IVERMECTIN

RECOMMENDATION

There is insufficient evidence to recommend 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 for the treatment of patients with severe 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

Studies that favored the use of ivermectin for the treatment of COVID-19 were of very low quality, and participants in these studies were given drugs other than ivermectin. The most common adverse events that were observed for ivermectin were gastrointestinal symptoms, headache, dizziness, and nausea. Esophagitis and dyspepsia were observed on the use of ivermectin combined with doxycycline. There is still a need for good quality evidence to show that ivermectin has a significant benefit for the treatment of COVID-19.

Furthermore, health equity may be decreased if budget will be allocated for ivermectin rather than efficacious medications and standard of care. The cost of and availability of human grade ivermectin is a 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.
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, which was highly variable across the trials.

EVIDENCE SUMMARY

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

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Key Findings

Our search yielded 16 randomized controlled trials (RCTs) that evaluated the effect of ivermectin against placebo or standard of care for patients with COVID-19. Eight of these 16 RCTs are preprints. Although we found evidence suggesting that ivermectin may significantly reduce mortality, this effect is still very uncertain due to very low quality of evidence. Downgrading occurred due to serious inconsistency, imprecision, and serious to very serious risk of bias in most of the studies.

Subgroup analysis revealed that the observed mortality benefit was only present for studies that had lower methodological quality, had not yet been peer-reviewed, or used high doses of ivermectin.

Ivermectin did not show any significant effect on virologic clearance at day 6-7, clinical deterioration, need for mechanical ventilation, clinical improvement at day 6-10, clinical deterioration, hospital discharge at day 10-14, duration of hospitalization, and time to complete symptom resolution.

The adverse effects observed from the use of ivermectin were not significantly different from those observed in the control groups. Gastrointestinal symptoms, dizziness, and rash were the most common adverse effects reported in the RCTs. However, significant adverse events (e.g., erosive esophagitis, non-ulcer dyspepsia) was reported in studies that combined ivermectin+doxycycline.

Based on very low certainty of evidence from 3 RCTs that compared ivermectin+doxycycline to placebo/standard of care, ivermectin+doxycycline was favored in terms of clinical improvement on D6-10, clinical deterioration, and time to symptom resolution, but not for virologic clearance or duration of hospitalization. There was no significant mortality benefit.

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 (e.g. 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].

Review Methods

MEDLINE, Cochrane Library, and gray literature in MedRxIV, and BioRxIV (initial search date up to 2 February 2021; updated 7 April 2021) were searched using the following keywords and MeSH terms: "ivermectin", and COVID-19 related terms. Ongoing trials were searched in

Clinicaltrials.gov and NMA-COVID-19 registry. We also searched for relevant evidence from the NICE Guidance (https://www.nice.org.uk/guidance), COVID-19 Open Living Evidence Synthesis to Inform Decision (https://covid-nma.com/; updated 25 March 2021), National COVID-19 Clinical Evidence Taskforce Living Guidelines (https://covid19evidence.net.au/) and WHO Living CPG. Included studies from systematic reviews on the same topic [22,23,24] were searched as well and included as long as they provided sufficient information to allow critical appraisal.

Observational studies or quasi-randomized trials were excluded. For the outcomes mortality and adverse effects, subgroup analysis was done according to ivermectin dose used and disease severity. We also performed sensitivity analysis to assess the robustness of the results or if the conclusions may be affected from the exclusion of studies with high / serious risk of bias. Separate analyses were done for (1) ivermectin as monotherapy, and (2) ivermectin in combination with doxycycline.

Articles that met the following eligibility criteria were included:

Intervention: Ivermectin as a treatment or adjunct to standard treatment, ivermectin with doxycyline.

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 PCR, adverse events.

Study design: randomized controlled trials (RCTs)

Results

Characteristics of included studies

Our initial search on 2 February, 2021 found 218 studies. Removal of duplicates and initial screening yielded 18 studies for full text assessment. 28 articles were excluded because of having a non-randomized controlled trial design, using ivermectin for prophylaxis, or other reasons (see Appendix 3).

As of 30 March 2021, we found 16 randomized controlled trials (RCTs) (N=1,923) that used ivermectin as treatment for adults with COVID-19 in Bangladesh [3,19,21], Spain [4], Pakistan [5,17], Egypt [6], Argentina [7], India [8,9], Iran [10], Turkey [11], Mexico [15], Brazil [18], Colombia [16], Iraq [20]. Sample sizes ranged from 20 to 473. Twelve studies enrolled only mild to moderate cases [3,4,5,7,8,9,16,17,18,19,21], while 3 enrolled only severe cases [6,11,15]. Three included a mix of mild to severe cases [10,6,20], with 1 RCT [10] not specifying the number of patients under each severity group. Ten of the 16 studies (63%) were pre-prints and have not yet been peer-reviewed [6,7,8,9,10,11,15,17,20,21].

Fourteen RCTs compared ivermectin with placebo/standard of care, while 2 RCTs compared ivermectin+doxycyline with placebo/standard of care [20,21]. Different treatment regimens of ivermectin were used: 13 RCTs used low dose ivermectin 200mcg/kg (12mg) [3,5,8-11,15-19, 20-21] and 6 RCTs used high dose ivermectin 400-600mcg/kg [4,6,7,8,10,18]. Duration of ivermectin

treatment ranged from 1-5 days. Seven studies were placebo-controlled [3,4,8,9,10,15,16] while 7 used standard of care [5,6,7,11,17,18,19]. Detailed characteristics of the included studies are available in Appendix 1.

Methodological quality

The overall rating for quality of evidence was very low for most of the outcomes; 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. Risk of bias was rated very serious in 9/16 (56.3%) studies [3,6,9,11,15,18,19,20,21] and serious in 5/16 studies [4,5,7,10,17]. Only 2 trials (Mohan et al., 2020; Lopez-Medina et al., 2021) exhibited no serious risk of bias [8,16].

Summary of results of included studies

the relevant Forest Plots are found in Appendix 4

Comparison 1: Ivermectin vs. placebo / standard of care

Mortality

Based on 9 RCTs, ivermectin significantly reduced overall mortality among COVID-19 patients (2% for ivermectin vs 7.8% for control) (RR 0.30 [95% CI 0.12, 0.73], n=1,559) (Figure 1.1). However, the certainty of this estimate for this outcome is affected by moderate heterogeneity (I^2=56%) across studies and high risk of bias in most (7/9) of the studies. Subgroup analysis was performed to explore if the inconsistency may be explained by differences in disease severity prior to treatment (mild-to-moderate, severe, mixed), ivermectin dosage (high vs. low), study quality (studies with higher vs. lower risk of bias). We observed that the mortality benefit was only present for studies that had lower methodological quality, had not yet been peer-reviewed, or used high doses of ivermectin.

Effect of study quality on mortality

In studies with higher methodological quality, ivermectin did not show any significant mortality benefit (RR 0.24 [95% CI 0.01, 5.87]) [8,16]. In contrast, studies that exhibited serious or very risk of bias issues, a significant effect was noted (RR 0.30 [95%CI 0.12, 0.79], 7 RCTs) [3,4,6,9,10,11,15]. Preprints more clearly favored ivermectin (RR 0.32 [95% CI 0.13, 0.79], 6 RCTs) (Figure 1.2) [4,6,9,10,11,15], compared to studies that have been peer-reviewed (RR 0.24 [95% CI 0.01, 5.87] 3 RCTs) [3,8,16] (Figure 1.3).

Effect of disease severity on mortality

In severe patients, very low quality evidence from 3 pre-print studies [6,11,15] suggested that ivermectin did not significantly reduce mortality in patients with severe COVID-19 (RR 0.42 [95% CI 0.12, 1.43] I^2=72%, n=333) (Figure 1.4). In the only RCT that reported mortality benefit, a very

serious risk of bias was noted due to unclear randomization methods and selection bias from enrolling more patients with ischemic heart disease in the control group 12/100 vs 5/100) [6].

In patients with mild-to-moderate disease, a significant mortality benefit was seen with ivermectin (RR 0.14 [95% CI 0.03,0.79] I^2=0%, n=1,009, 6 RCTs) (Figure 1.4). In patients with mixed disease severity, the Iranian RCT by Niaee *et al.* also showed significant reduction in mortality from ivermectin use (RR 0.18 [95% CI 0.06,0.55], n=60) (Figure 1.4) [10]. This study showed serious risk of bias due to unclear blinding of patients and physicians, 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.

Effect of ivermectin dose on mortality

Significant benefit was noted only with high dose (RR 0.08 [95% CI 0.03, 0.27] I^2=0%, 4 RCTs, n=591) [Mohan, Chaccour, Niaee, Elgazzar] but *not* with low dose ivermectin (RR 0.55 [95% CI 0.30, 1.00] I^2=0%, 7 RCTs, n=931) [Mohan, Ahmed, Ravikirti, Lopez-Medina, Niaee, Okumus, Gonzalez] (Figure 1.5).

Adverse effects

Ivermectin was not associated with increased adverse effects (RR 0.87 [95% CI 0.70, 1.09] I^2=36%; n=1369; 10 RCTs) (Figure 1.6). Subgroup analysis showed similar findings regardless of dose, with an RR of 0.80 for high dose ([95% CI 0.57, 1.11], I^2=6, 5 RCTs) and RR of 1.05 for low dose ([95% CI 0.65, 1.69], I^2=31%, 7 RCTs) (Figure 1.7). A very low GRADE rating was assigned to this body of evidence due to small number of events, imprecision, inconsistency and serious risk of bias in most studies from unclear randomization, allocation and blinding methods.

Gastrointestinal symptoms, dizziness, headache, and rash were the most common side effects reported. One patient in the ivermectin group reported hyponatremia (unspecified degree or serum sodium values) as a serious adverse effect [7]. One high-quality RCT [16] reported serious adverse events (e.g., multi-organ failure) in 4 patients (2/198 in control, 2/200 ivermectin group), but considered these to be unrelated to ivermectin.

Other outcomes

The proportion of patients showing virologic clearance at day 6 to 10 (RR 1.08 [95% CI 0.90, 1.30] I^2=71%; n=770) (Figure 1.8) was not significantly different based on 9 RCTs [3,4,5,8,9,11,17,18,19].

