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

EVIDENCE SUMMARY

RESEARCH QUESTION: **Among COVID-19 patients, should ivermectin be used for treatment?**

Latest Update by: April P. Padua-Zamora, MD, Natasha Ann R. Esteban-Ipac, MD, Mario M. Panaligan, MD, Ivan N. Villespin, MD, Arnel Gerald Q. Jiao, MD, Marissa M. Alejandria, MD, MSc
Previous Update by: Marquis Von Angelo Syquio Go Joson, MD, Carol Stephanie C. Tan-Lim, MD, MSc, Natasha Ann R. Esteban-Ipac MD, Marissa M. Alejandria, MD, MSc
Initial review by: Marquis Von Angelo Syquio Go Joson, MD, John Jefferson V. Besa, MD, Frangelo Conrad Tampus, MD, Dan Louie Renz O. Tating, RN, MSc (cand.), Marie Gene D. Cruz, MD, Howell Henrian G. Bayona, MSc, MSc (cand.)
Advisers: Antonio Dans, MD, MSc, Leonila F. Dans, MD, MSc, Carmela Lapitan, MD, MSc, Marissa M. Alejandria, MD, MSc

RECOMMENDATION

Recommendation	Certainty of Evidence	Strength of Recommendation
We recommend against the use of ivermectin in the treatment of children and adults with COVID-19 regardless disease severity.	Very low	Strong

Consensus Issues

The panel unanimously recommended against the use of ivermectin in the treatment of children and adults with COVID-19 based on the most recent evidence which included a total of 27 randomized controlled trials (RCTs). The addition of twelve (12) new RCTs brought the total number of participants to 8,700, compared with 1,700 participants from the previous review, and further confirmed that ivermectin has no benefit in all the critical outcomes, including all-cause mortality, clinical improvement, need for hospitalization, clinical deterioration, and need for ICU admission or mechanical ventilation. The panel acknowledged that the extent of misuse and abuse of ivermectin in COVID-19 treatment has markedly subsided probably because the public is now more knowledgeable and informed, and that more effective treatment options are locally available. The panel also emphasized that although ivermectin is not expensive per se, spending for the drug may still be considered costly, as it would incur unnecessary expense.

KEY FINDINGS

- Twenty-seven (27) randomized controlled trials investigated the effect of ivermectin compared to placebo or standard of care as treatment for patients with COVID-19.
- Evidence showed that although ivermectin did not cause significant harm compared with placebo or standard of care, there remains lack of conclusive benefit in any of the critical and important outcomes.
- Ivermectin did not show significant benefit on all-cause mortality, regardless of severity, hospitalization status, or dose of ivermectin used.
- Ivermectin did not show significant benefit in other critical or important outcomes, including clinical deterioration, need for mechanical ventilation, ICU admission, clinical improvement, time to symptom resolution, hospitalization and duration of hospitalization and virologic clearance.
- Adverse events and serious adverse events did not significantly differ between ivermectin and control groups.
- These results must be interpreted in the context of very low certainty of evidence. The certainty of evidence was downgraded due to varying degrees of risk of bias in most studies, inconsistency, and imprecision in several critical outcomes.

- Evidence on the use of ivermectin in children is lacking, hence the recommendation for pediatric patients were extrapolated from adult studies.

WHAT'S NEW IN THIS VERSION?

This version includes 27 randomized controlled trials (RCTs) with twelve (12) new trials comparing ivermectin and standard of care or placebo (Abbas 2022, Bramante 2022, Buonfrate 2022, Chahla 2022, Dela Rocha 2022, Lim 2022, Manomaipiboon 2022, Mirahmadizadeh 2022, Naggie 2022, Reis 2022, Rezai 2022A, Rezai 2022B). One RCT is a preprint (Bukhari 2021). Two RCTs were excluded in this update due to their retraction (Pott-Junior 2021, Elgazzar 2020).

PREVIOUS RECOMMENDATIONS
As of 06 December 2021

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

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

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

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

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

INTRODUCTION

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

Several systematic reviews on the use of ivermectin in COVID-19 have been published, with varying eligibility criteria and conflicting conclusions. The latest Cochrane systematic review published in June 2022 included 11 trials, 10 of which were also included in this review; one study was excluded because it was already retracted [16]. This review included nine of the excluded studies from the Cochrane review, most of which were excluded because the trials were not prospectively registered in a trial registry according to WHO guidelines. In the Cochrane review, ivermectin showed no beneficial effect for patients with mild COVID-19 (mild or WHO score 1-3), with low to moderate certainty of evidence. For inpatients with moderate to severe COVID-19 or WHO score of at least 4-9, ivermectin had no benefit in preventing death, clinical worsening, or serious adverse events with very low certainty of evidence, and it also had no benefit on clinical improvement, viral clearance, and adverse events with low-certainty of evidence [4]. To date, completed trials on ivermectin continue to be published and a number of trials are still ongoing.

REVIEW METHODS

A systematic search was done from the date of the last search September 10, 2021 until October 24, 2022, using Medline, Cochrane COVID-19 Study Register, Google Scholar with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and ivermectin. We also looked at the COVID-NMA Living Data and searched for ongoing studies in the NIH clinicaltrials.gov and various trial registries (Chinese Clinical Trial Registry and WHO International Clinical Trials Registry). Preprints were also searched using medrxiv, chinaxiv, and biorxiv. As appropriate, authors of potentially eligible studies for this review were contacted via email to obtain additional data. The full search strategy used for each source is detailed in Appendix 2.

