)
(4) Low dose, mild-moderate; multiorgan failure (both groups)
(5) Low and high dose, mild-moderate; ICU admission for ventilatory support
(6) High dose, mild-moderate; longer dizziness, blurred vision in 1 pt with presbyopia
(7) Low and high dose, mild-moderate; epigastric burning sensation
(8) Low dose, moderate-to-severe
(9) Low dose, mild-moderate
(10) Low dose, mild-moderate

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 1.8. Serious adverse events.



Footnotes
(1) Defined as admission to ICU

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...
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Blinding of outcome assessment (detection bias)

Figure 1.9. Clinical deterioration.

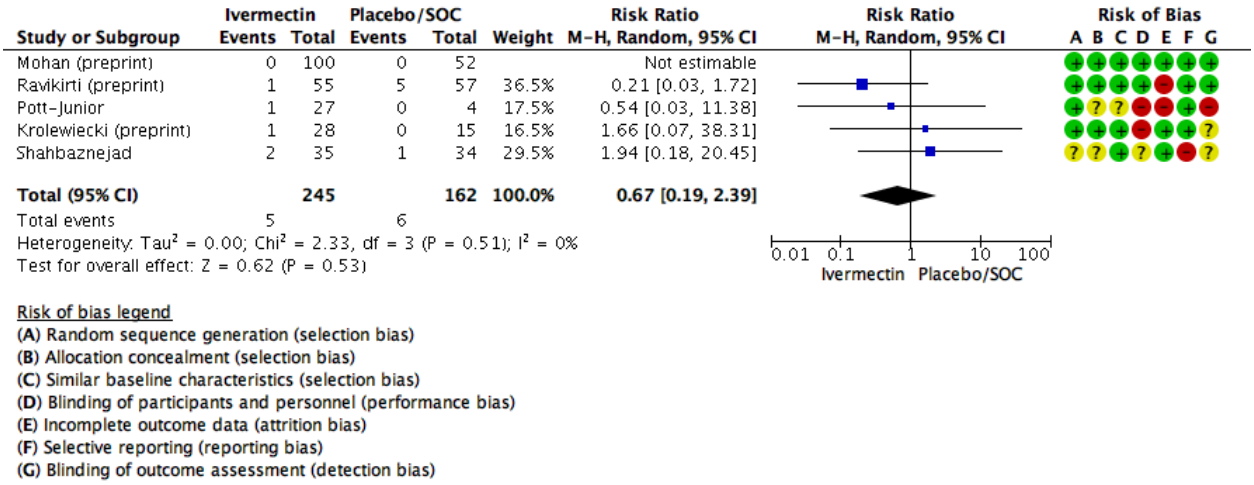


Figure 1.10. Need for mechanical ventilation.

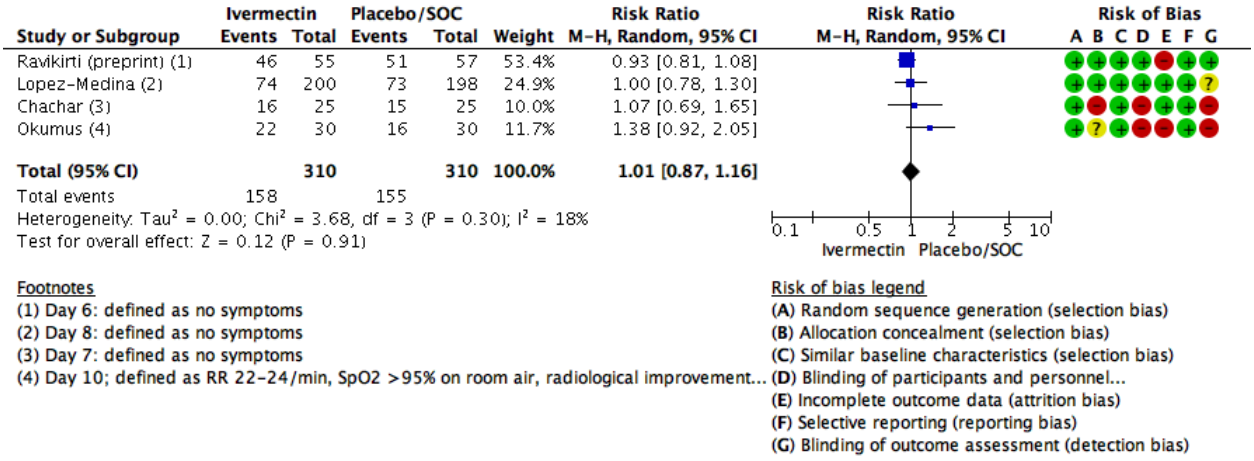


Figure 1.11. Clinical Improvement (D6-D10).

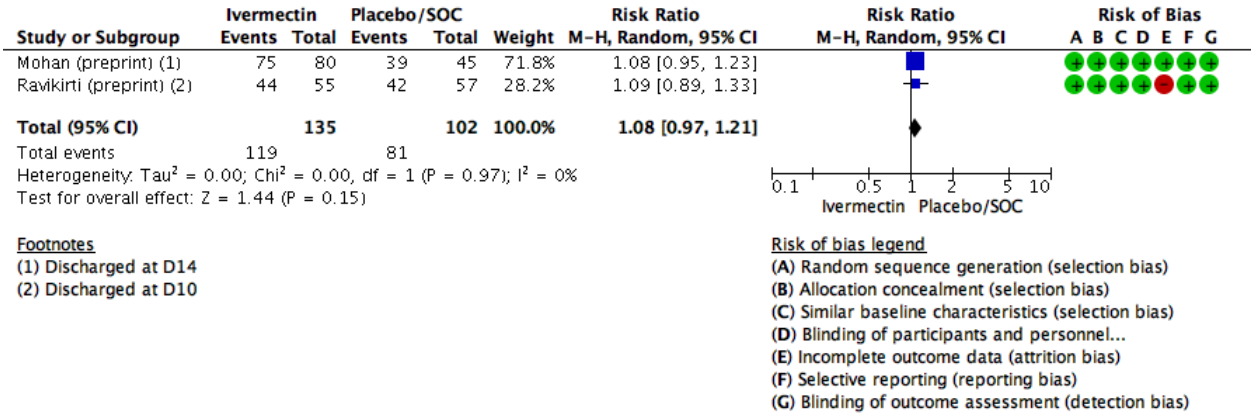


Figure 1.12. Hospital Discharge at D10-14.

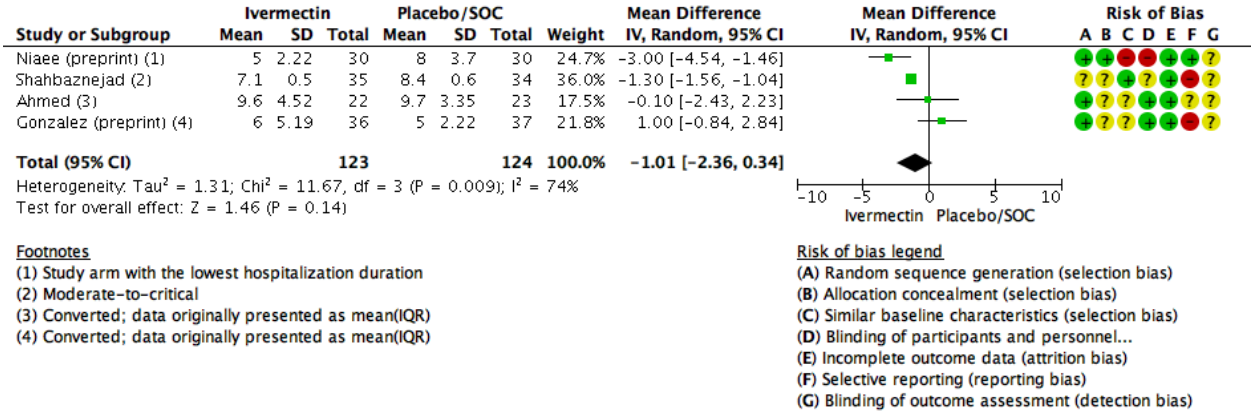


Figure 1.13. Duration of hospitalization.