The effects of ivermectin were not significantly different from control on other outcomes: clinical deterioration (RR 0.66 [95% CI 0.34, 1.26] I^2=0%; n=837) (Figure 1.9) ([3,7,8,9,16], need for mechanical ventilation (RR 0.40 [95% CI 0.06,2.55] I^2=8%; n=309) (Figure 1.10)[7,8,9], clinical improvement at day 6-10 (RR 1.01 [95% CI 0.87,1.16] I^2=18%; n=933) (Figure 1.11) [5,11,9,16], hospital discharge at day 10-14 (RR 1.08 [95% CI 0.97, 1.21] I^2=0%; n=237) (Figure 1.12) [8,9], duration of hospitalization (mean difference (MD) -0.82 [95% CI -3.86, 2.22] I^2=82%) (Figure 1.13) [3,15,10].

Three RCTs [8,16,19] showed that ivermectin had no effect in shortening the number of days to complete symptom resolution. Based on 1 high quality RCT [16] that enrolled mild-to-moderate patients, the average time to resolution of symptoms was 10 days (IQR, 9-13) in the ivermectin group compared with 12 days (IQR, 9-13) in the placebo group. This difference was not statistically significant (hazard ratio for resolution of symptoms, 1.07 [95%CI, 0.87 to 1.32]; p = .53 by log-rank test). The other two RCTs [8,19] that reported mean (SD) data showed a mean difference of -0.56 days (95% CI -1.61, 0.48] (Figure 1.14).

Low quality evidence from 1 RCT showed that ivermectin significantly reduced the number of symptomatic days of mild-moderate cases by 30% (RR 0.70, 95% CI [0.63 to 0.78]; n=577 days reported) [4]. This study had unclear blinding of participants and investigators as well as allocation concealment.

Comparison 2: Ivermectin+doxycycline vs. placebo / standard of care

Based on very low quality evidence from 3 RCTs [3,20,21], combining ivermectin with doxycycline did not significantly reduce mortality (RR 0.28 [95% CI 0.07, 1.06] I^2=0%, n=561) (Figure 2.1). This effect was observed in for both mild-to-moderate patients (RR 0.14 [95% CI 0.01, 2.70) I^2=0%, 3 RCTs, n=508) and severe patients (RR 0.33 [95% CI 0.08, 1.47], n=53) [20] (Figure 2.2). It also did not significantly affect virologic clearance on day 7-14 (RR 0.87 [95% CI 0.15, 5.08] I^2=85%, n=409) (Figure 2.3) [3, 21] as well as duration of hospitalization (MD 0.40 [95% CI -1.71, 2.51]) (Figure 2.4) [3].

For clinical outcomes, ivermectin+doxycycline was found to have significant effects in terms of clinical improvement at D6-10 (RR 1.36 [95% CI 1.12, 1.67], n=363) (Figure 2.5) [21], preventing clinical deterioration (RR 0.49 [95% CI 0.28, 0.86], n=409) (Figure 2.6)[3, 21], and shortening time to symptom resolution (MD -7.29 [95% CI -9.31, -5.27]) (Figure 2.7) [20].

Significant harm was found with ivermectin+doxycycline based on 2 RCTs (4.4% vs. 0%; RR 18.7 [95% CI 1.10, 318.75], n=409) (Figure 2.8). Unpublished data from Mahmud (2021) reported 2 serious adverse events (erosive esophagitis) and 7 other adverse events (non-ulcer dyspepsia) only in the ivermectin+doxycycline group.

Recommendations from Other Groups

The US NIH (11 Feb 2021) did not recommend either for or against the use of ivermectin for the treatment of COVID-19 due to insufficient level of evidence [12]. 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 Infectious Diseases Society of America (IDSA) (13 Feb 2021) suggests against the use of ivermectin for 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) [13]. The IDSA Guidelines were based on 7 RCTs and 2 non-randomized trials.

Likewise, the Australian COVID-19 Living CPG (February 2021) does not recommend the use of ivermectin outside of trials [12-14].

The WHO living guideline on COVID-19 therapeutics (31 March 2021) does not recommend to use ivermectin in patients with COVID-19 except in the context of a clinical trial. This recommendation applies to patients with any disease severity, any duration of symptoms.

Research Gaps

As of 30 March 2021, there were at least 73 ongoing clinical trials investigating the efficacy of ivermectin as treatment for COVID-19 based on the COVID-19 NMA database.

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Appendix 1: Characteristics of Included Studies for Ivermectin vs Placebo/Standard of Care

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. Follow up 14 days	Bangladesh	Double blind RCT (N=76) Treatment	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 ivermectin, 12 mg once daily for 5 days. [n=22] 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
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. Follow up 28 days	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]	Mortality Clinical improvement Virologic clearance: proportion of patients who become negative at day 7 and viral culture Adverse effects
3	Chachar 2020 Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients Follow up 7 days	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	Clinical improvement Adverse effects
4	Elgazzar 2020 Efficacy and Safety of Ivermectin for Treatment and prophylaxis of COVID-19 Pandemic	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]	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,	Mortality Clinical deterioration Clinical improvement Virologic clearance Adverse events

	Follow up 25 days				Group II: severe COVID-19; IVM [n=100]	Lactoferrin, Acetylcysteine Group III: mild-moderate COVID-19, SOC [n=100] Group IV: severe COVID-19; SOC [n=100]	
5	Królewiecki 2020 Antiviral effect of high-dose ivermectin in adults with COVID-19: a pilot randomised, controlled, open label, multicentre trial. Follow up 30 days	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	Clinical deterioration Adverse effects
6	Mohan 2021 Ivermectin in mild and moderate COVID-19 (RIVETCOV): a randomized, placebo-controlled trial Follow up 14 days	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]	Mortality Clinical deterioration Progression to ventilation Clinical improvement Duration of hospitalization Viral clearance Adverse effects
7	Niaee 2020 Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial Follow up 45 days	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]	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.	Mortality Duration of hospitalization Clinical improvement

					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		
8	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),	Mortality Clinical improvement Viral clearance D10 Adverse effects
9	Ravikirti 2021 Ivermectin as a potential treatment for mild to moderate COVID-19 – A double blind randomized placebo-controlled trial Follow up 10 days	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	Mortality Clinical deterioration Progression to Ventilation Clinical improvement Viral Clearance
10	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)	% patients with 2 negative PCR tests w/in 7 days Adverse events
11	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)	Time to resolution of symptoms (D21); % patients with resolved symptoms % patient with clinical deterioration Fever since randomization Escalation of care

							Deaths
12	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	Viral clearance (days to RT-PCR negativity) Adverse effects
13	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)	Placebo (n=37)	Duration of hospitalization Hospital discharge, n(%) Discharged without respiratory deterioration or death, n(%) Respiratory deterioration or death, n(%)
14	Podder 2020 Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study	Bangladesh	Open-label RCT (N=62)	Mild-moderate COVID-19 Age more than 18 years old	single dose of ivermectin 200 micrograms/kg on the day 1 of randomisation Low dose Ivermectin	symptomatic treatment which included antipyretics, cough suppressants, and capsule doxycycline (100 mg every 12 hours for seven days)	time needed for resolution of fever, cough, shortness of breath time needed for full recovery from all symptoms repeat RT-PCR on day 10

Appendix 2: Characteristics of Included Studies for Ivermectin + Doxycycline vs Placebo/Standard of Care

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. Follow up 14 days	Bangladesh	Double blind RCT (N=76) Treatment	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 ivermectin, 12 mg once daily for 5 days. [n=22] 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
2	Mahmud 2020 Clinical Trial of Ivermectin Plus Doxycycline for the Treatment of Confirmed Covid-19 Infection Follow up 30 days	Bangladesh	Double blind RCT (N=400) Treatment	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
3	Hashim 2020 Controlled randomized clinical trial on using Ivermectin with Doxycycline for	Iraq	Single blind RCT (N=140) Treatment	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)	Standard care [n=70] Acetaminophen, Vitamin C 1000mg twice/	Mortality Clinical Deterioration

	treating COVID-19 patients in Baghdad, Iraq Follow up 56 days			Low dose ivermectin	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	Mean days to symptomatic resolution

Appendix 3: Characteristics of Excluded Studies (n=28)

No.	Author, year Title	Study design	Reason for exclusion
1	Camprubi 2020 Lack of efficacy of standard doses of ivermectin in severe COVID-19 patients	Retrospective cohort (n - 26)	Non-RCT
2	Khan 2020 Ivermectin treatment may improve the prognosis of patients with COVID-19	Retrospective cohort (n = 325)	Non-RCT
3	Procter 2020 Clinical outcomes after early ambulatory multidrug therapy for high risk SARS-CoV-2 (COVID-19) infection	Prospective cohort (n = 922)	Non-RCT
4	Fonseca 2020 Risk of hospitalization for Covid-19 outpatients treated with various drug regimens in Brazil: Comparative analysis	Prospective cohort (n = 717)	Non-RCT
5	Malik 2020 Clinical Presentation, Management and In-Hospital Outcome of Healthcare Personnel With COVID-19 Disease	Cross sectional study (n = 1409)	Non-RCT
6	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
7	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
8	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
9	Mondal 2020 Socio-demographic, clinical, hospital admission and oxygen requirement characteristics of COVID-19 patients of Bangladesh	Cross-sectional study (n = 305)	Non-RCT
10	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
11	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

12	Chowdhury 2021 A Comparative Study on Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin Therapy on COVID-19 Patients	Randomized controlled trial (n = 116)	No placebo or standard of care as control group
13	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
14	Carvallo 2020 USEFULNESS of Topic Ivermectin and Carrageenan to Prevent Contagion of Covid 19 (IVERCAR)	Prospective cohort (n = 229)	Non-RCT
15	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.		
16	Afsar 2020 Ivermectin use associated with reduced duration of COVID-19 febrile illness in a community setting	Case-control study (n = 95)	Non-RCT
17	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
18	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
19	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
20	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
21	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
22	Behera 2021	Case-control study (n = 117)	Ivermectin as prophylaxis

	Role of ivermectin in the prevention of SARSCoV-2 infection among healthcare workers in India: A matched case-control study		
23	Hellwig 2020 A COVID-19 Prophylaxis? Lower incidence associated with prophylactic administration of Ivermectin	Ecological study	Ivermectin as prophylaxis, non-RCT
24	Bernigaud 2020 Ivermectin benefit: from scabies to COVID-19, an example of serendipity	Retrospective cohort (n = 121)	Ivermectin as prophylaxis
25	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
26	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
27	Tanioka 2021 Why COVID-19 is not so spread in Africa: How does Ivermectin affect it?	Ecological study	Non-RCT
28	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