Only randomized controlled trials that compared ivermectin against placebo or standard of care (SOC) among confirmed COVID-19 patients were included in this review. We excluded studies that included patients who were diagnosed with COVID-19 based on radiographic evidence but were negative for COVID-19 RT-PCR or COVID-19 antigen test. Outcomes of interest included mortality, clinical deterioration or improvement, development of acute respiratory syndrome, need for mechanical ventilation, need for hospitalization, duration of hospitalization, time to clinical recovery, improvement of radiographic findings, virologic clearance, and adverse events. No limits were placed on age, COVID-19 severity, hospitalization status, and dosing strategy of ivermectin. Subgroup analysis by dose and disease severity was planned. For the outcome of clinical deterioration, subgroup analysis by admission to ICU, deterioration in WHO ordinal scale, progression in O_2 support, and need for hospitalization were also planned. We performed sensitivity analysis to assess the robustness of the results when studies with serious risk of bias concerns were excluded.

RESULTS

Literature search

The literature search yielded twelve new RCTs [5–15] with two RCTs reported in 1 publication [15]. Two RCTs were excluded due to their retraction [16,17]. Two RCTs were excluded due to inclusion of participants who had unknown or negative SARS CoV-2 status [18,19].

In total, 27 RCTs were analyzed, one of which was a preprint [20] and one was published as a short communication [5]. The trials were performed in different geographical regions. Most studies were from Asia, namely Bangladesh [21,22], China [5], India [23–25], Iran [12,15], Israel [26], Malaysia [10], Pakistan [20,27], and Thailand [11]. Other RCTs were from Europe (Italy [7], Spain [28], Turkey [29]), Latin America (Argentina [8,30,31], Brazil [14], Colombia [32], Mexico [9,33]), Egypt [34], and the United States of America [6,13].

Twelve (12) RCTs enrolled hospitalized patients with disease severity varying from mild [21,23], mild-moderate [10,11,20,24,25,30,34] moderate-severe [15] and severe [29,33]. Fifteen (15) RCTs enrolled outpatients, majority of which enrolled patients with mild disease severity [5,6,8,9,12,15,27,28,31,32], while the rest enrolled asymptomatic-mild [7], or mild-moderate [13,22,26] disease severity; and 1 RCT did not specify disease severity, but only included patients with at least 1 risk factor for disease progression [14]. Treatment regimen of ivermectin differed across studies: 14 RCTs used low dose (200-300mcg/kg or 12-18mg/day) [5,9,11,20–23,25,26,29,31–34]. 11 RCTs used high dose (400-1200mcg/kg or 24mg/day or higher) [6–8,10,13–15,27,28,30] and 2 RCT used mixed dose (12mg and 24mg) [12,24]. Treatment duration ranged from 1-5 days, and 1 RCT [8] gave high dose ivermectin (24mg) once a week for 4 weeks. Seventeen (17) studies were placebo-controlled [5–7,9,12–15,21,24–26,28,31–33] while 10 studies used standard of care in their respective countries at the time when the studies were performed [8,10,11,20,22,23,27,29,30,34]. The characteristics of included studies are summarized in Appendix 3.

Certainty of evidence

The overall certainty of evidence was rated very low due to serious risk of bias in the included studies, as well as issues with inconsistency and imprecision in several critical outcomes. Of the 21 included studies, 7 had high risk of performance and detection bias due to lack of blinding [10,20,22,23,27,29,34]. Two studies had issues in selection bias [22,27] in addition to issues in performance bias, four studies had high risk of attrition bias [9,14,15,29]. The risk of bias summary is shown in Appendix 4. The GRADE evidence profile is in Appendix 5.

All-cause mortality

Pooled analysis of 21 RCTs (n=8,700) did not show significant difference in reducing all-cause mortality among patients given ivermectin compared to placebo or standard care (RR 0.76, 95% CI 0.55-1.05, I^2=0%). Subgroup analysis according to disease severity showed that ivermectin had no significant benefit in all-cause mortality among patients with mild disease (RR 1.17, 95% CI 0.41-3.34, I^2=0%), mild to moderate disease (RR 0.45, 95% CI 0.19-1.10, I^2=1%), moderate to severe disease (RR 0.72, 95% CI 0.36-1.45) or severe disease (RR 0.74, 95% CI 0.37-1.48, I^2=0%).

Subgroup analysis by dose showed no significant difference in all-cause mortality among those given low-dose ivermectin (RR 0.74, 95% CI 0.43-1.28, I^2=0%) and high dose ivermectin (RR 0.77, 95% CI 0.51-1.15, I^2=0%) compared with control.

Sensitivity analysis by exclusion of studies [8,14,15,29,33] with issues in selection, attrition, and/or reporting bias yielded similar results that ivermectin had no significant effect on the all-cause mortality (RR 0.67, 95% 0.34-1.31, I^2=0%). Exclusion of 1 RCT published as a short communication showed similar result (RR 0.75, 95% CI 0.54-1.05).

Other significant outcomes

In 6 RCTs with confirmed COVID-19 outpatients, the need for hospitalization was not significantly reduced in the ivermectin group (RR 0.91, 95% CI 0.65-1.28, I^2=27%; n=3,053). In another 5 RCTs with COVID-19 confirmed hospitalized patients, duration of hospital stay was not significantly different in the ivermectin group (MD 0.13 days, 95% CI -0.79 to 1.04, I^2=70%; n=1,676) compared with control group, but with significant heterogeneity. Another study [14] reported that there was no significant difference in the median number of days of hospitalization between ivermectin (6 days, IQR 4-10 days) and control group (6 days, IQR 3-11 days) [14].

There was also no significant difference in clinical deterioration, defined as deterioration in WHO ordinal scale or progression to severe disease (RR 1.03, 95% 0.76-1.41, I^2=0%; 7 studies, n=1,470), regardless of disease severity. Ivermectin did not significantly reduce the number of patients need for mechanical ventilation (RR 0.91, 95% CI 0.82-1.02, I^2=0%; 10 studies, n=4,178) nor ICU admission (RR 0.85, 95% 0.57-1.28, I^2=0%; 5 studies, n=2,162), regardless of the disease severity.