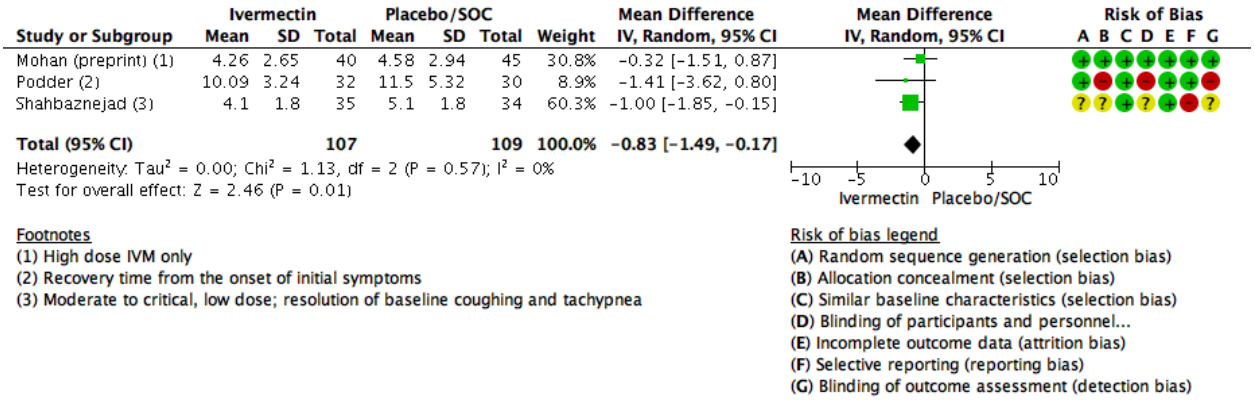
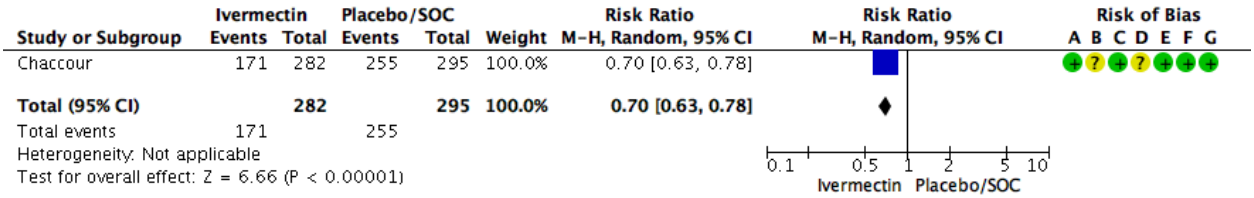
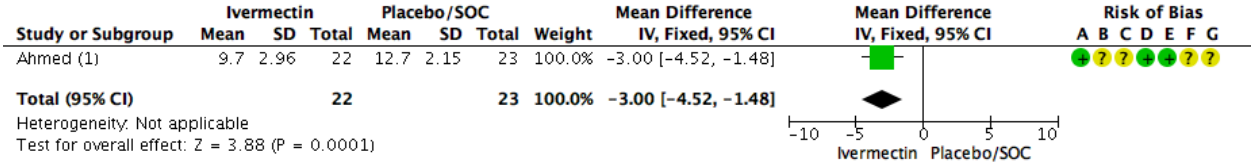


Figure 1.14. Time to symptom resolution (in days).



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 bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Blinding of outcome assessment (detection bias)

Figure 1.15. Number of symptomatic days.



Footnotes
(1) IVM 12mg once daily for 5 days

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...
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Blinding of outcome assessment (detection bias)

Figure 1.16. Time to PCR negativity [days].

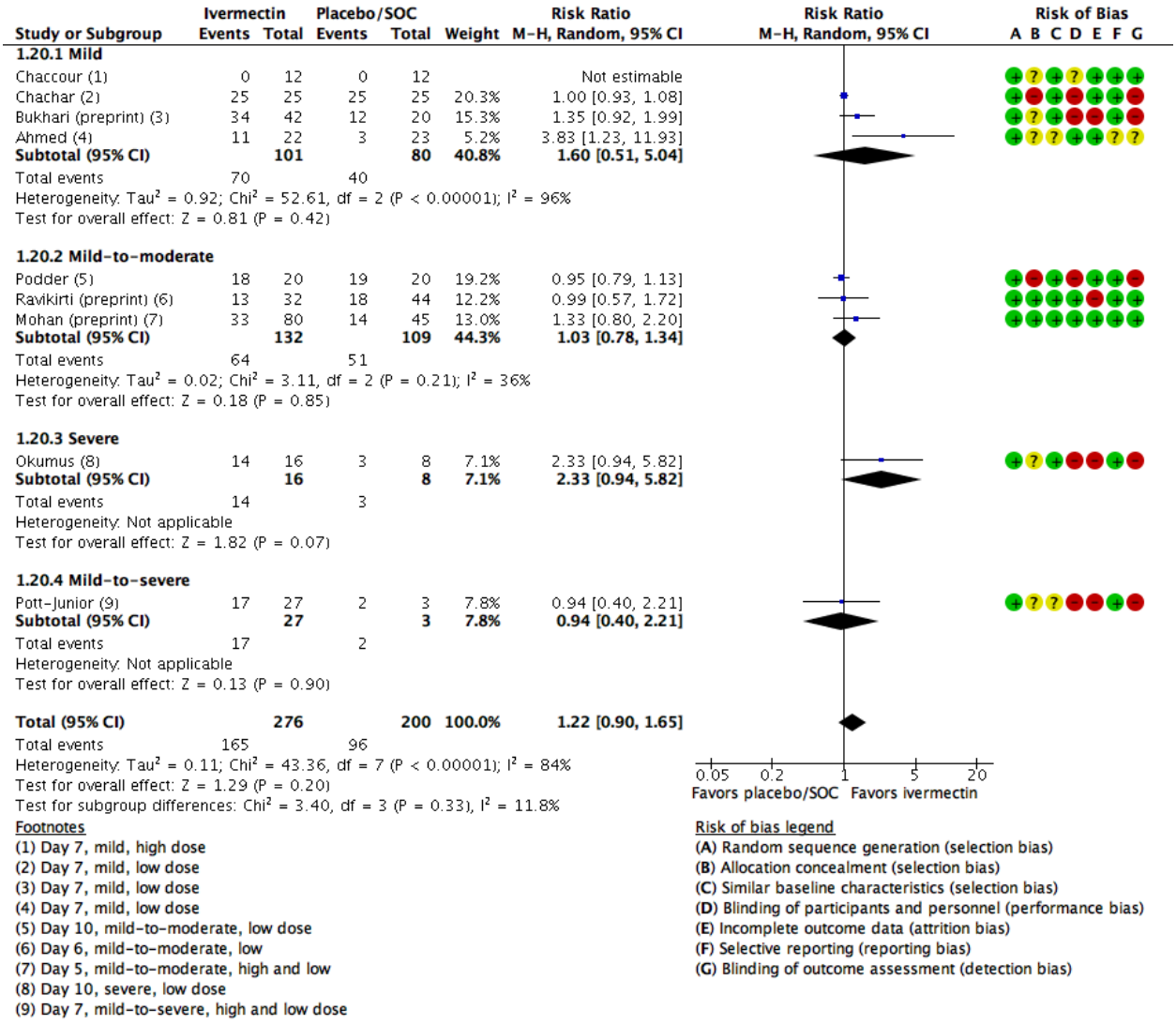


Figure 1.17. Viral clearance (D7-10).

2. Ivermectin vs. hydroxychloroquine

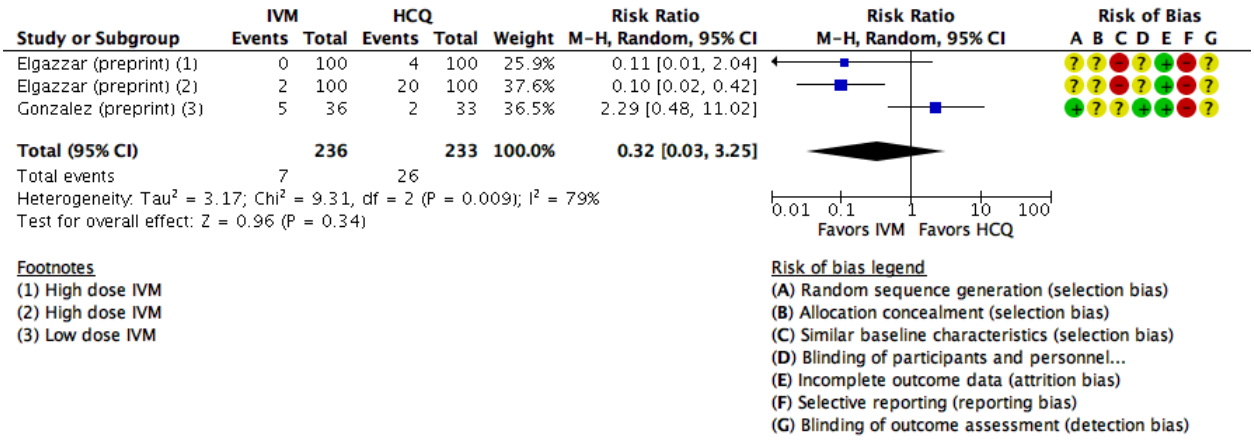


Figure 2.1. Mortality (per protocol).