Appendix 4: GRADE Evidence Profile

Author(s): Joson MVASG, Bayona HHG, Besa JJV, Tampus FC, Tating DLRO
Question: Ivermectin compared to standard of care or placebo as treatment for COVID-19
Setting: worldwide
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												
9 [a]	randomised trials	very serious [b]	serious [c]	not serious	very serious [d]	none	17/752 (2.3%)	55/570 (9.6%)	**RR 0.30** (0.12 to 0.73)	**68 fewer per 1,000** (from 85 fewer to 26 fewer)	⨁◯◯◯ VERY LOW	
Adverse Events												
10	randomised trials	serious [e]	serious [f]	not serious	serious [g]	none	324/764 (42.4%)	271/605 (44.8%)	**RR 0.87** (0.70 to 1.09)	**58 fewer per 1,000** (from 134 fewer to 40 more)	⨁◯◯◯ VERY LOW	
Clinical improvement (follow up: 6-10 days)												
4	randomised trials	serious [h]	not serious	not serious	not serious	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)	⨁⨁⨁◯ MODERATE	
Clinical deterioration												
5	randomised trials	serious [i]	serious [i]	not serious	serious [k]	none	16/464 (3.4%)	18/339 (5.3%)	**RR 0.66** (0.34 to 1.26)	**18 fewer per 1,000** (from 35 fewer to 14 more)	⨁◯◯◯ VERY LOW	
Need for mechanical ventilation												
3	randomised trials	serious [l]	not serious	not serious	very serious [d]	none	2/185 (1.1%)	5/124 (4.0%)	**RR 0.40** (0.06 to 2.55)	**24 fewer per 1,000** (from 38 fewer to 62 more)	⨁◯◯◯ VERY LOW	
Virologic clearance (negative RT-PCR) (follow up: 6-10 days)												
9	randomised trials	very serious [m]	very serious [n]	not serious	serious [o]	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 [g]	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	

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)		
Time to symptom resolution (in days)												
3	randomised trials	serious [p]	not serious	not serious	not serious	none	Pooled mean difference for Mohan 2020 and Podder 2020: -0.56 (95% CI -1.61, 0.48). 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.				⨁⨁⨁◯ MODERATE	
Duration of hospitalization (days)												
3	randomised trials	serious [q]	serious [r]	serious [s]	serious [t]	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.				⨁◯◯◯ VERY LOW	
Number of symptomatic days												
1	randomised trials	very serious [u]	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. Okumus 2020 assessed mortality at D60
b. Serious to very serious risk of bias noted for 7/9 studies. Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviations from intended interventions and selection of reported results.
c. Moderate heterogeneity (I2 = 56%)
d. Imprecision due to small number of events and wide confidence interval that crosses threshold for benefit and harm
e. Serious to very serious risk of bias in 8/10 studies.
f. Moderate heterogeneity (I2 = 36%)
g. Some concern for imprecision due to confidence interval between benefit and harm
h. Serious concern for bias over the clinical outcome measured since the study of Chachar and Okmus are open-label in design.
i. Included 3 studies with serious risk of bias (Ahmed et al. 2020; Krolewiecki et al., 2020; Ravikirti et al., 2020)
j. Outcome measures were different (ICU admission, Progression of O2 requirement, Need for mechanical ventilation)
k. Some concern for wide confidence interval
l. Included 2 studies with at least serious risk of bias (Krolewiecki et al., 2020; Ravikirti et al, 2020)
m. 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.
n. Some concern for inconsistency. I2 = 71%
o. 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
p. Very serious risk of bias for Podder 2020
q. Two studies (Ahmed, Niaee) had unclear blinding of patients and outcome assessors.
r. Results varied across 3 studies
s. Some concern with how the data was represented among the two studies.
t. The duration of hospitalization between the two studies cannot be pooled.
u. Some concerns with the patient reported outcome since the placebo was not identical to the ivermectin tablet. patients may not be blinded.

Appendix 5: Appraisal of Included Studies for Ivermectin vs Placebo/Standard of Care

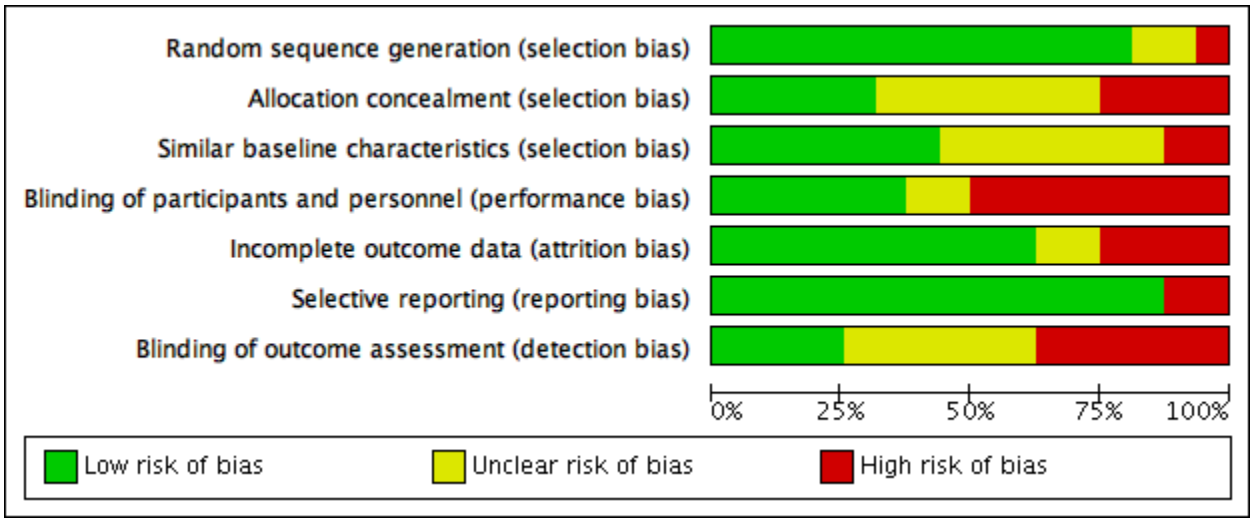
	Risk of bias	Random assignment	Allocation concealment	Similar baseline characteristics	Patients blinded	Caregivers blinded	Assessors blinded[1]	Intention-to-treat analysis	Adequate follow-up rate	Published?
Summary	Not serious: 2 Serious: 6 Very serious: 6	Yes: 11 Unclear: 1 No: 0	Yes: 5 Unclear: 7 No: 2	Yes: 8 Unclear: 5 No: 1	Yes: 4 Unclear: 2 No: 8	Yes: 5 Unclear:2 No: 7	Yes: Unclear:6 No:	Yes: 11 Unclear: 0 No: 3	Yes: 9 Unclear: 2 No: 3	Yes: 8 No: 6
1. Ahmed	**Serious**	Yes	Unclear	Unclear	Yes	Yes	Unclear	No[3]	Unclear	No
2. Bukhari*	**Very serious**	Yes	Unclear	Yes	No	No	No	Yes	No	Yes
3. Chaccour	**Serious**	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	No
4. Chachar	**Serious**	Yes	No	Yes	No	No	No	Yes	Yes	No
5. Elgazzar*	**Very serious**	Unclear	Unclear	No	Unclear	Unclear	Unclear	Yes	Yes	Yes
6. Gonzalez*	**Very serious**	Yes	Unclear	Unclear	No	Unclear	Unclear	Yes	Yes	Yes
7. Królewiecki*	**Serious**	Yes	Yes	Yes	No	No	No	Yes	No	Yes
8. Lopez-Medina	**Not serious**	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No
9. Mohan*	**Not serious**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Niaee*	**Serious**	Yes	Yes	Unclear	No	No	Unclear	Yes	Yes	Yes
11. Okumuş*	**Very serious**	Yes	Unclear	Yes	No	No	No	Yes	No	Yes
12. Podder	**Very serious**	Yes	No	Yes	No	No	No	No	Yes	No
13. Pott-Junior	**Very serious**	Yes	Unclear	Unclear	No	No	No	Yes	Unclear	No
14. Ravikirti*	**Very serious**	Yes	Yes	Yes	Yes	Yes	Yes	No[2]	Yes	Yes

[1]For outcomes of mortality and viral clearance, risk of bias for assessor blinding was rated low as these objective outcomes.
[2]DHigh rop-out rate
[3]Used non-ITT data for the Kaplan Meier analysis.

Appendix 6: Appraisal of Included Studies for Ivermectin + Doxycycline vs Placebo/Standard of Care

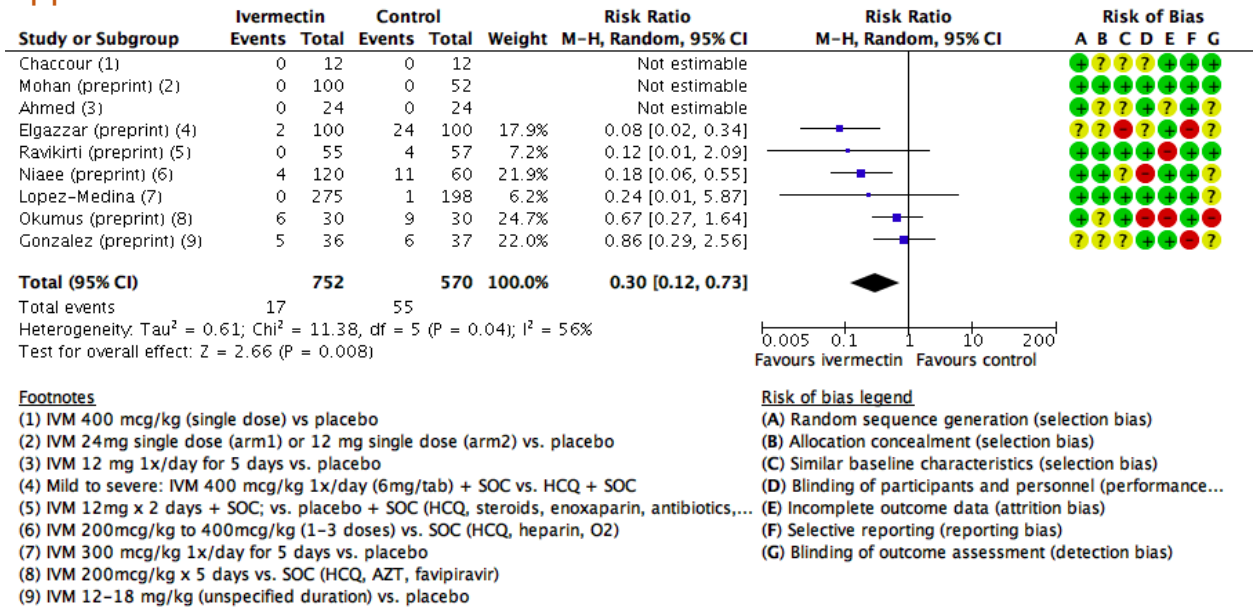
	Risk of bias	Random assignment	Allocation concealment	Similar baseline characteristics	Patients blinded	Caregivers blinded	Assessors blinded	Intention-to-treat analysis	Adequate follow-up rate	Published? (preprints)
Summary	Not serious: 0 Serious: 1 Very serious: 2	Yes: 3 Unclear: 0 No: 0	Yes: 1 Unclear: 1 No: 1	Yes: 0 Unclear: 3 No: 0	Yes: 2 Unclear: 0 No: 1	Yes: 2 Unclear:0 No: 1	Yes: 1 Unclear:1 No: 1	Yes: 2 Unclear: 0 No: 1	Yes: 1 Unclear: 1 No: 1	Yes: 2 No: 0
1. Ahmed	Serious	Yes	Unclear	Unclear	Yes	Yes	Unclear	No	Unclear	No
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	Yes