Clinical improvement on Day 6-10 (RR 1.01, 95% CI 0.96-1.07, I^2=0%; 9 studies, n=2,128) were not significantly improved among those given ivermectin, regardless of hospital status. Time to symptom resolution (mean difference -0.53 days, 95% -1.50 to 0.44, I^2=0%; 2 studies, n=165) was also not significantly improved among patients given ivermectin compared with control. Three (3) other studies reported no significant difference in time to symptom resolution between ivermectin and placebo/standard of care. Lopez-Medina et al [23] reported that COVID-19 symptoms in Ivermectin group lasted for 10 days (IQR 9 to 13) compared to 12 days (IQR 9 to 13) in the placebo group (HR 1.07 95% CI 0.87-1.32). Manomaipiboon et al [11] reported patients who received ivermectin had symptoms for a median of 8 days (IQR 3.5 to 14 days) compared with 8 days (IQR 5 to 14 days) in the placebo group (HR 1.18 95% CI 0.67 to 2.08). Lastly, Naggie et al [13] reported that the median time to recovery was 12 days (IQR, 11 to 13) in the ivermectin group and 13 days (IQR, 12 to 14) in the placebo group (HR 1.07, 95% CI 0.96-1.17).

Pooling thirteen RCTs (n=1,532), virologic clearance from day 3 to 14 was not significantly different between ivermectin and control groups (RR 1.15, 95% CI 0.94-1.42, I^2=70%), with significant heterogeneity. Subgroup analysis according to disease severity showed that ivermectin had no significant effect among those mild disease (RR 0.98, 95% 0.77-1.25, I^2=57%; 6 RCTs, n=842) or mild to moderate disease (RR 1.21, 95% CI 0.91-1.61, I^2=59%; 6 RCTs, n=624) but had a significant benefit among patients with severe disease (RR 3.89, 95% CI 1.2-12.27, 1 RCT, n=66). Careful consideration should be exercised, as this result was based on a single study wherein a greater proportion of participants in the ivermectin group had available data on virologic status (16/36 or 44%), as compared with the control group (3/30 or 10%) [29]. Subgroup analysis by hospitalization status did not show significant difference for both outpatient (RR 1.01, 95% CI 0.83-1.23, I^2=62%, n=937) and hospitalized patients (RR 1.41, 95% CI 0.97-2.04, I^2=57%, n=595), both with moderate heterogeneity.

Adverse events

Ivermectin was not significantly associated with an over-all increased risk of adverse events (RR 1.07, 95% CI 0.86-1.34, I^2=50%; 18 RCTs, n=7,345) with moderate heterogeneity. Subgroup analysis according to dose showed no significant difference in adverse events with use of low-dose ivermectin (RR 0.95, 95% CI 0.84-1.07, I^2=0%; 8 RCTs, n=1,545), high-dose ivermectin (RR 1.35, 95% CI 0.79-2.32, I^2=74%; 8 RCTs, n=5,250) or mixed doses (RR 1.26, 95% CI 0.58-2.75, I^2=0%; 2 RCTs, n=550). Results on high-dose Ivermectin showed significant heterogeneity. Two studies reported the adverse events experienced by the participants instead of the number of participants who experienced adverse events. The study by Abbas et al showed almost similar results between the experimental (124 events among 99 participants) and control group (129 events among 103 participants) [5]. However, the study by Buonfrate et al showed that the number of adverse events is 1.79-fold greater in the experimental group (181 events among 71 participants) compared to the control (46 events among 32 participants) [7]. Gastrointestinal symptoms such as nausea, epigastric pain and diarrhea, neurologic symptoms such as headache, agitation, confusion, dizziness, and transient eye disorders were the most common adverse events reported across studies.

There was no significant difference in serious adverse events (SAEs) among patients given ivermectin compared to control group (RR 1.49, 95% CI 0.75-2.94, I^2=0%; 15 RCTs, n=4,932). Subgroup analysis according to dose showed no significant difference in SAEs with use of low-dose ivermectin (RR 1.76, 95% CI 0.41-7.55, I^2=0%; 7 RCTs, n=1,373), high-dose ivermectin (RR 1.42, 95% CI 0.65-3.06, I^2=0%; 7 RCTs, n=3,402). The study by Abbas et al reported almost similar number of serious adverse events in both the experimental group (5 events among 99 participants) and control group (6 events among 103 participants) [5]. The most common SAEs among patients who received ivermectin were worsening of COVID-19 requiring hospitalization and multiorgan failure related to disease progression. Other SAEs reported were myocardial infarction, severe anemia, hypovolemic shock secondary to severe diarrhea, hyponatremia, and delirium-like behavior among patients who tested positive for mutation of either MDR-1/ABCB1 or CYP3A4 genes affecting ivermectin metabolism.

Pediatric considerations

Two of the included RCTs enrolled patients <18 years old. Rezai et al [15] included COVID-19 confirmed outpatients 5 years old and above weighing at least 15kg while Bukhari et al [20] included patients at least 15 years old with mild to moderate COVID-19. However, the number of pediatric patients enrolled and their outcome were not specified in both studies. Raw data were sought from the authors, pending feedback at the time of writing this update. Observational studies which described ivermectin use in hospitalized children with COVID-19 were limited as well. Two cross sectional studies which described the management of pediatric patients in Bangladesh [35] and India [36] cited ivermectin as one of the drugs given to very few patients, along with other medications such as steroids, antibiotics, antiviral, and antimalarial drugs. Ivermectin use was reported in 1 out 126 (0.7%) and 3 out of 25 (8.3%) by Chowdhury and Kumar, respectively.