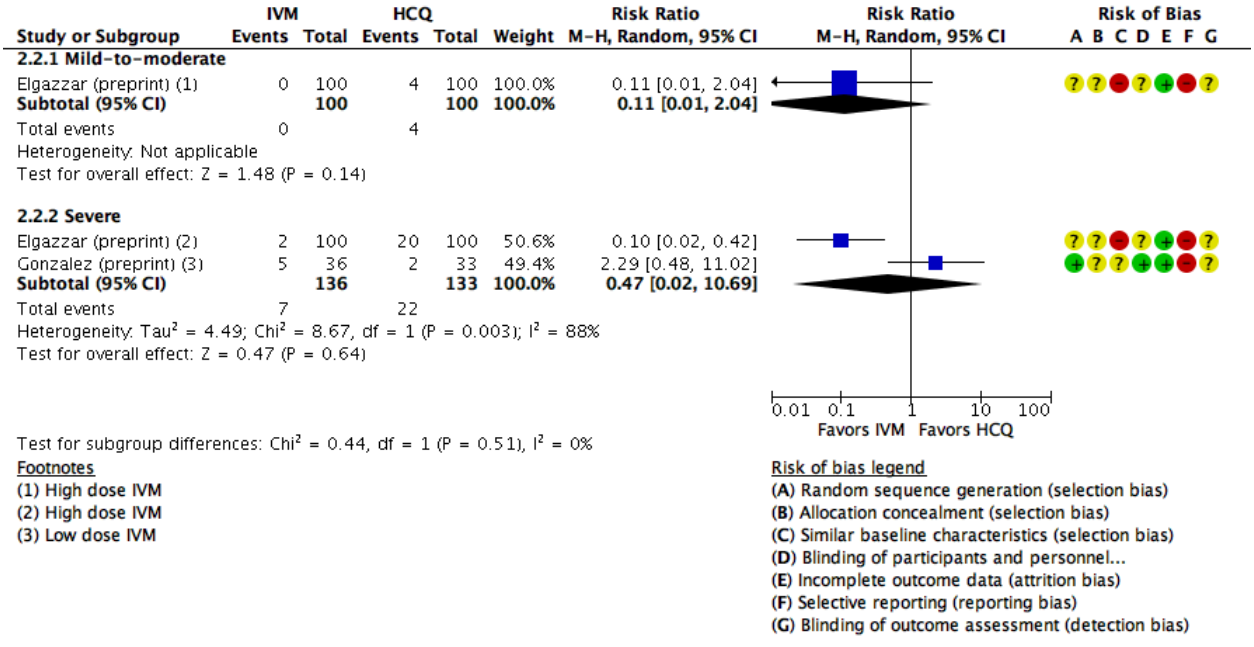


Figure 2.2. Mortality, by disease severity (per protocol).

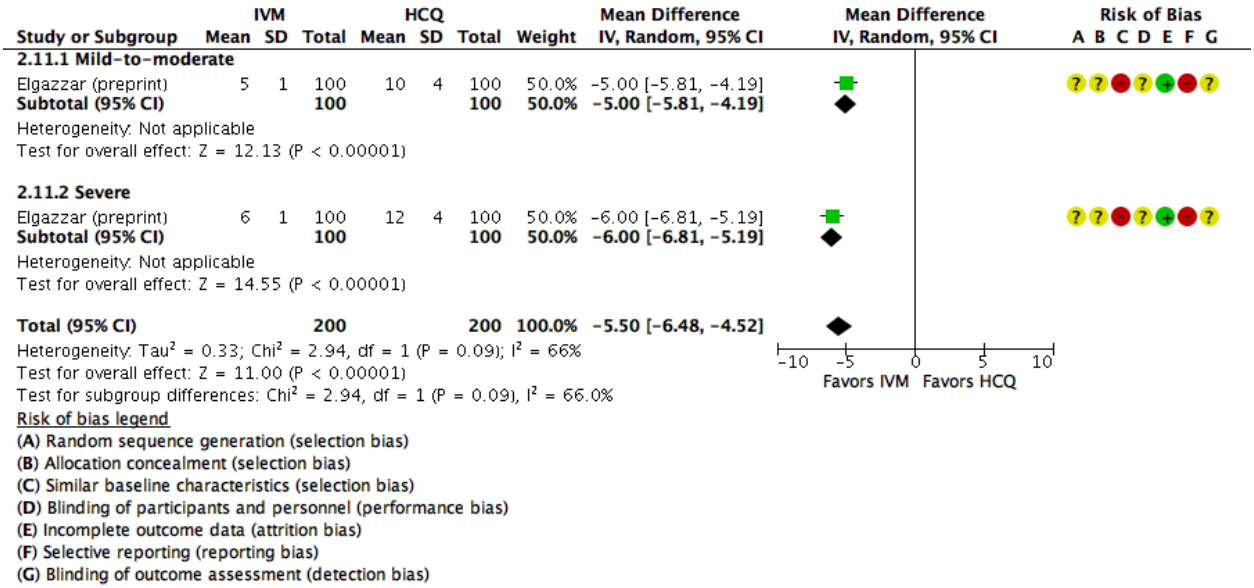


Figure 2.3. Time to PCR negativity (days).

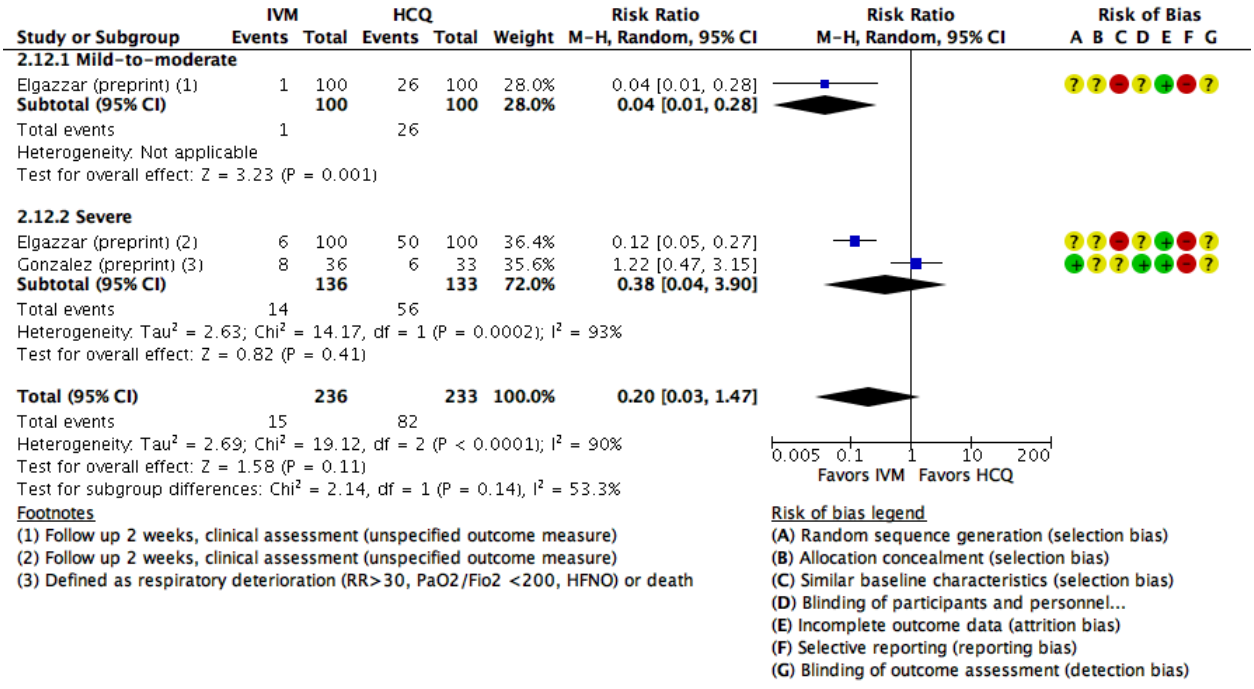


Figure 2.4. Clinical deterioration.

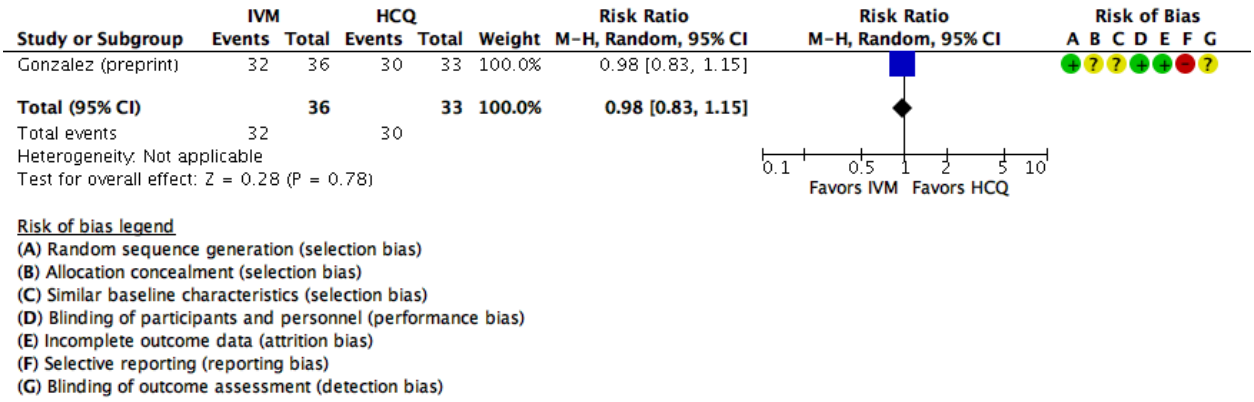


Figure 2.5. Hospital discharge (unspecified ff-up).