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



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

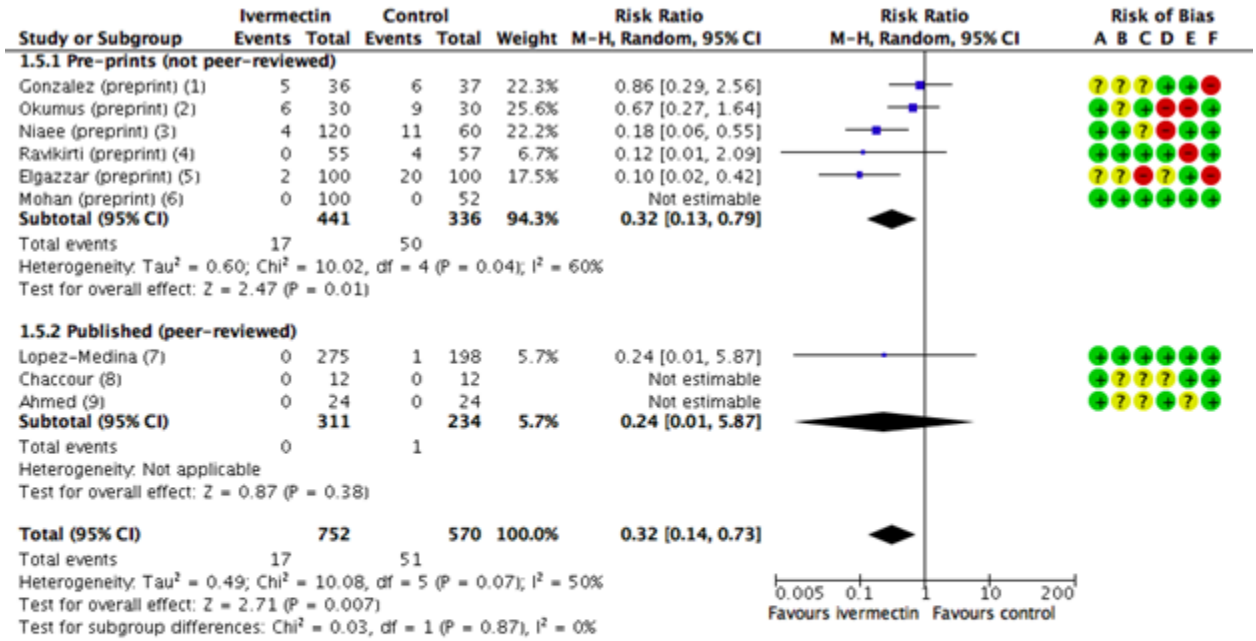
Appendix 7: Forest Plots



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 12 mg 1x/day for 5 days vs. placebo
(4) Mild to severe: IVM 400 mcg/kg 1x/day (6mg/tab) + SOC vs. HCQ + SOC
(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

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

Figure 1.1. Forest plots comparing ivermectin and control for the outcome of mortality (overall).



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

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)

Figure 1.2. Mortality, subgroup analysis according to publication status

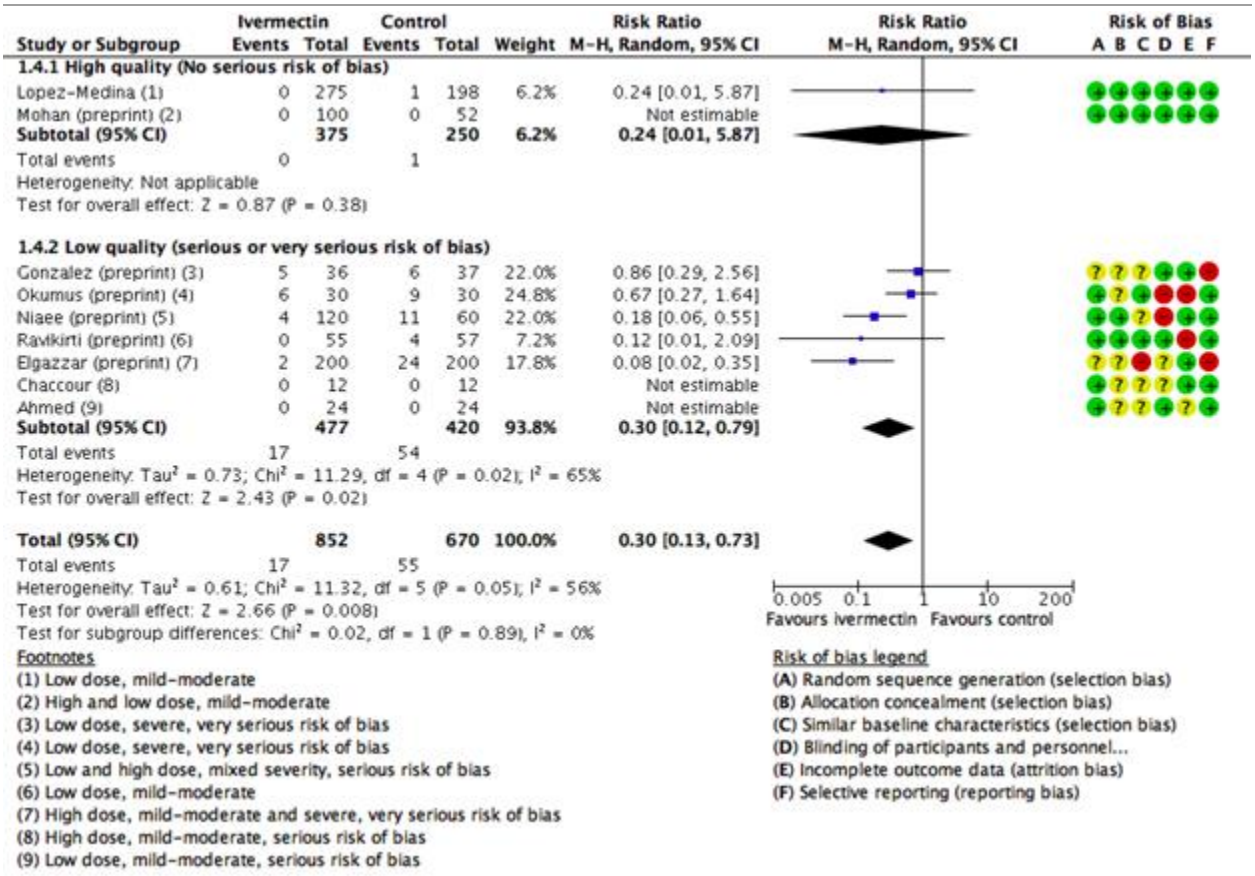


Figure 1.3. Mortality, subgroup analysis according to study quality

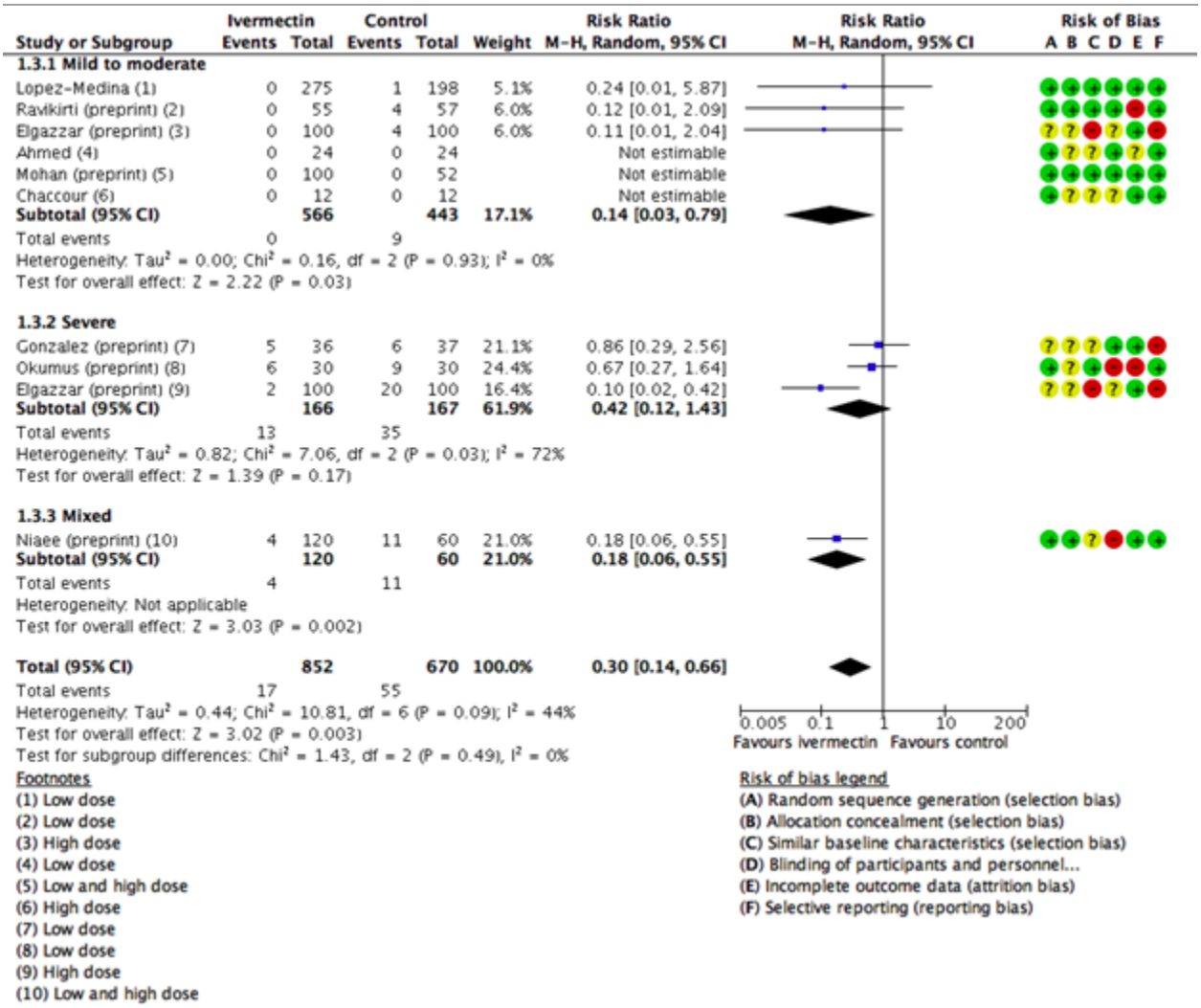


Figure 1.4. Mortality, subgroup analysis according to disease severity, ivermectin vs. control