RECOMMENDATIONS FROM OTHER GROUPS

Group or Agency	Recommendation	Strength of Recommendation / Certainty of Evidence
US-NIH [38] (as of April 29,2022)	Recommends against the use of ivermectin for the treatment of COVID-10 except in clinical trials.	Strong Recommendation
Infectious Diseases Society of America (IDSA) [39] (as of October 18, 2022)	In hospitalized patients with COVID-19, the IDSA panel suggests against ivermectin.	Conditional recommendation, Very low certainty of evidence
	In ambulatory persons with COVID-19, the IDSA panel recommends against ivermectin.	Strong recommendation, Moderate certainty of evidence
WHO Living Guideline on COVID-19 Therapeutics [40] (as of July 14, 2022)	Recommends not to use ivermectin regardless of disease severity and any duration of symptoms, except in the context of a clinical trial.	Recommended only in research settings
India COVID-19 Guidelines [41] (as of May 15, 2021)	Recommends against using Ivermectin for treatment of patients with any severity of COVID-19. Ivermectin should only be used in the context of a randomized clinical trial.	
Australian COVID-19 Guidelines [42] (as of May 27, 2022)	Does not recommend the use of ivermectin outside of properly conducted clinical trials with appropriate ethical approval.	

ONGOING STUDIES AND RESEARCH GAPS

There are 44 studies registered in various clinical trial registries. 23 studies are recruiting or not yet recruiting, while 11 had unknown status. There were 5 terminated studies, 2 of which were discontinued due to poor response or futility, 2 studies due to inadequate accrual of participants, and 1 was terminated due to findings of a pilot study that suggested that the administration of ivermectin in patients with SARS-CoV-2 is safe, reducing symptoms and viral load. 2 trials were withdrawn, 1 due to insufficient funding and the other due to WHO report. A clinical trial in the Philippines was terminated on May 2022 due to ivermectin's lack of clinical benefits based on recently published studies and availability of effective alternative treatment.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

The cost of ivermectin is around ₱20-27 per tablet depending on concentration, based from the website of Dr. Zen's Research, Inc., a subsidiary of InnoGen Pharmaceuticals, Inc.[37]

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

No studies were found informing on its cost-effectiveness, feasibility, and acceptability in COVID-19 treatment.

REFERENCES

[1] Yang SNY, Atkinson SC, Wang C, Lee A, Bogoyevitch MA, Borg NA, et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. Antiviral Res. 2020 May;177:104760.

[2] Lehrer S, Rheinstein PH. Ivermectin Docks to the SARS-CoV-2 Spike Receptor-binding Domain Attached to ACE2. Vivo Athens Greece. 2020 Oct;34(5):3023–6.

[3] Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020 Jun;178:104787.

[4] Popp M, Reis S, Schießer S, Hausinger RI, Stegemann M, Metzendorf MI, et al. Ivermectin for preventing and treating COVID-19. Cochrane Database Syst Rev [Internet]. 2022 [cited 2022 Jun 23];(6). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD015017.pub3/full

[5] Abbas KU, Muhammad S, Ding SF. The Effect of Ivermectin on Reducing Viral Symptoms in Patients with Mild COVID-19. Indian J Pharm Sci. 2022;(1):5.

[6] Bramante CT, Huling JD, Tignanelli CJ, Buse JB, Liebovitz DM, Nicklas JM, et al. Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19. N Engl J Med. 2022 Aug 18;387(7):599–610.

[7] Buonfrate D, Chesini F, Martini D, Roncaglioni MC, Ojeda Fernandez ML, Alvisi MF, et al. High-dose ivermectin for early treatment of COVID-19 (COVER study): a randomised, double-blind, multicentre, phase II, dose-finding, proof-of-concept clinical trial. Int J Antimicrob Agents. 2022 Feb;59(2):106516.

[8] Chahla RE, Ruiz LM, Mena T, Brepe Y, Terranova P, Ortega ES, et al. Randomized trials - Ivermectin repurposing for COVID-19 treatment of outpatients with mild disease in primary health care centers. Res Soc Dev. 2022 Jun 21;11(8):e35511830844–e35511830844.

[9] de la Rocha C, Cid-López MA, Venegas-López BI, Gómez-Méndez SC, Sánchez-Ortiz A, Pérez-Ríos AM, et al. Ivermectin compared with placebo in the clinical course in Mexican patients with asymptomatic and mild COVID-19: a randomized clinical trial. BMC Infect Dis. 2022 Dec 8;22:917.

[10] Lim SCL, Hor CP, Tay KH, Mat Jelani A, Tan WH, Ker HB, et al. Efficacy of Ivermectin Treatment on Disease Progression Among Adults With Mild to Moderate COVID-19 and Comorbidities: The I-TECH Randomized Clinical Trial. JAMA Intern Med. 2022 Apr 1;182(4):426–35.

[11] Manomaipiboon A, Pholtawornkulchai K, Poopipatpab S, Suraamornkul S, Maneerit J, Ruksakul W, et al. Efficacy and safety of ivermectin in the treatment of mild to moderate COVID-19 infection: a randomized, double-blind, placebo-controlled trial. Trials. 2022 Aug 26;23(1):714.

[12] Mirahmadizadeh A, Semati A, Heiran A, Ebrahimi M, Hemmati A, Karimi M, et al. Efficacy of single-dose and double-dose ivermectin early treatment in preventing progression to hospitalization in mild COVID-19: A multi-arm, parallel-group randomized, double-blind, placebo-controlled trial. Respirol Carlton Vic. 2022 Jun 23;10.1111/resp.14318.

[13] Naggie S, Boulware DR, Lindsell CJ, Stewart TG, Gentile N, Collins S, et al. Effect of Ivermectin vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA [Internet]. 2022 Oct 21 [cited 2022 Oct 24]; Available from: https://doi.org/10.1001/jama.2022.18590

[14] Reis G, dos Santos Moreira-Silva EA, Silva DCM, Thabane L, Milagres AC, Ferreira TS, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. Lancet Glob Health. 2021 Oct;S2214109X21004484.