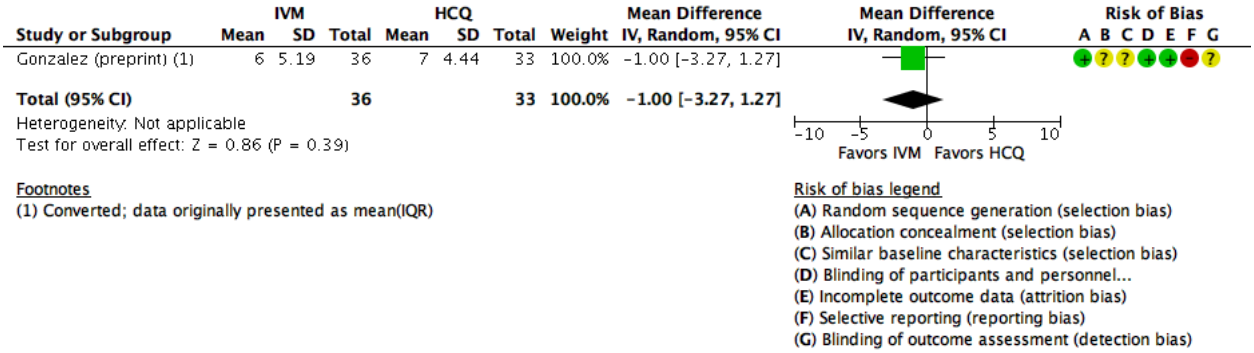


Figure 2.6. Duration of hospitalization.

3. Ivermectin vs. lopinavir/ritonavir

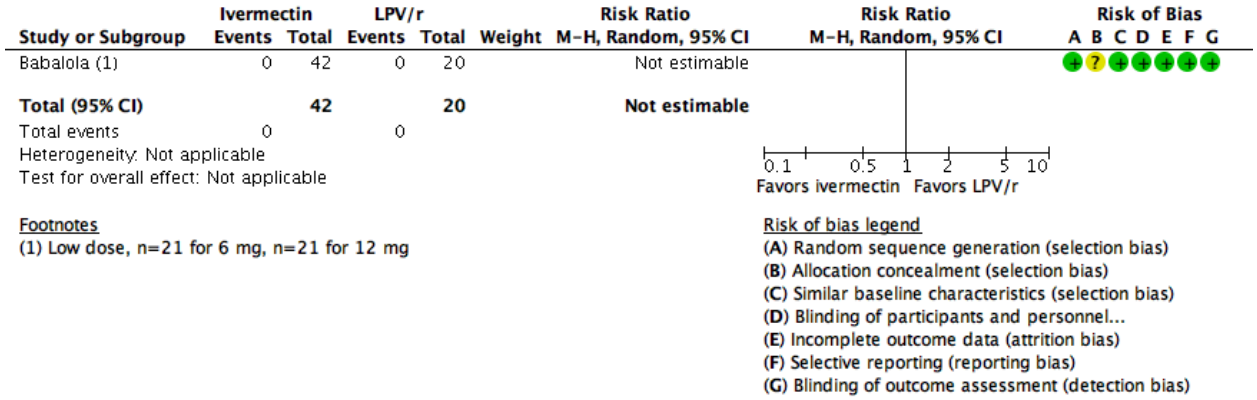


Figure 3.1. Mortality.

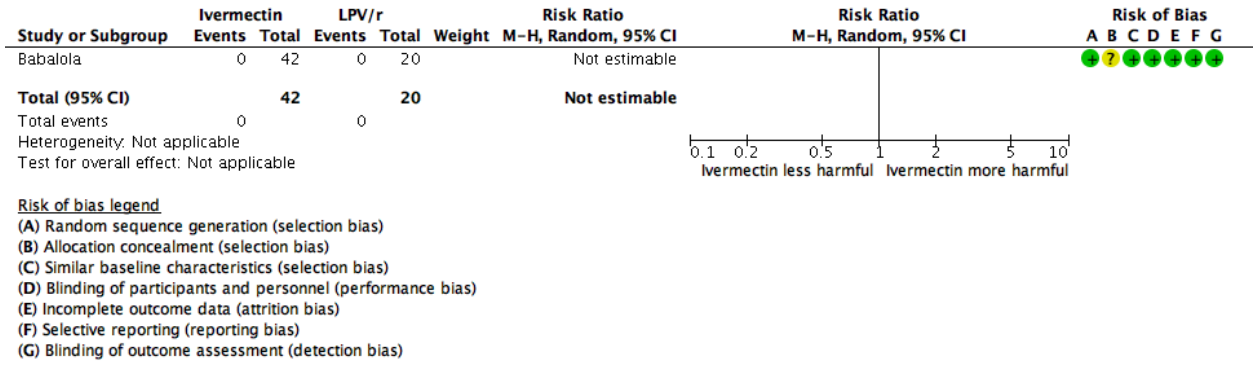


Figure 3.2. Adverse events.

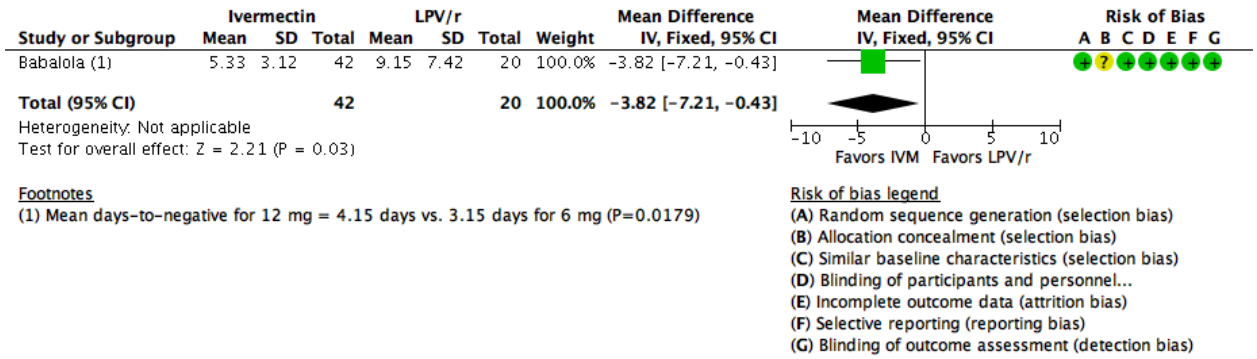


Figure 3.3. Time to PCR negativity, in days.

4. Ivermectin + doxycycline vs. placebo/standard of care

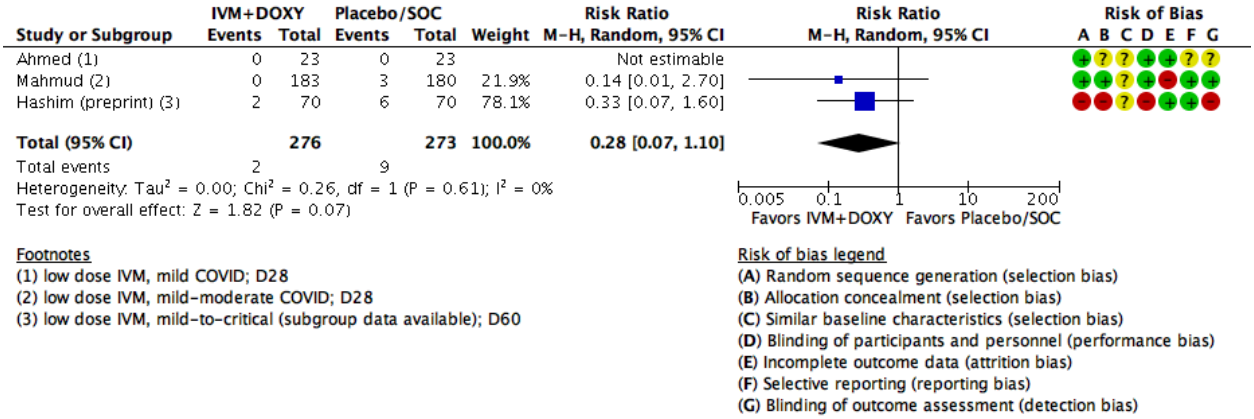


Figure 4.1. Mortality, overall (per protocol).