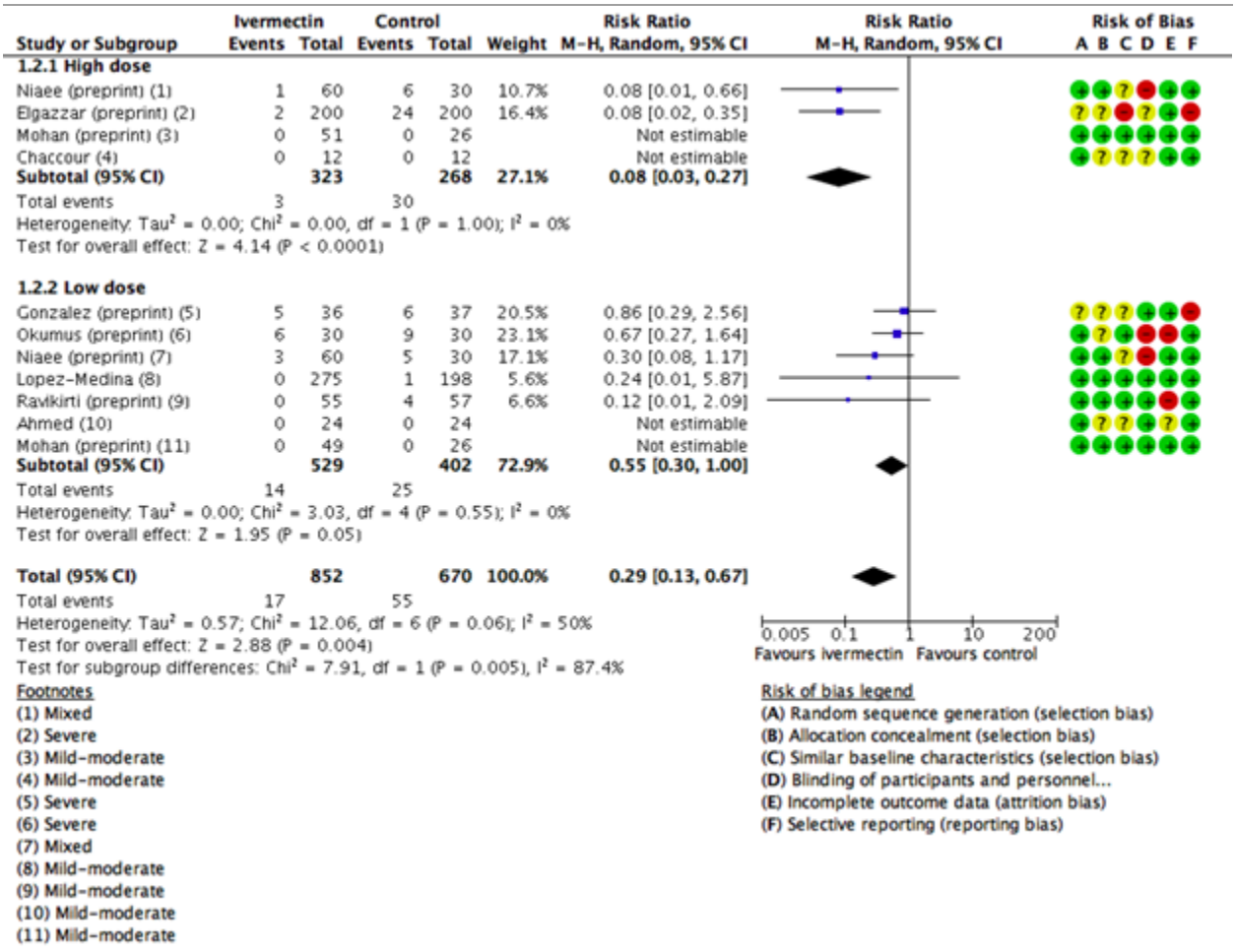


Figure 1.5. Mortality, subgroup analysis according to dose

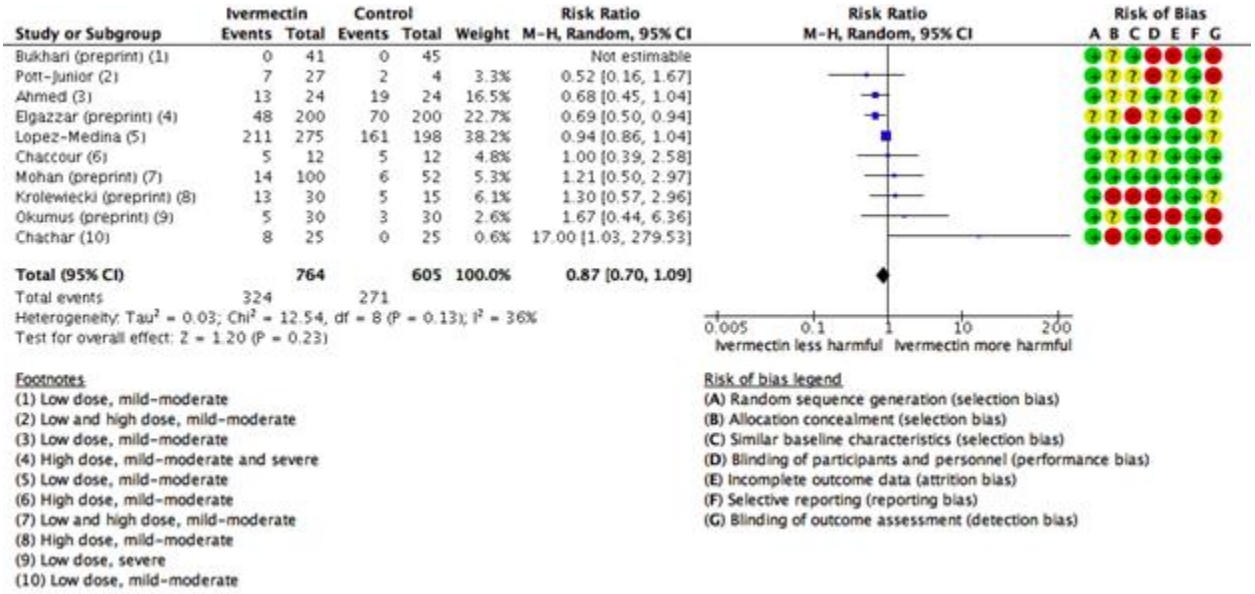


Figure 1.6. Adverse effects of ivermectin compared to placebo (overall)**.**

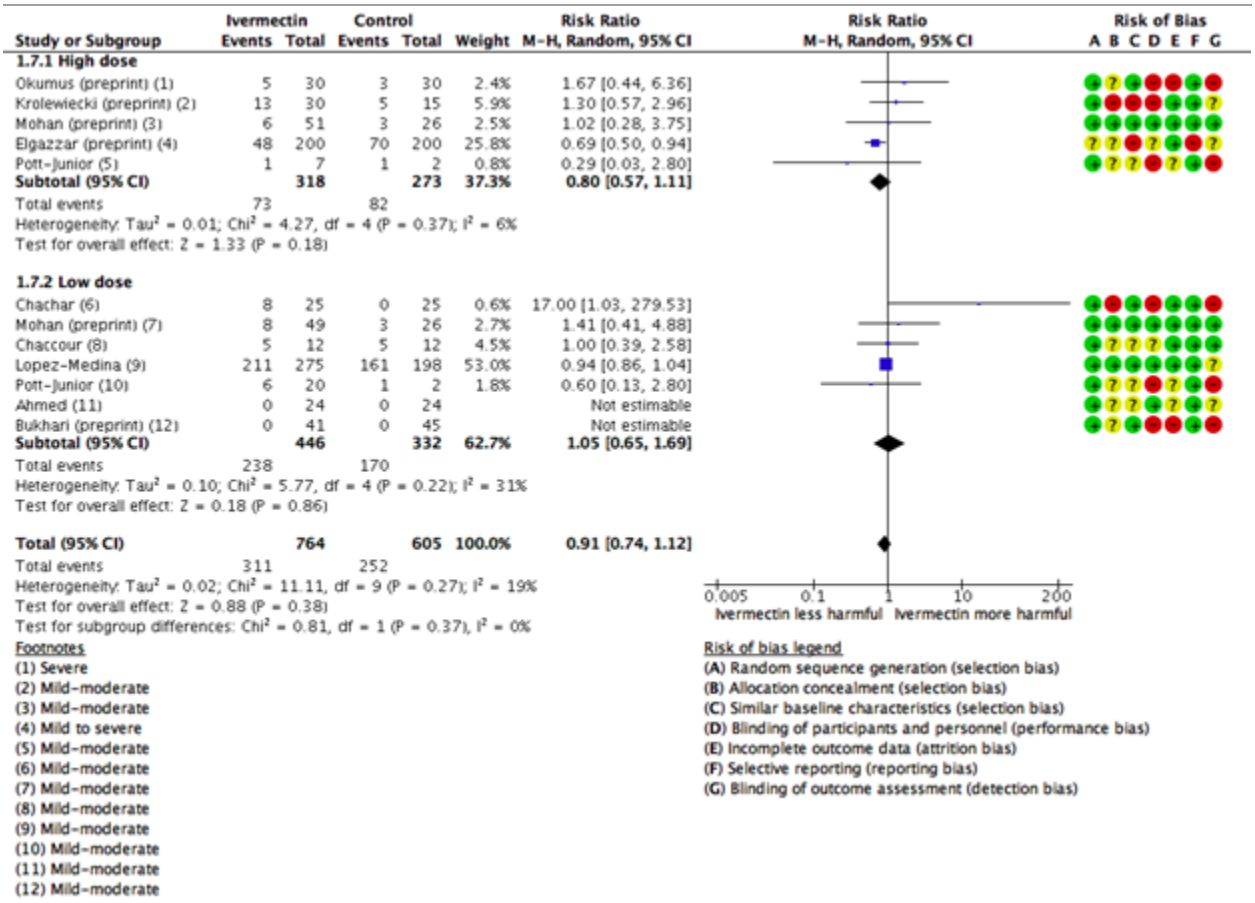


Figure 1.7. Adverse effects of ivermectin compared to placebo, subgroup analysis according to dose.