[15] Rezai MS, Ahangarkani F, Hill A, Ellis L, Mirchandani M, Davoudi A, et al. Non-effectiveness of Ivermectin on Inpatients and Outpatients With COVID-19; Results of Two Randomized, Double-

Blinded, Placebo-Controlled Clinical Trials. Front Med [Internet]. 2022 [cited 2022 Sep 18];9. Available from: https://www.frontiersin.org/articles/10.3389/fmed.2022.919708

[16] Pott-Junior H, Paoliello MMB, Miguel A de QC, da Cunha AF, de Melo Freire CC, Neves FF, et al. Retraction notice to “Use of ivermectin in the treatment of Covid-19: A pilot trial” [Toxicol. Rep. 8 (2021) 505–510]. Toxicol Rep. 2022 May 2;9:1023.

[17] Elgazzar A, Hany B, Youssef S, Hafez M, Moussa H, Eltaweel A. Efficacy and Safety of Ivermectin for Treatment and prophylaxis of COVID-19 Pandemic | Research Square. Res Sq [Internet]. 2020 [cited 2022 Nov 29]; Available from: https://www.researchsquare.com/article/rs-100956/v2

[18] Shahbaznejad L, Davoudi A, Eslami G, Markowitz JS, Navaeifar MR, Hosseinzadeh F, et al. Effects of Ivermectin in Patients With COVID-19: A Multicenter, Double-blind, Randomized, Controlled Clinical Trial. Clin Ther. 2021 Jun;43(6):1007–19.

[19] Shakhsi Niaee M, Namdar P, Allami A, Varnaseri M, Bijani B, Cheraghi F, et al. Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial. Asian Pac J Trop Med. 2021;14:266–73.

[20] Bukhari KHS, Asghar A, Perveen N, Hayat A, Mangat SA, Butt KR, et al. Efficacy of Ivermectin in COVID-19 Patients with Mild to Moderate Disease [Internet]. medRxiv; 2021 [cited 2022 May 27]. p. 2021.02.02.21250840. Available from: https://www.medrxiv.org/content/10.1101/2021.02.02.21250840v1

[21] Ahmed S, Karim MM, Ross AG, Hossain MS, Clemens JD, Sumiya MK, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2021 Feb;103:214–6.

[22] Podder CS, Chowdhury N, Sina MI, Haque WMMU. Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study. IMC J Med Sci. 2020;14(2):11–8.

[23] Kishoria N, Mathur S, Parmar V, Jeet R, Agrawal H, Parihar b. Ivermectin As Adjuvant To Hydroxycholoroquine In Patients Resistant To Standard Treatment For Sars-Cov-2: Results Of An Open-Label Randomized Clinical Study. Paripex Indian J Res. 2020 Sep 18;

[24] Mohan A, Tiwari P, Suri TM, Mittal S, Patel A, Jain A, et al. Single-dose oral ivermectin in mild and moderate COVID-19 (RIVET-COV): A single-centre randomized, placebo-controlled trial. J Infect Chemother Off J Jpn Soc Chemother. 2021 Dec;27(12):1743–9.

[25] Ravikirti null, Roy R, Pattadar C, Raj R, Agarwal N, Biswas B, et al. Evaluation of Ivermectin as a Potential Treatment for Mild to Moderate COVID-19: A Double-Blind Randomized Placebo Controlled Trial in Eastern India. J Pharm Pharm Sci Publ Can Soc Pharm Sci Soc Can Sci Pharm. 2021;24:343–50.

[26] Biber A, Harmelin G, Lev D, Ram L, Shaham A, Nemet I, et al. The effect of ivermectin on the viral load and culture viability in early treatment of nonhospitalized patients with mild COVID-19 - a double-blind, randomized placebo-controlled trial. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2022 Sep;122:733–40.

[27] Chachar AZK, Khan KA, Asif M, Tanveer K, Khaqan A, Basri R. Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients. Int J Sci. 2020;9(09):31–5.

[28] Chaccour C, Casellas A, Blanco-Di Matteo A, Pineda I, Fernandez-Montero A, Ruiz-Castillo P, et al. The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial. EClinicalMedicine. 2021 Feb;32:100720.

[29] Okumuş N, Demirtürk N, Çetinkaya RA, Güner R, Avcı İY, Orhan S, et al. Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients. BMC Infect Dis. 2021 May 4;21(1):411.

[30] Krolewiecki A, Lifschitz A, Moragas M, Travacio M, Valentini R, Alonso DF, et al. Antiviral effect of high-dose ivermectin in adults with COVID-19: A proof-of-concept randomized trial. EClinicalMedicine. 2021 Jul;37:100959.

[31] Vallejos J, Zoni R, Bangher M, Villamandos S, Bobadilla A, Plano F, et al. Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial. BMC Infect Dis. 2021 Jul 2;21(1):635.

[32] López-Medina E, López P, Hurtado IC, Dávalos DM, Ramirez O, Martínez E, et al. Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial. JAMA. 2021 Apr 13;325(14):1426–35.

[33] Beltran Gonzalez JL, González Gámez M, Mendoza Enciso EA, Esparza Maldonado RJ, Hernández Palacios D, Dueñas Campos S, et al. Efficacy and Safety of Ivermectin and Hydroxychloroquine in Patients with Severe COVID-19: A Randomized Controlled Trial. Infect Dis Rep. 2022 Mar 3;14(2):160–8.

[34] Abd-Elsalam S, Noor RA, Badawi R, Khalaf M, Esmail ES, Soliman S, et al. Clinical study evaluating the efficacy of ivermectin in COVID-19 treatment: A randomized controlled study. J Med Virol. 2021 Oct;93(10):5833–8.

[35] Chowdhury K, Haque M, Nusrat N, Adnan N, Islam S, Lutfor AB, et al. Management of Children Admitted to Hospitals across Bangladesh with Suspected or Confirmed COVID-19 and the Implications for the Future: A Nationwide Cross-Sectional Study. Antibiotics. 2022 Jan;11(1):105.

[36] Kumar S, Haque M, Shetty A, Acharya J, Kumar M, Sinha V, et al. Current management of children with COVID-19 in hospitals in India; Pilot study and findings. Adv Hum Biol. 2022;12(1):16.