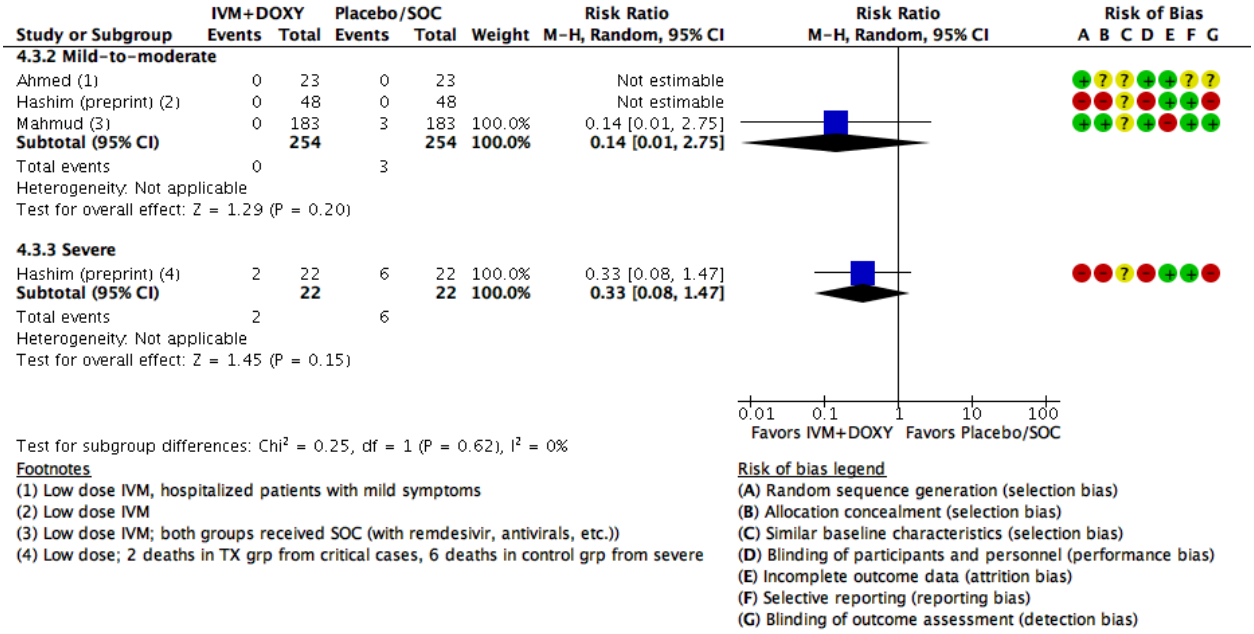


Figure 4.2. Mortality, by disease severity (per protocol).

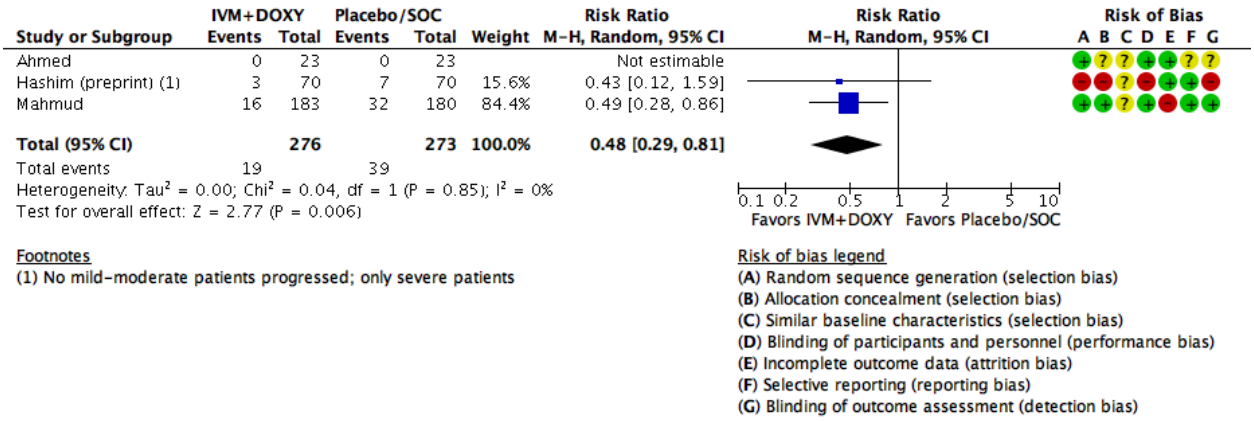


Figure 4.3. Clinical deterioration.

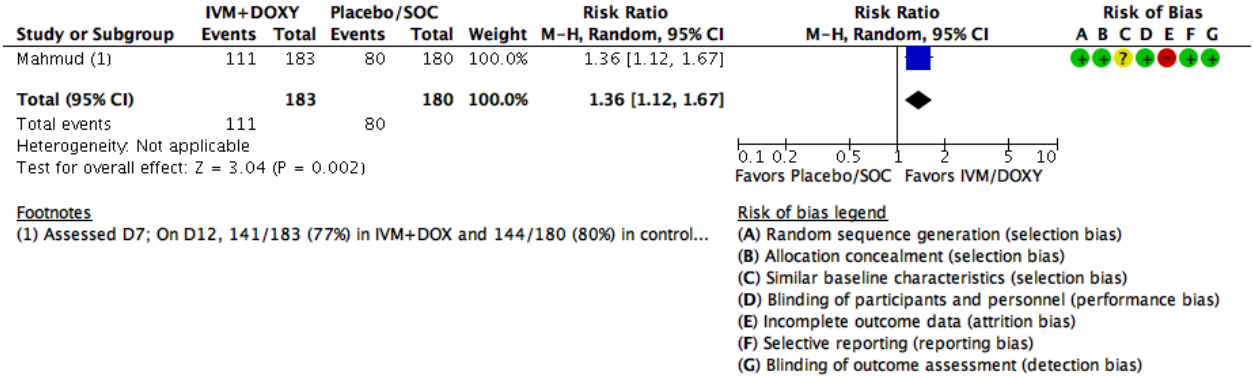


Figure 4.4. Clinical Improvement (D6-D10).

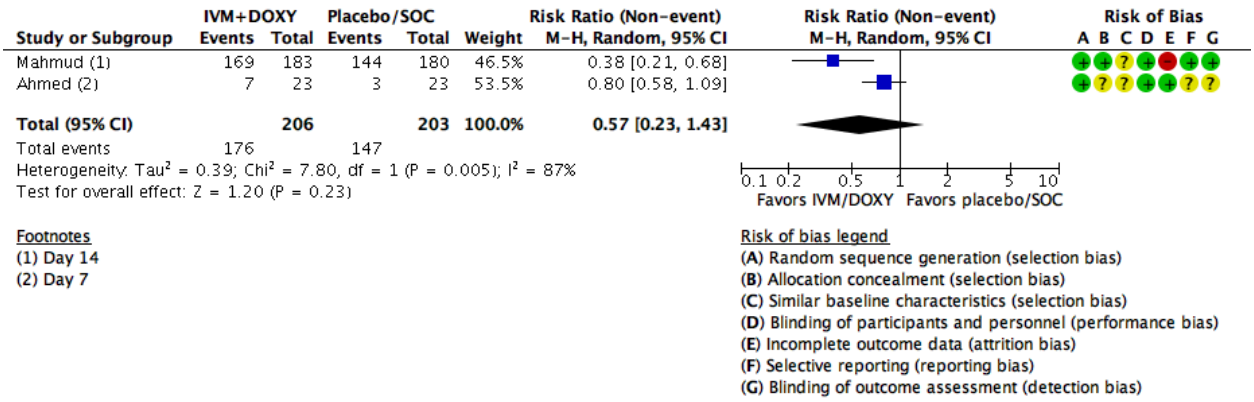


Figure 4.5. Virologic clearance (D7-14).

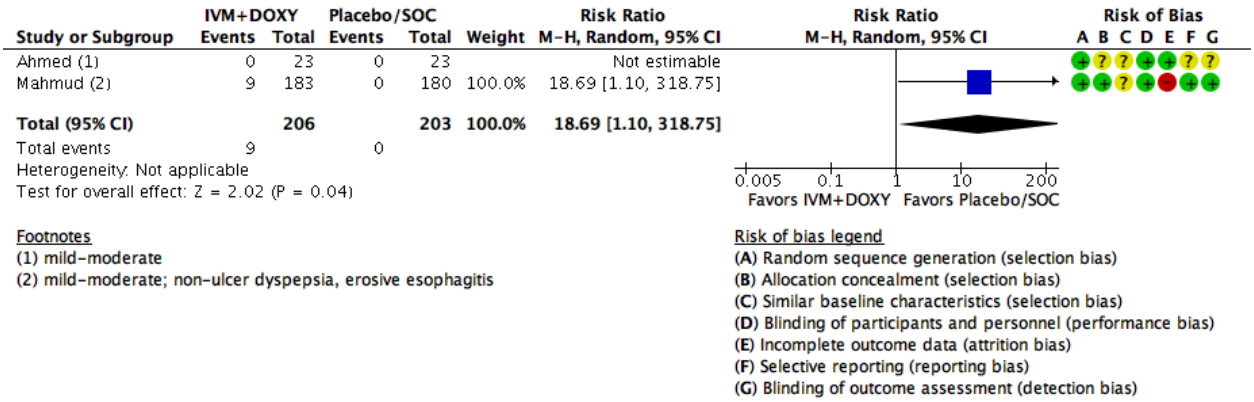


Figure 4.6. Any adverse events.