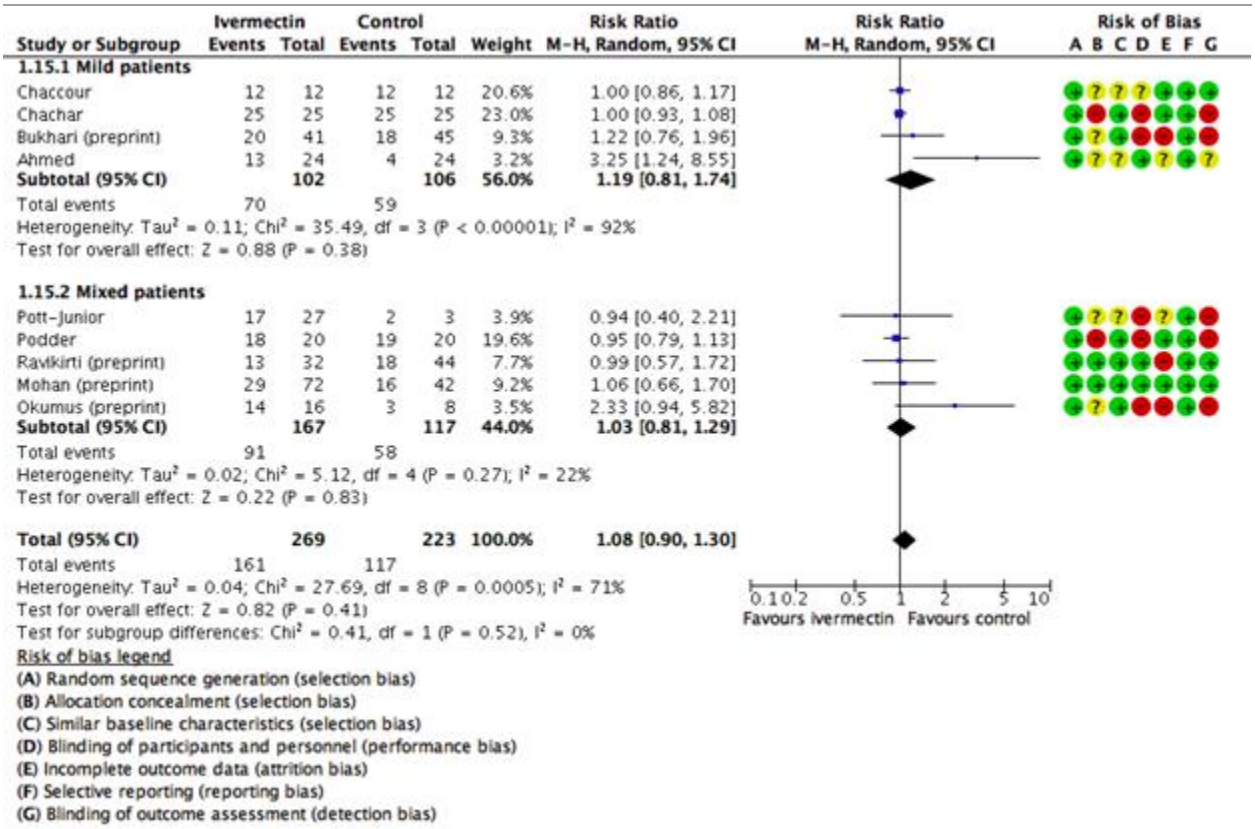


Figure 1.8. Virologic clearance (PCR negativity on D6-10), ivermectin vs. control