[37] Dr. Zen's Research Inc. Ivermectin. Available from: https://www.drzens.com/products/ivermectin-1?variant=39416240144467. Accesed 24 October 2022.

[38] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 24 October 2022.

[39] Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2021; Version 10.0.1. Accessed 24 October 2022.

[40] World Health Organization. Therapeutics and COVID-19: Living guideline v12, 14 July 2022. Available from https://app.magicapp.org/#/guideline/nBkO1E. Accessed 24 October 2022.

[41] India COVID Guidelines. Available from https://indiacovidguidelines.org. Accessed 24 October 2022

[42] Australian National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical cure of people with COVID-19 v57. Available at https://app.magicapp.org/#/guideline/6687. Accessed 24 October 2022.

Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=6/10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)					• COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.
Benefits	Large	Moderate (2)	Small (2)	Uncertain (1)	Trivial (1)		• No significant benefit for all-cause mortality (RR 0.76, 95% CI 0.55-1.05), clinical deterioration (RR 1.03, 95% CI 0.76-1.41), need for mechanical ventilation (RR 0.91, 95% CI 0.82-1.02), ICU admission (RR 0.85, 95% CI 0.57-1.28), clinical improvement (RR 1.01, 95% CI 0.96-1.07), time to symptom resolution (MD -0.53 days, 95% CI -1.50 to 0.44), hospitalization (RR 0.91, 95% CI 0.65-1.28) and length of hospital stay (MD 0.13 days, 95% CI -0.79 to 1.04)
Harm	Large (1)	Moderate (3)	Small	Trivial (1)	Varies	Uncertain (1)	• No significant difference in adverse events (RR 1.07, 95% CI 0.86-1.34) and serious adverse events (RR 1.49, 95% CI 0.75-2.94). • GI symptoms such as epigastric pain, diarrhea and nausea, neurologic symptoms such as headache, agitation, confusion, dizziness and transient eye disorders were the most common adverse

							events reported across studies. ● Most common SAEs were worsening of COVID-19 and multiorgan failure from progression of the disease. Other SAEs reported were myocardial infarction, hyponatremia, hypovolemic shock secondary to severe diarrhea (n=1), delirium-like behavior.
Certainty of Evidence	High	Moderate (1)	Low	Very low (5)			● The overall certainty of evidence was rated very low, downgraded due to serious risk of bias in most studies and issues in inconsistency, and imprecision in several critical outcomes.
Balance of effects	Favors intervention	Probably favors intervention	Does not favor intervention	Probably favors no intervention (2)	Favors no intervention (3)	Varies (1)	● There is uncertainty in the overall efficacy and safety of ivermectin as treatment for COVID-19.
Values	Important uncertainty or variability	Possibly important uncertainty or variability (4)	Probably no important uncertainty or variability (1)	No important uncertainty or variability (1)			
Resources Required	Uncertain	Large cost	Moderate Cost (1)	Negligible cost or savings (2)	Moderate savings (3)	Large savings	● Cost is around ₱20-27 per tablet depending on concentration.
Certainty of evidence of required resources	No included studies (1)	Very low (2)	Low (2)	Moderate	High (1)		● Pricing information is taken from the website of Dr. Zen's Research, Inc. is a subsidiary of InnoGen Pharmaceuticals, Inc.
Cost effectiveness	No included studies (3)	Favors using the comparison (1)	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the invention	Varies (1)	

Equity	Don't know (1)	Varies (1)	Probably reduced	Reduced (1)	Probably increased (1)	Probably no impact (2)	
Acceptability	Uncertain	Varies (3)	No	Probably no (2)	Probably yes (1)	Yes	
Feasibility	Uncertain	Varies (2)	No	Probably no (2)	Probably yes (2)	Yes	
Recommendation	For	Against (6)					
Strength	Weak (5)	Strong (1)					

Other considerations:

- Severity of COVID-19 illness

Appendix 2: Search Strategy

Database	Search Strategy	Date and Time of Search	Yield	Eligible
MEDLINE (PubMed)	(("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("ivermectin"[MeSH Terms] OR "ivermectin"[All Fields] OR "ivermectine"[All Fields] OR "ivermectin s"[All Fields] OR "ivermectins"[All Fields])) AND ((clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (2021/9/10:2022/5/27[pdat]))	October 24, 2022 9:00 AM	70	7
CENTRAL	MeSH descriptor: [COVID-19] explode all trees AND [Ivermectin] explode all trees Filter: September 10, 2021 to May 27, 2022	October 24, 2022 10:00 AM	28	5
COVID-NMA Initiative	Ivermectin	October 24, 2022 10:30 AM	25	5
COVID-19 Evidence Alerts McMaster Plus	Ivermectin	October 24, 2022 10:45 AM	38	9
Google Scholar	Ivermectin AND COVID AND clinical trial	October 24, 2022 1:00 PM	35	2
MedRxiv	Advanced search: “Ivermectin AND COVID” with “match all” parameters Filter: September 10, 2021 to May 27, 2022	October 24, 2022 1:30 PM	54	1
BioRxiv	Advanced search: “Ivermectin AND COVID” with “match all” parameters Filter: September 10, 2021 to May 27, 2022	October 24, 2022 2:00 PM	22	0
ChinaXiv	Advanced search: “Ivermectin AND COVID” with “all fields” parameters	October 24, 2022 2:15 PM	0	0
ClinicalTrials.gov	Ivermectin AND COVID-19	October 24, 2022 2:30 PM	27	0
EU Clinical Trials Register	Ivermectin AND COVID-19	October 24, 2022 3:00 PM	4	0