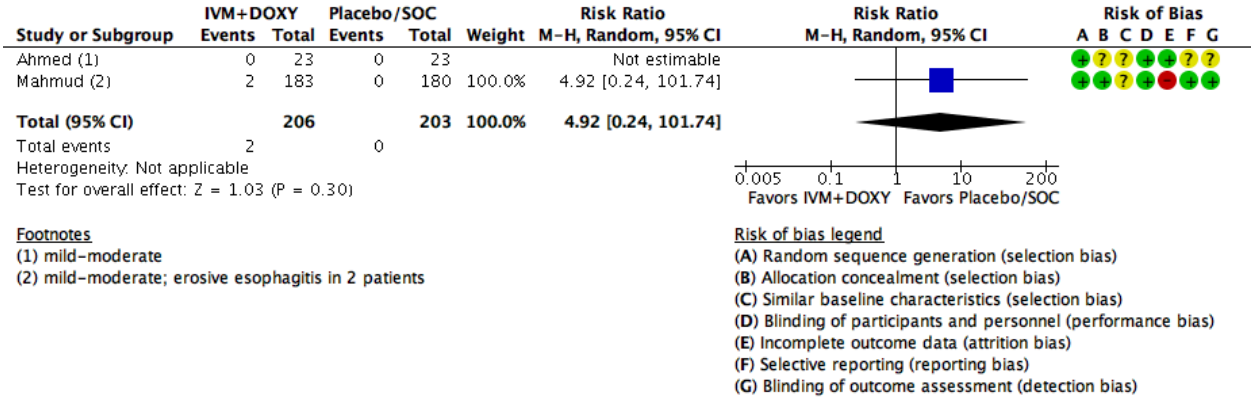


Figure 4.7. Serious adverse events.

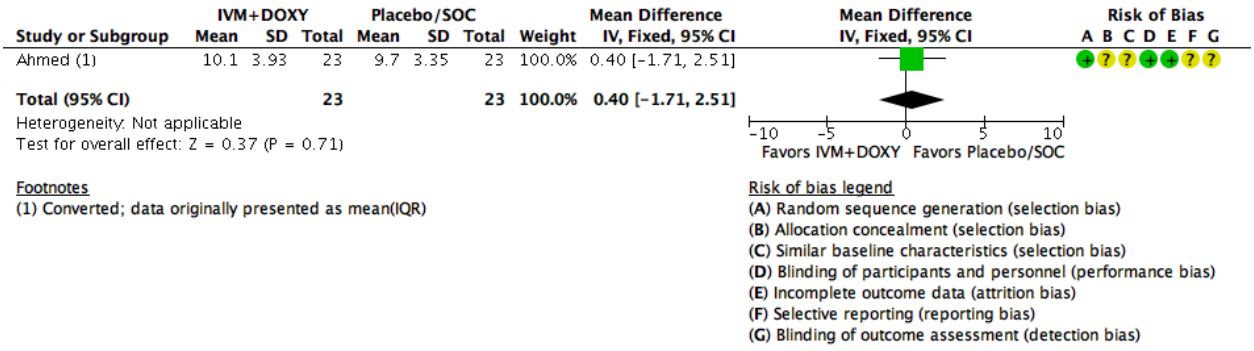


Figure 4.8. Duration of hospitalization.

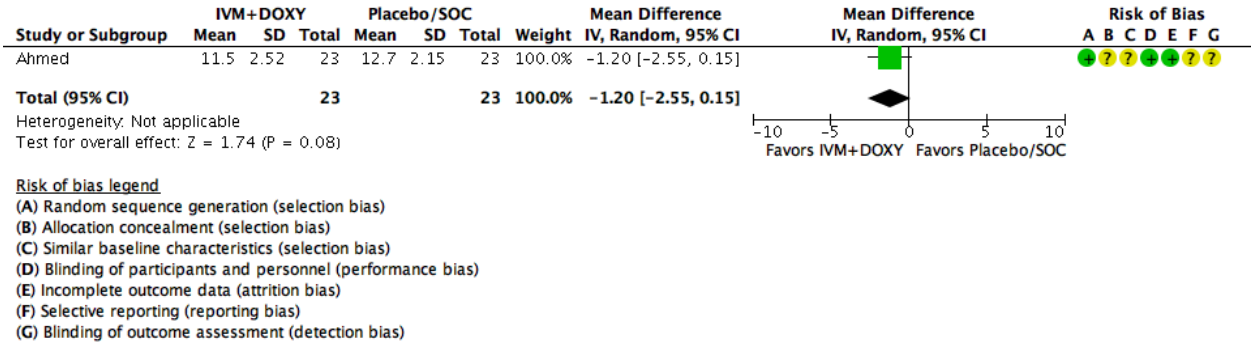


Figure 4.9. Time to PCR negativity (days).

5. Ivermectin + doxycycline vs. hydroxychloroquine + azithromycin

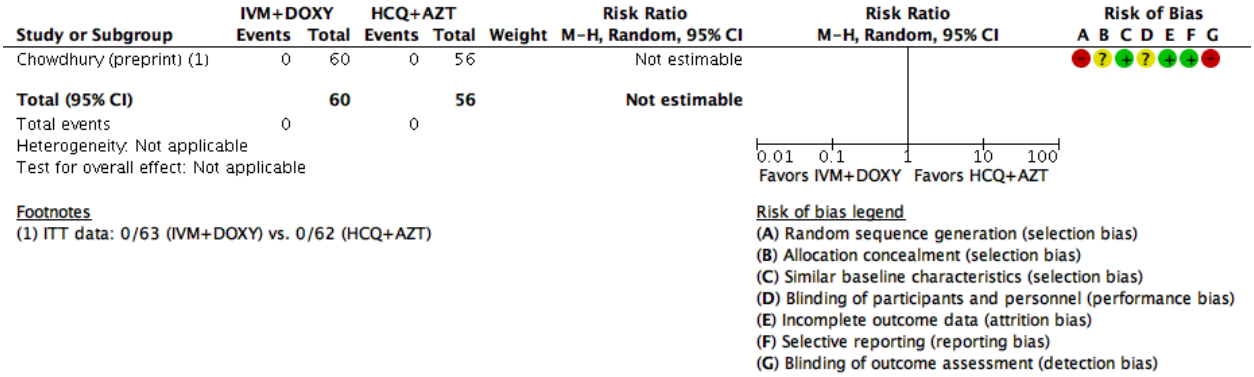


Figure 5.1. Mortality.

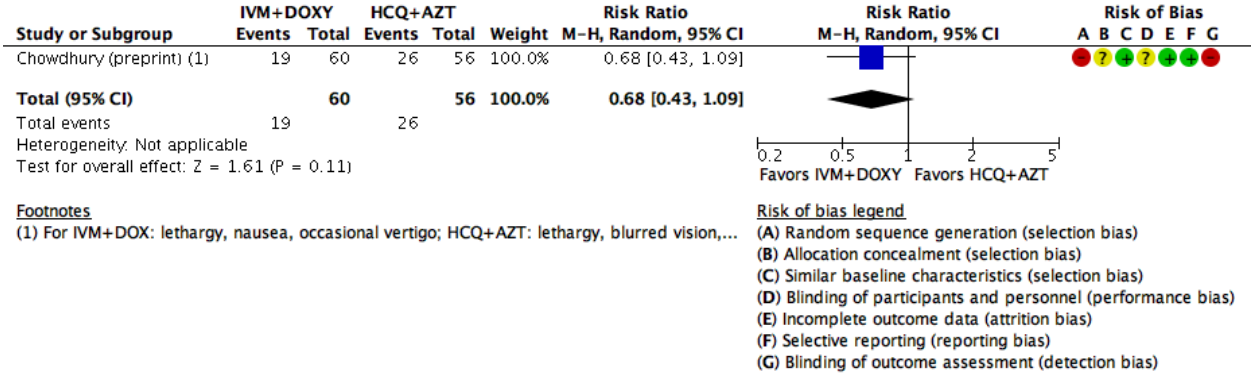


Figure 5.2. Adverse events.