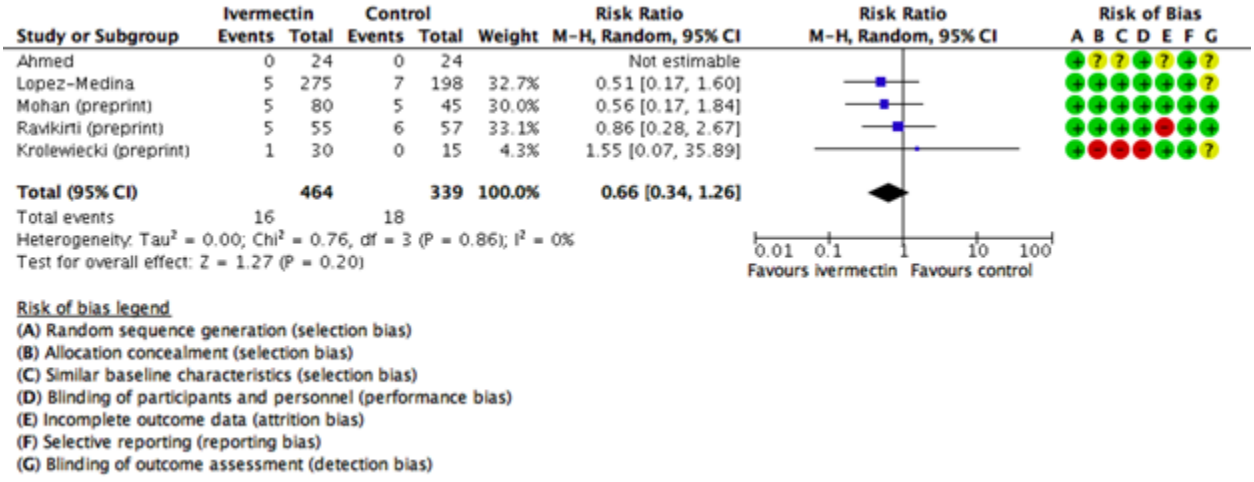


Figure 1.9. Clinical deterioration, ivermectin vs. control

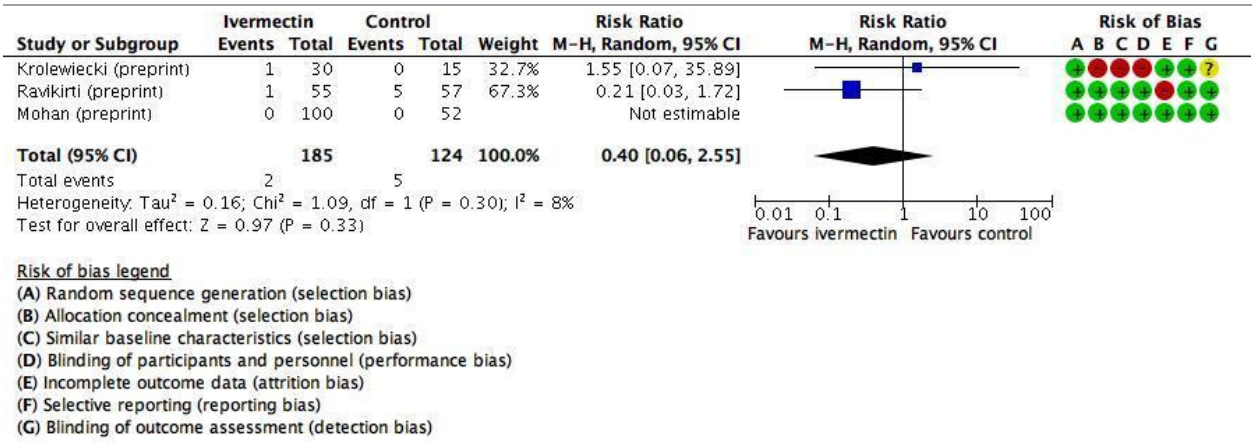


Figure 1.10. Need for Mechanical ventilation, ivermectin vs. control

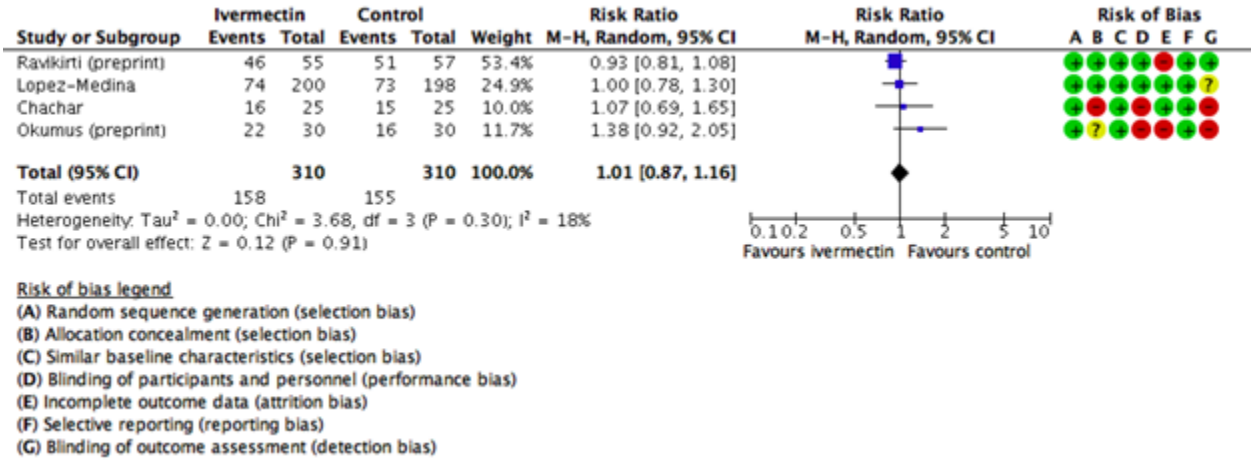


Figure 1.11. Clinical improvement on day 6-10, ivermectin vs. control

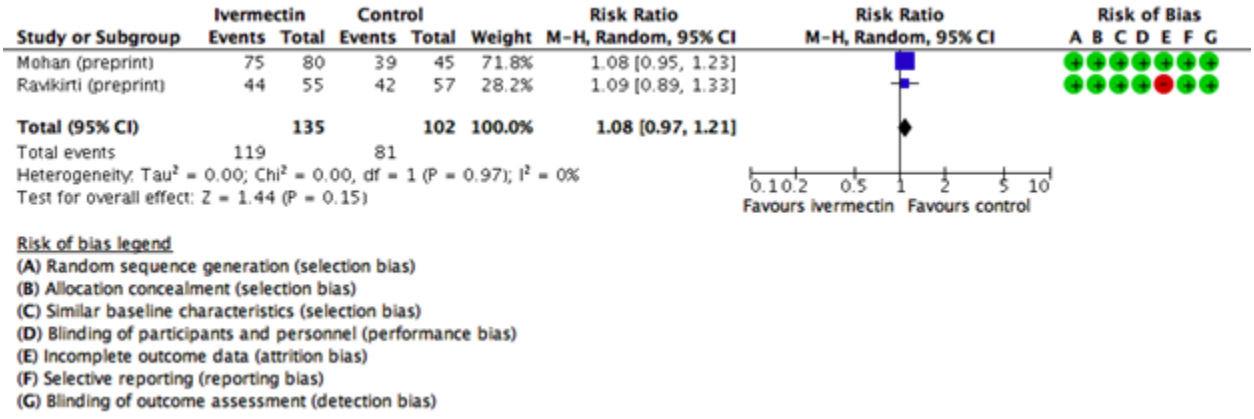


Figure 1.12. Hospital discharge at day 10-14

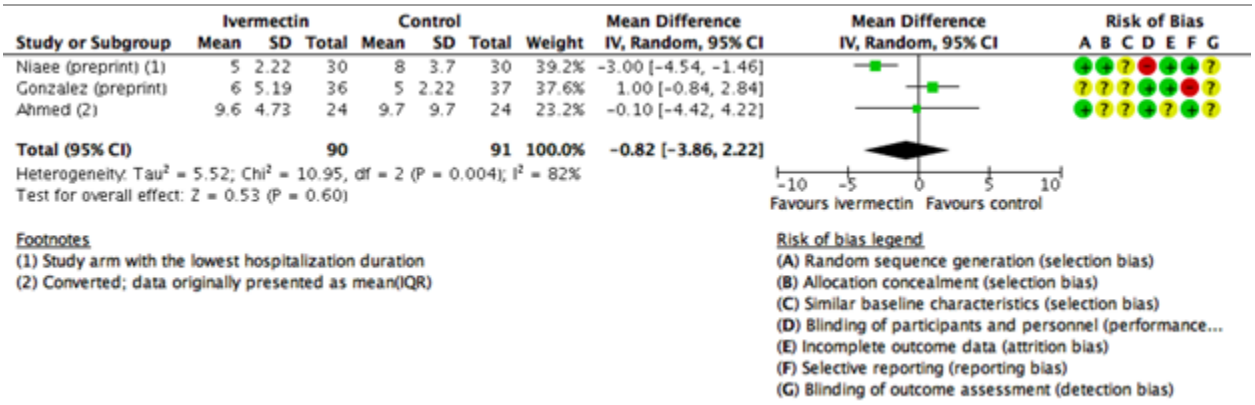


Figure 1.13 Duration of hospitalization, ivermectin vs. control

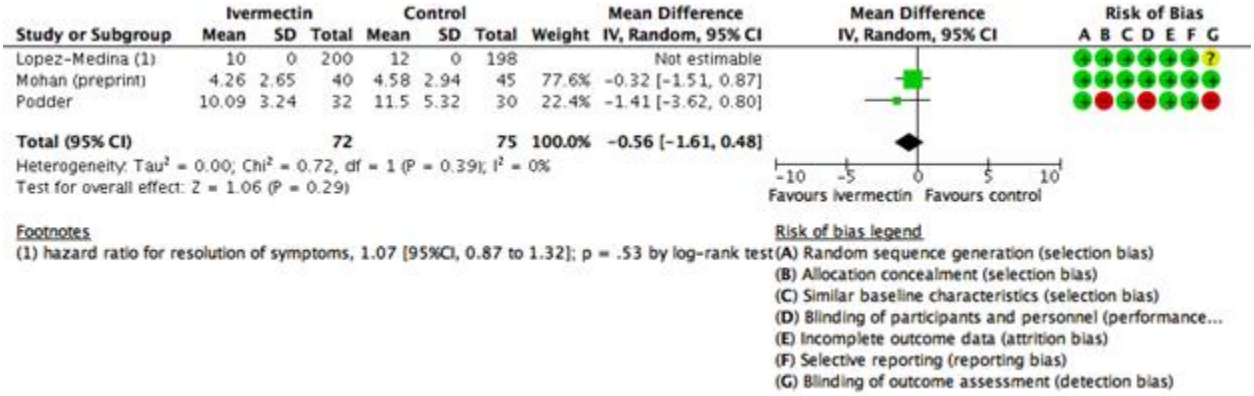


Figure 1.14 Time to symptom resolution (ivermectin vs. control)

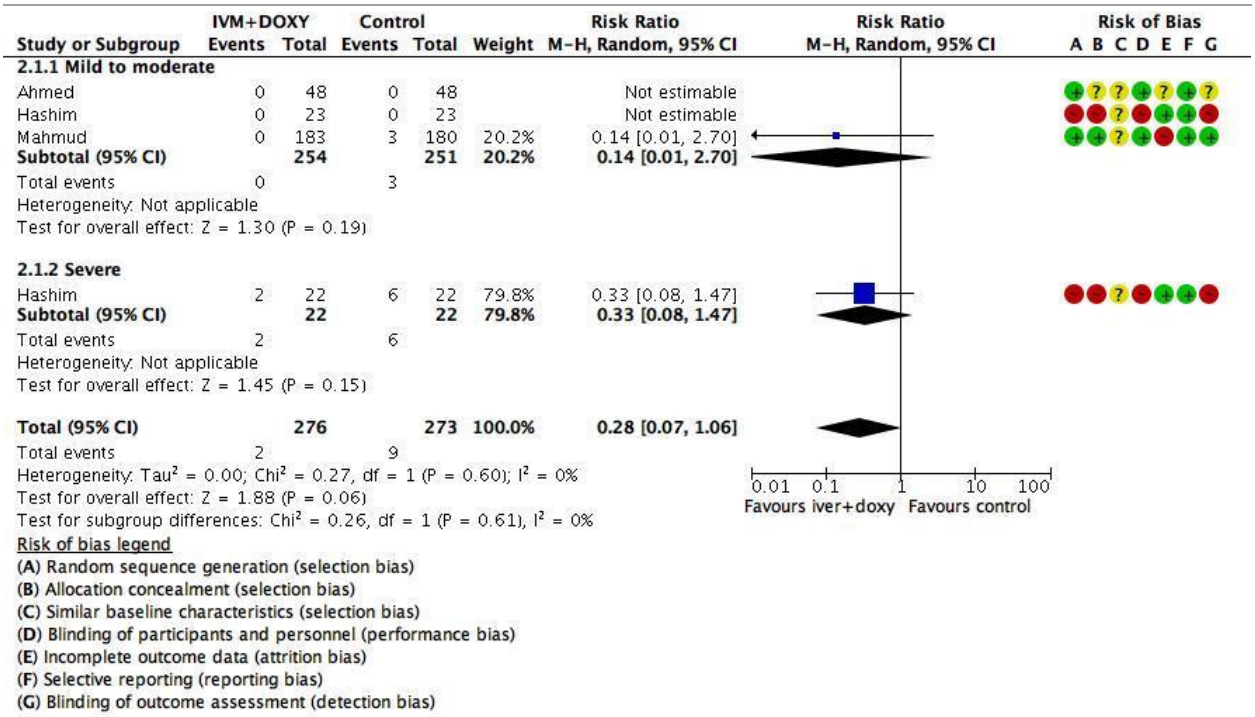


Figure 2.1. Forest plots comparing ivermectin + doxycycline vs control for the outcome of mortality (overall)

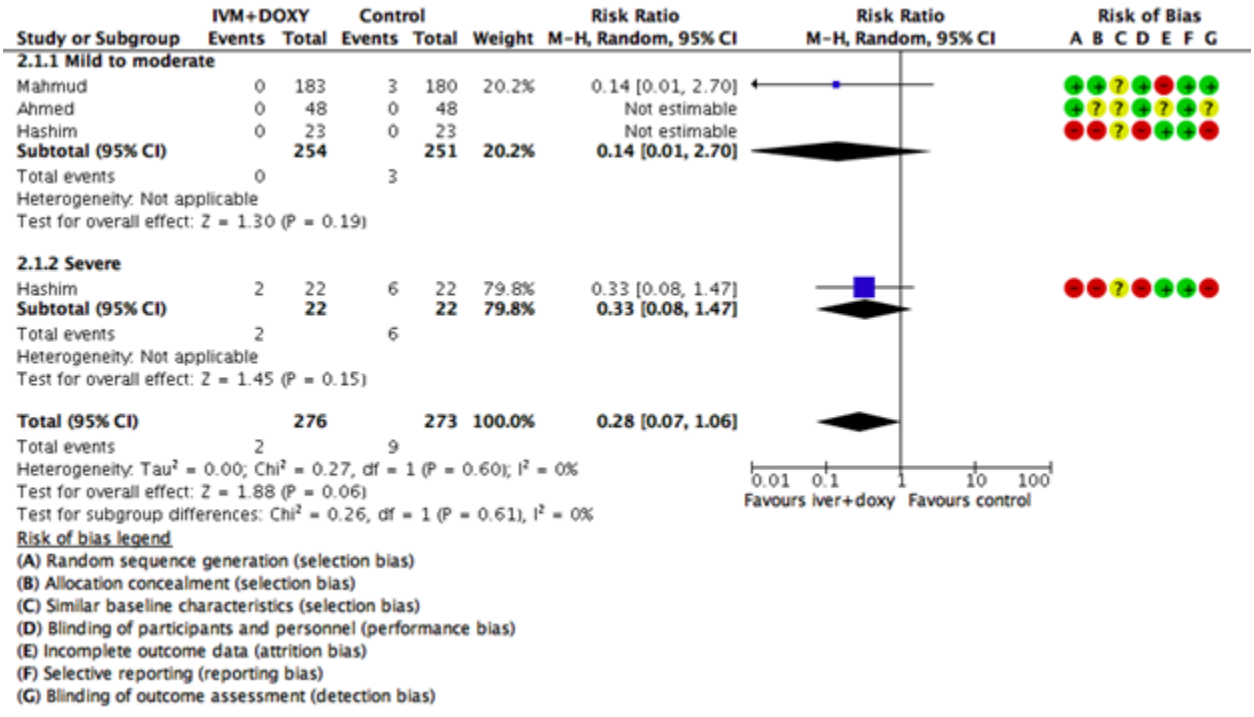


Figure 2.2. Mortality, subgroup analysis according to disease severity, ivermectin+doxycycline vs. control