Republic of Korea – Clinical Research Information Service (CRIS)	Ivermectin AND COVID-19	October 24, 2022 3:15 PM	0	0
Chinese Clinical Trial Registry	Under trial search (with more option), the search syntax “Ivermectin”, under intervention and “COVID-19”, under target disease was used	October 24, 2022 3:30 PM	1	0
Cochrane COVID-19 study register	Ivermectin Filters: September 10, 2021 to May 27, 2022 Study type: Interventional	October 24, 2022 3:45 PM	4	0
WHO ICTRP	Ivermectin Filters: Restrict to COVID-19, September 10, 2021 to May 27, 2022	October 24, 2022 4:15 PM	9	0

Appendix 3: Characteristics of Included Studies

Table 2. Ivermectin versus placebo or standard care (27 RCTs)

No.	Clinical Trial ID/ Title	Country	Study design	Population	Intervention	Comparator	Outcomes
1	Abd-Elsalam 2021 Clinical study evaluating the efficacy of Ivermectin in COVID-19 treatment: A randomized controlled study	Egypt	Open-label RCT (N=164)	Mild-moderate COVID-19 Age 20 to 65 years old	Oral Ivermectin, 12 mg once a day for 3 days. (n=82) Low dose Ivermectin	Standard care (n=82) Standard care: paracetamol, empiric antibiotics, oseltamivir if needed.	1. Mortality 2. Need for mechanical ventilation 3. Safety
2	Ahmed 2020 A five day course of Ivermectin for the treatment of COVID-19 may reduce the duration of illness.	Bangladesh	Double-blind RCT (N=76)	Mild COVID-19 Age 18 to 65 years hospitalized within the last 7 days; with either fever (≥37.5C); cough or sore throat; and diagnosed positive for SARS-CoV-2 by RT-PCR.	Oral Ivermectin, 12 mg once a day for 5 days. (n=24) Low dose Ivermectin	Placebo (n=24)	1. Mortality 2. Clinical deterioration 3. Duration of hospitalization 4. Remission of symptoms 5. Time to PCR negativity 6. Adverse effects
3	Beltran-Gonzalez 2021 Efficacy and safety of Ivermectin and hydroxychloroquine in patients with severe COVID-19	Mexico	Double-blind RCT (N=106)	Severe COVID-19 Mean age 53	Oral Ivermectin 12 or 18 mg according to weight (n=36) Low dose Ivermectin	Placebo (n=37)	1. Duration of hospitalization 2. Hospital discharge, n(%) 3. Discharged without respiratory deterioration or death, n(%) 4. Respiratory deterioration or death, n(%)
4	Biber 2022 Favorable outcome on viral load and culture viability using Ivermectin in early treatment of non-hospitalized patients with mild COVID-19 – A double-blind, randomized placebo-controlled trial.	Israel	Double-blind RCT (N=89)	Mild-moderate COVID-19 Age 18 years and older	Oral Ivermectin, 12 or 15 mg according to weight (n=57) Low dose Ivermectin	Placebo (n=59)	1. Viral clearance (repeat RT-PCR on D4,6,8,10)
5	Bukhari 2021 (preprint) Efficacy of Ivermectin in COVID-19 patients with mild to moderate disease	Pakistan	Open-label RCT (N=100)	Mild-moderate COVID-19 Age 15 to 65 years	Oral Ivermectin 12 mg single dose at admission (n=50) Low dose Ivermectin	Standard care (n=50) Standard care: Vit C 500mg OD, Vit D3 200k IU once weekly, paracetamol 500mg	1. Viral clearance (days to RT-PCR negativity) 2. Adverse effects

6	Chaccour 2020 The effect of early treatment with Ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot,double-blind, placebo-controlled, randomized clinical trial.	Spain	Double-blind RCT (N=24)	Mild COVID-19 Age 18 to 59 years Outpatient setting. without comorbidities considered as risk factors to 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
7	Chachar 2020 Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients	Pakistan	Open-label RCT (N=50)	Mild COVID-19 Age 18 to 75 years excluded severe COVID-19, with malignancy, chronic kidney disease, and liver cirrhosis	Oral Ivermectin, 12 mg on D0, then 12 mg after 12 hours, and 12 mg after 24 hours. (n=25) Low dose Ivermectin	Standard care (n=25) Standard care: conventional symptomatic treatment	1. Clinical improvement 2. Adverse effects
8	Kishoria 2020 Ivermectin as adjuvant to hydroxychloroquine in patients resistant to standard treatment for sars-cov-2:results of an open-label randomized clinical study	India	Open-label RCT (N=32)	Mild COVID-19 Age 18 years and older Patients who remain positive after 6 days of standard care treatment.	Oral Ivermectin, 12 mg single dose on D1 (n=19) Standard care: HCQ 400 mg/tab twice a day for 5 days Paracetamol 500mg/tab prn, Vitamin C BID. Low dose Ivermectin	Standard care (n=16) Standard care: HCQ 400 mg/tab twice a day for 5 days Paracetamol 500mg/tab prn, Vitamin C BID.	1. Viral clearance D5 2. Hospital Discharge D5
9	Królewiecki 2020 Antiviral effect of high-dose Ivermectin in adults with COVID-19: a pilot randomised, controlled, open label, multicentre trial.	Argentina	Single-blind (outcome-assessor) RCT (N=45)	Mild-Moderate COVID-19 Age 18 to 69 years hospitalized patients not requiring ICU admission excluded patients with poorly controlled comorbidities	Oral Ivermectin, 600mcg/kg, once a day for 5 days (n=30) Co-Intervention: Standard care High dose Ivermectin	Standard care (n=15) Standard care: uncertain	1. Mortality 2. Clinical deterioration 3. Adverse effects