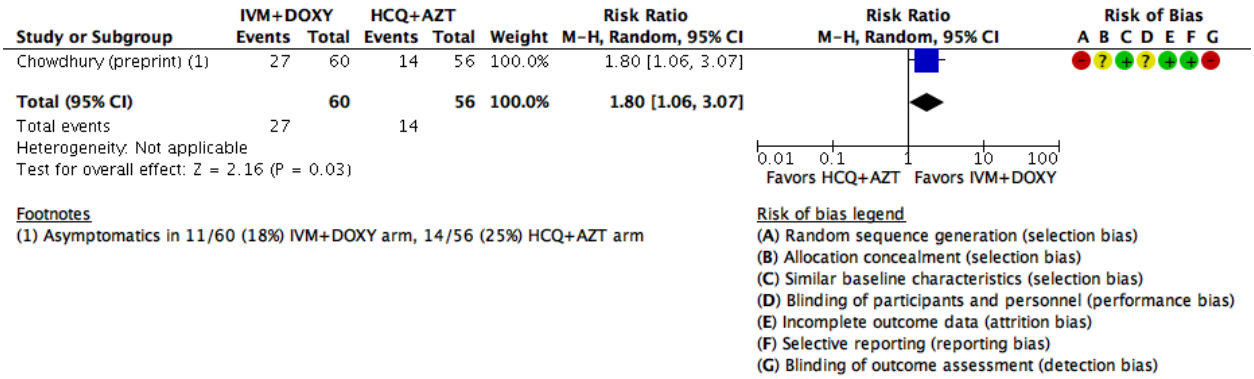


Figure 5.3. Symptom resolution (D5).

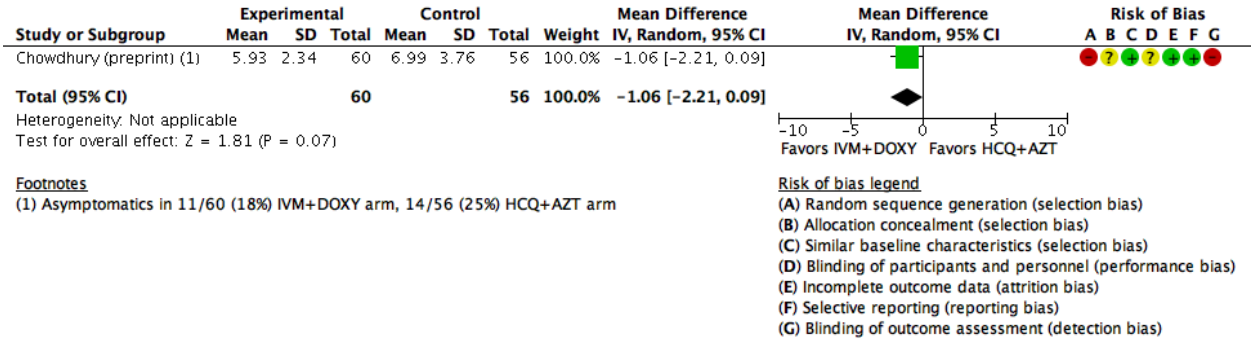


Figure 5.4. Time to symptom resolution (days).

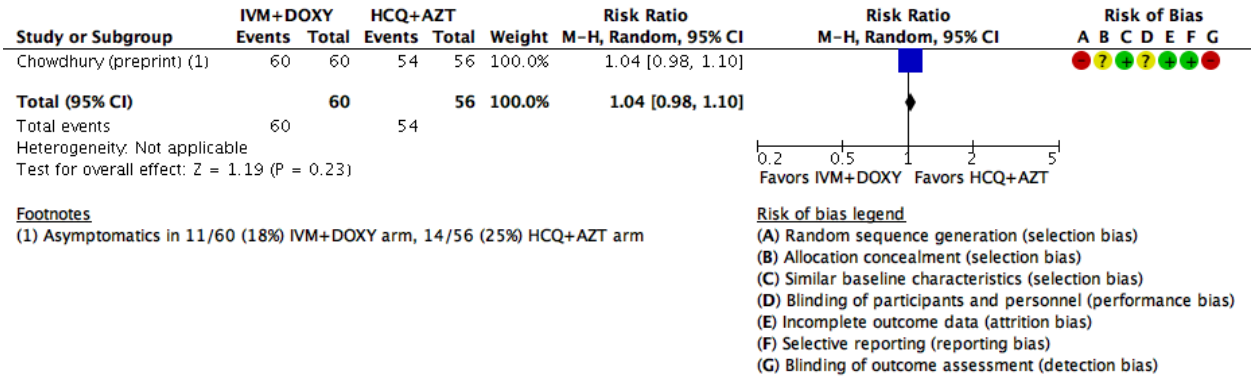


Figure 5.5. Viral negativity (D7).

Appendix 7: GRADE Evidence Profile

Author(s): MVASGJoson, HHGBayona, JJVBesa, DLROTating, MGCCruz
Question: Ivermectin compared to standard of care or placebo as treatment for COVID-19
Setting: Any setting
Bibliography:

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	very serious [b]	serious [c]	not serious	serious [d]	none	206/524 (39.3%)	182/439 (41.5%)	**RR 0.48** (0.23 to 0.99)	**216 fewer per 1,000** (from 319 fewer to 4 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse Events												
10 [e]	randomised trials	serious [f]	serious [g]	not serious	serious [h]	none	324/806 (40.2%)	271/625 (43.4%)	**RR 1.05** (0.75 to 1.47)	**22 more per 1,000** (from 108 fewer to 204 more)	⨁◯◯◯ VERY LOW	
Clinical improvement (follow up: 6-10 days)												
4	randomised trials	serious [i]	not serious	not serious	serious [d]	none	158/310 (51.0%)	155/310 (50.0%)	**RR 1.01** (0.87 to 1.16)	**5 more per 1,000** (from 65 fewer to 80 more)	⨁⨁◯◯ LOW	
Clinical deterioration												
6	randomised trials	serious [j]	not serious [k]	not serious	serious [l]	none	25/496 (5.0%)	28/375 (7.5%)	**RR 0.74** (0.45 to 1.23)	**19 fewer per 1,000** (from 41 fewer to 17 more)	⨁⨁◯◯ LOW	
Need for mechanical ventilation												
5	randomised trials	very serious [m]	not serious	not serious	serious [n]	none	5/245 (2.0%)	6/162 (3.7%)	**RR 0.67** (0.19 to 2.39)	**12 fewer per 1,000** (from 30 fewer to 51 more)	⨁◯◯◯ VERY LOW	
Virologic clearance (negative RT-PCR) (follow up: 6-10 days)												
9	randomised trials	very serious [o]	very serious [p]	not serious	serious [q]	none	161/269 (59.9%)	117/223 (52.5%)	**RR 1.08** (0.90 to 1.30)	**42 more per 1,000** (from 52 fewer to 157 more)	⨁◯◯◯ VERY LOW	
Hospital discharge (follow up: 10-14 days)												

2	randomised trials	not serious	not serious	not serious	serious [h]	none	119/135 (88.1%)	81/102 (79.4%)	**RR 1.08** (0.97 to 1.21)	**64 more per 1,000** (from 24 fewer to 167 more)	⊕⊕⊕◯ MODERATE	
Duration of hospitalization (days)												
3	randomised trials	serious [r]	serious [s]	serious [t]	serious [u]	none	Ahmed: mean duration of hospitalization was 9.6 days, 95% CI [7.7 to 11.7] for ivermectin and 9.7 days, 95% CI [8.1 to 11.0] for the placebo group. Niaee: mean range of hospitalization was 5-7 days [IQR 4-10] for ivermectin and 8 days [IQR 6-11] for the control group. Shahbaznejad reported 7.1 days (SD 0.5) for IVM vs 8.4 days (SD 0.6) for control. MD -1.01 [-2.36, 0.34] days				⊕◯◯◯ VERY LOW	
Time to symptom resolution (in days)												
3	randomised trials	serious [v]	serious	not serious	not serious	none	Pooled mean difference for Mohan 2020, Podder 2020:, Shahbaznejad: MD -0.83 [-1.49, -0.17] 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.				⊕⊕◯◯ LOW	
Number of symptomatic days												
1	randomised trials	very serious [w]	not serious	not serious	not serious	none	171/282 (60.6%)	255/295 (86.4%)	**RR 0.70** (0.63 to 0.78)	**259 fewer per 1,000** (from 320 fewer to 190 fewer)	⊕⊕◯◯ LOW	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Trials: Chaccour, Mohan, Krolewiecki, Ahmed, Ravikirti, Niaee, Lopez-Medina, Okumus, Gonzalez, Shahbaznejad; Okumus 2020 assessed mortality at D60
b. Serious to very serious risk of bias noted for 8/10 studies. Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviations from intended interventions and selection of reported results.
c. Low heterogeneity (I2 = 26%)
d. Wide confidence interval containing 1.00
e. Trials: Ahmed, Bukhari, Shahbaznejad, Pott-Junior, Lopez-Medina, Chaccour, Mohan, Krolewiecki, Okumus, Chachar
f. Serious to very serious risk of bias in 8/10 studies.
g. Moderate heterogeneity (I2 = 36%)
h. Some concern for imprecision due to confidence interval between benefit and harm
i. Serious concern for bias over the clinical outcome measured since the study of Chachar and Okmus are open-label in design.
j. Included 3 studies with serious risk of bias (Ahmed et al. 2020; Krolewiecki et al., 2020; Ravikirti et al., 2020)
k. Outcome measures were different (ICU admission, Progression of O2 requirement, Need for mechanical ventilation)
l. Some concern for wide confidence interval
m. Included 3 studies with at least serious risk of bias (Krolewiecki et al., 2020; Ravikirti et al, 2020; Pott-Junior 2020)
n. Imprecision due to small number of events and wide confidence interval that crosses threshold for benefit and harm upon use of intention-to-treat data
o. 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.
p. Some concern for inconsistency. I2 = 71%
q. Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for no effect and low number of particpants
r. The only RCT that reported a significant difference in hospital length of stay enrolled patients with mixed levels of disease severity (including mild), and had very serious risk of bias due to the lack of blinding among assessors, participants, and investigators [10].
s. Results varied across 3 studies
t. Some concern with how the data was represented among the two studies.
u. The duration of hospitalization between the two studies cannot be pooled.
v. Very serious risk of bias for Podder 2020

w. Some concerns with the patient reported outcome since the placebo was not identical to the ivermectin tablet. patients may not be blinded.