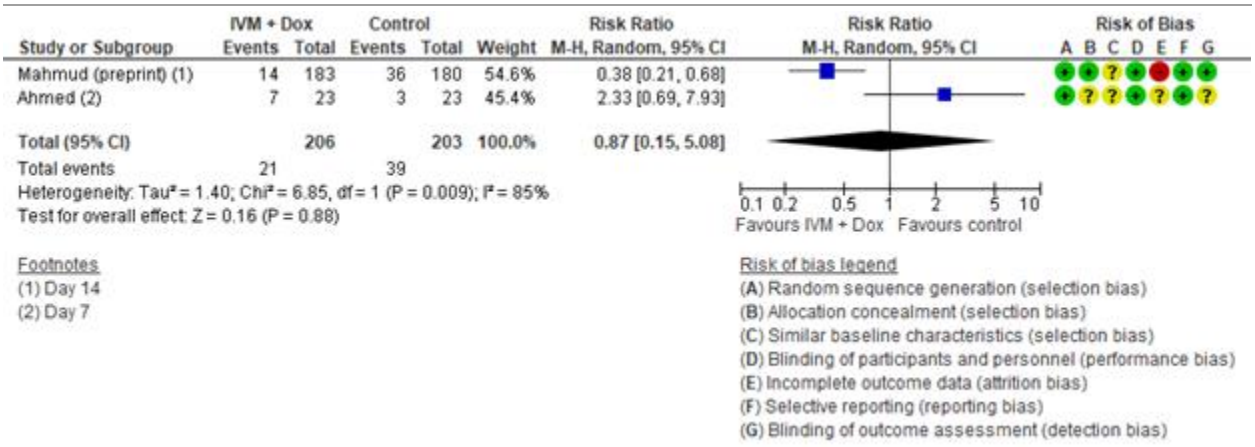


Figure 2.3. Virologic clearance (PCR negativity on D7-14), ivermectin+doxycycline vs. control

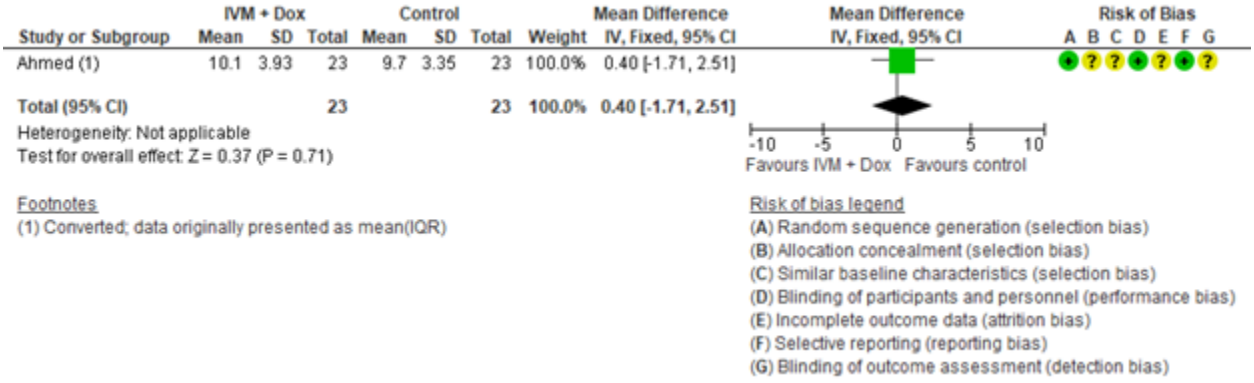


Figure 2.4. Duration of hospitalization, ivermectin+doxycycline vs. control

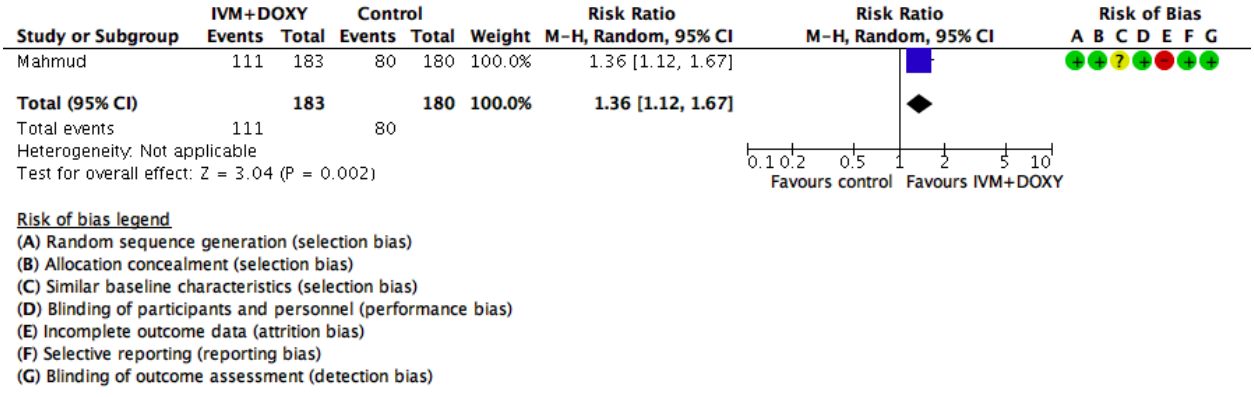


Figure 2.5. Clinical improvement on day 6-10, ivermectin+doxycycline vs. control

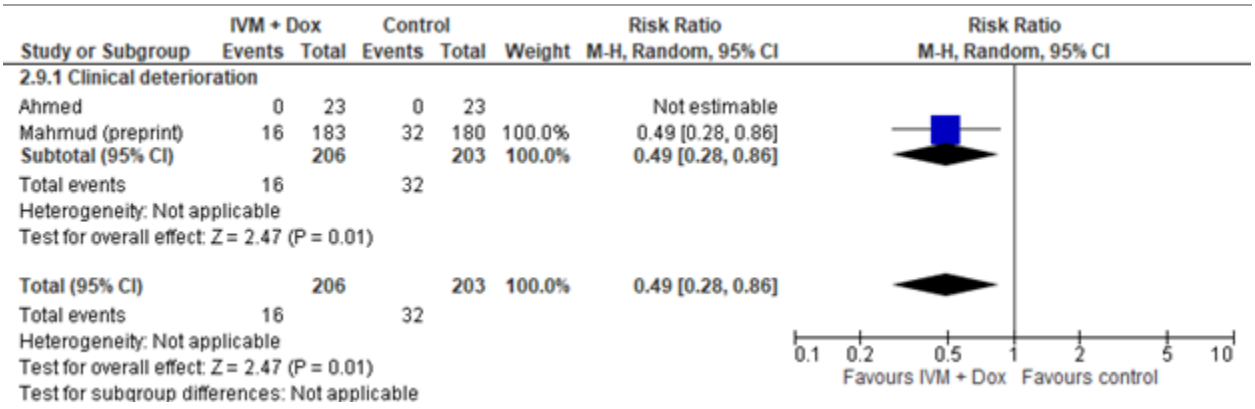


Figure 2.6. Clinical deterioration, ivermectin+doxycycline vs. control

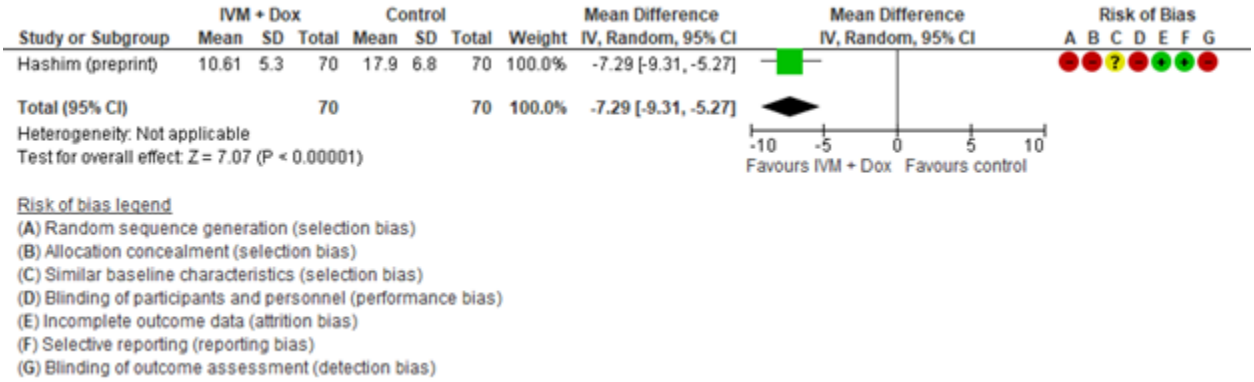


Figure 2.7. Time to symptom resolution (ivermectin+doxycycline vs control)

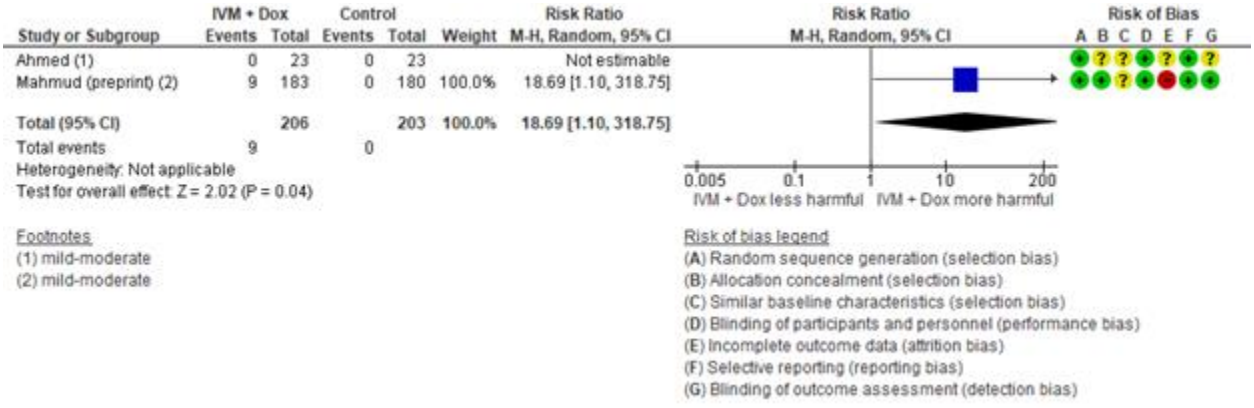


Figure 2.8. Adverse effects of ivermectin+doxycycline compared to placebo