Author(s): MVASGJoson, HHGBayona, JJVBesa, DLROTating, MGCCruz
Question: Ivermectin compared to hydroxychloroquine for COVID-19
Setting: Any setting
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivermectin	hydroxychloroquine	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2 [a]	randomised trials	very serious [b]	serious [c]	not serious	serious [d]	none	7/236 (3.0%)	26/233 (11.2%)	**RR 0.32** (0.03 to 3.25)	**76 fewer per 1,000** (from 108 fewer to 251 more)	⨁◯◯◯ VERY LOW	CRITICAL
Clinical deterioration												
2	randomised trials	very serious [b]	very serious [e]	not serious	serious [f]	none	15/236 (6.4%)	82/233 (35.2%)	**RR 0.20** (0.03 to 1.47)	**282 fewer per 1,000** (from 341 fewer to 165 more)	⨁◯◯◯ VERY LOW	CRITICAL
Hospital discharge (follow up: unspecified)												
1 [g]	randomised trials	very serious [b]	not serious	not serious	serious [h]	none	32/36 (88.9%)	30/33 (90.9%)	**RR 0.98** (0.83 to 1.15)	**18 fewer per 1,000** (from 155 fewer to 136 more)	⨁◯◯◯ VERY LOW	
Duration of hospitalization (follow up: unspecified; assessed with: days)												
1	randomised trials	very serious [b]	not serious	not serious	serious [i]	none	IVM: Mean 6 days (SD 5.19) HCQ: Mean 7 days (SD 4.44) MD -1.00 [-3.27, 1.27] days				⨁◯◯◯ VERY LOW	
Time to PCR negativity												
1 [j]	randomised trials	very serious [b]	not serious	not serious	not serious	none	IVM: 5 days (SD 1) for mild-to-moderate, 6 days (SD 1) for severe HCQ: 10 days (SD 4) for mild-to-moderate, 12 days (SD 4) for severe MD -5.50 [-6.48, -4.52] days				⨁⨁◯◯ LOW	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Elgazzar 2020, Beltran-Gonzalez 2021
b. Selection bias, selective reporting, unclear blinding methods,
c. I2 = 79%
d. Wide confidence intervals (0.03 - 3.25), small number of events
e. I2 = 90%

f. Wide confidence intervals
g. Beltran-Gonzalez 2021
h. Crosses 1.00
i. wide confidence intervals, crosses 1.00
j. Elgazzar 2020

Author(s): MVASGJoson, HHGBayona, JJVBesa, DLROTating, MGCCruz
Question: Ivermectin compared to lopinavir/ritonavir for COVID-19
Setting: Any setting
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivermectin	lopinavir/ritonavir	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1 [a]	randomised trials	not serious	not serious	not serious	serious [b]	none	0/42 (0.0%)	0/20 (0.0%)	not estimable		⨁⨁⨁◯ MODERATE	
Any adverse events												
1	randomised trials	not serious	not serious	not serious	serious [b]	none	0/42 (0.0%)	0/20 (0.0%)	not estimable		⨁⨁⨁◯ MODERATE	
Time to PCR negativity												
1	randomised trials	not serious	not serious	not serious	serious [c]	none	MD -3.82 [-7.21, -0.43] days Mean days-to-negative for 12 mg = 4.15 days vs. 3.15 days for 6 mg (P=0.0179)				⨁⨁⨁◯ MODERATE	

CI: Confidence interval

Explanations

a. Babalola 2021
b. No events
c. wide confidence intervals; difference may not be clinically significant

Author(s): MVASGJoson, HHGBayona, JJVBesa, DLROTating, MGCCruz
Question: Should ivermectin with doxycycline compared to placebo or standard of care for COVID-19
Setting: Any setting
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Should ivermectin with doxycycline	placebo or standard of care	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3 [a]	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	2/276 (0.7%)	9/273 (3.3%)	**RR 0.28** (0.07 to 1.10)	**24 fewer per 1,000** (from 31 fewer to 3 more)	⨁◯◯◯ VERY LOW	CRITICAL
Clinical deterioration												
3	randomised trials	very serious [b]	not serious	not serious	not serious	none	19/276 (6.9%)	39/273 (14.3%)	**RR 0.48** (0.29 to 0.81)	**74 fewer per 1,000** (from 101 fewer to 27 fewer)	⨁⨁◯◯ LOW	CRITICAL
Clinical improvement (D6-10)												
1 [d]	randomised trials	very serious [e]	not serious	not serious	not serious	none	111/183 (60.7%)	80/180 (44.4%)	**RR 1.36** (1.12 to 1.67)	**160 more per 1,000** (from 53 more to 298 more)	⨁⨁◯◯ LOW	CRITICAL
Virologic clearance (D7-14)												
2 [f]	randomised trials	very serious [g]	serious [h]	not serious	serious [c]	none	176/206 (85.4%)	147/203 (72.4%)	**RR 0.57** (0.23 to 1.43)	**311 fewer per 1,000** (from 558 fewer to 311 more)	⨁◯◯◯ VERY LOW	
Any adverse events												
2	randomised trials	very serious [g]	not serious	not serious	serious [i]	none	9/206 (4.4%)	0/203 (0.0%)	**RR 18.69** (1.10 to 318.75)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Time to PCR negativity												

1	randomised trials	serious	not serious	not serious	serious [i]	none	IVM+DOXY: 11.5 days (SD 2.52) Placebo/SOC: 12.7 days (SD 2.15) MD -1.20 [-2.55, 0.15]	⊕⊕◯◯ LOW	
Duration of hospitalization									
1	randomised trials	serious	not serious	not serious	serious [i]	none	IVM+DOXY: 10.1 (SD 3.9) days Placebo/SOC: 9.7 (SD 3.4) days MD 0.40 [-1.71, 2.51] days	⊕⊕◯◯ LOW	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Ahmed 2020, Mahmud 2021, Hashim 2021
b. high risk of bias concerns for Hashim (randomization, blinding); incomplete outcome data for Mahmud and unclear baseline comparability; unclear allocation concealment and baseline comparability, selective reporting for Ahmed
c. wide confidence intervals, crosses 1.00
d. Mahmud 2021
e. Unclear baseline comparability, incomplete outcome data
f. Mahmud 2021, Ahmed 2020
g. incomplete outcome data for Mahmud and unclear baseline comparability; unclear allocation concealment and baseline comparability, selective reporting for Ahmed
h. I2 = 87%
i. Wide confidence intervals
j. crosses 1.00

Author(s): MVASGJoson, HHGBayona, JJVBesa, DLROTating, MGCCruz
Question: Ivermectin with doxycycline compared to hydroxychloroquine with azithromycin for COVID-19
Setting: Any setting
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivermectin with doxycycline	hydroxychloroquine with azithromycin	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	0/60 (0.0%)	0/56 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	
Any adverse events												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	19/60 (31.7%)	26/56 (46.4%)	**RR 0.68** (0.43 to 1.09)	**149 fewer per 1,000** (from 265 fewer to 42 more)	⨁◯◯◯ VERY LOW	
Symptom resolution (follow up: 5 days)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	27/60 (45.0%)	14/56 (25.0%)	**RR 1.80** (1.06 to 3.07)	**200 more per 1,000** (from 15 more to 518 more)	⨁⨁◯◯ LOW	
Time to symptom resolution												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	IVM+DOXY: 5.9 (SD 2.3) days Control: 7 (SD 3.8) days MD -1.06 [-2.21, 0.09] days				⨁⨁◯◯ LOW	
Viral clearance (follow up: 7 days)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	60/60 (100.0%)	54/56 (96.4%)	**RR 1.04** (0.98 to 1.10)	**39 more per 1,000** (from 19 fewer to 96 more)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Random sequence generation (odd-even), unclear allocation concealment, unclear blinding of patients and investigators, unblinded assessors; enrolled asymptomatics
b. no events
c. confidence interval crosses 1.00