10	Lopez-Medina 2021 Effect of Ivermectin on time to resolution of symptoms among adults with mild COVID-19	Colombia	Double-blind RCT (N=476)	Mild COVID-19 Mean age 37 (range: 28-49)	Oral Ivermectin, 300 mcg/kg, once a day for 5 days (n=238) Low dose Ivermectin	Placebo (n=238)	1. Time to resolution of symptoms (D21); % patients with resolved symptoms 2. Clinical deterioration (% patient with clinical deterioration) 3. Fever since randomization 4. Escalation of care 5. Mortality
11	Mohan 2021 Single-dose oral ivermectin in mild and moderate COVID-19 (RIVET-COV): A single-centre 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=52) Oral Ivermectin, 24 mg, single dose (n=52) Low dose and high dose Ivermectin	Placebo (n=53)	1. Mortality 2. Clinical deterioration 3. Progression to ventilation 4. Clinical improvement 5. Duration of hospitalization 6. Viral clearance 7. Adverse effects
12	Okumus 2021 The Effectiveness and Safety of Ivermectin as add-on Therapy in Severe COVID-19 Management	Turkey	Randomized open label (N=66)	Severe COVID-19 Age 18 years and older	Oral Ivermectin 200 mcg/kg, once a day for 5 days (n=30) Co-intervention: Standard care Low dose Ivermectin	Standard care (n=30) Standard care: Hydroxychloroquine, favipiravir and azithromycin (HFA) HCQ (2x400mg loading dose followed by 2x200mg, PO, 5 days), favipiravir (2x1600mg loading dose followed by 2x600mg maintenance dose, PO, total 5 days) and azithromycin (500mg 1st day loading dose, followed by 250mg/day, PO, total 5 days)	1. Mortality 2. Clinical improvement 3. Viral clearance D10 4. Adverse effects
13	Podder 2020 Outcome of Ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study	Bangladesh	Open-label RCT (N=62)	Mild-moderate COVID-19 Age 18 years and older	single dose of Ivermectin 200 mcg/kg on the day 1 of randomization (n=32) Low dose Ivermectin	Standard care (n=30) Standard care: symptomatic treatment which included antipyretics, cough suppressants, and capsule doxycycline (100 mg every 12 hours for seven days)	1. time needed for resolution of fever, cough, shortness of breath 2. time needed for full recovery from all symptoms 3. Viral clearance (repeat RT-PCR on day 10)

14	Ravikirti 2021 Ivermectin as a potential treatment for mild to moderate COVID-19 – A Double-blind randomized placebo-controlled trial	India	Double-blind RCT (N=115)	Mild-Moderate COVID-19 Age 18 years and older	Oral Ivermectin 12mg on D1 and D2 (n=57) Co-intervention: standard care Low dose Ivermectin	Placebo (n=58) Standard care: Hydroxychloroquine, steroids, enoxaparin, antibiotics, remdesivir, convalescent plasma, tocilizumab	1. Mortality 2. Clinical deterioration 3. Progression to Ventilation 4. Clinical improvement 5. Viral Clearance
15	Vallejos 2021 Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo controlled trial	Argentina	Double-blind RCT (N=501)	Mild COVID-19 Age 18 years and older	Oral Ivermectin, 150-200mcg/kg, once a day for 2 days (n=250) Low dose Ivermectin	Placebo (n=251)	1. Clinical deterioration (need for hospitalization) 2. Mortality 3. Need for mechanical ventilation 4. Safety
New studies							
16	Abbas 2022 (short communication) The Effect of Ivermectin on Reducing Viral Symptoms in Patients with Mild COVID-19	China	Double blind RCT (N=202)	Outpatients Age 18-50y Mild severity	Ivermectin 300mcg/kg x 5 days (n=99) x 5d Low dose Ivermectin	Placebo (n=103)	1. Complete resolution of symptoms during 21d follow-up No other outcomes pre-specified
17	Bramante 2022 Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19	USA	Double blind RCT (N=1341)	Outpatients Age 30-85y with BMI $\geq$ 25kg/m^2 Symptoms within 7 days	Ivermectin 390-470 mcg/kg x 3d (n=443) High dose ivermectin	Placebo (n=437)	1. Severe COVID-19 D14 (composite of hypoxemia, ED visit, hospitalization or death) 2. Daily symptom severity 3. Modified total symptom score 4. Drug discontinuation Length of follow-up: 14 days
18	Buonfrate 2022 High-dose ivermectin for early treatment of COVID-19 (COVER study): a multicenter, double-blind, multicenter, phase II, dose-finding, proof-of-concept clinical trial	Italy	Double blind RCT (N=93)	Outpatients Age 18 years and older Asymptomatic (14%), Mild, symptomatic (COVID severity score <3) (86%)	Ivermectin 0.6 mg/kg x 5 days (n=29) Ivermectin 1.2 mg/kg x 5 days (n=32) High dose Ivermectin	Placebo (n=32)	1. SAE 2. Change of viral load D7 3. Time to clinical resolution 4. Virologic clearance D14 and D30 5. Hospitalization 6. COVID-19 severity score at D14 and D30
19	Chahla 2022 Cluster Randomised Trials - Ivermectin Repurposing For COVID-19 Treatment Of Outpatients With Mild Disease In Primary Health Care Centers	Argentina	Open label RCT (N=254)	Mild COVID-19 Age 18 years and older	Ivermectin 24 mg every 7 days x 4 weeks + SC (n = 110) Low dose Ivermectin	Standard care (n = 144) *Paracetamol, Aspirin, Ranitidine (symptomatic treatment)	1. Proportion of patients with symptoms (fever, diarrhea, taste and/or smell disturbance, SpO2, polyarthralgia, headache, body pain, abdominal pain, ALRI symptoms and signs) [Time Frame: from 5th to 9th day]; [

							Time Frame: from 10th to 14th day] 2. Increase discharge from outpatient care with COVID-19 mild disease
20	Dela Rocha 2022 Ivermectin compared with placebo in the clinical evolution of Mexican patients with asymptomatic and mild COVID-19: a randomized clinical trial	Mexico	Double blind RCT (N=	Mild COVID-19 ≥18y	Ivermectin 12mg/day x 3 days Low dose ivermectin	Placebo	1. Disease severity progression D14 (oxygen saturation (SpO2) < 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) < 300 mm Hg, a respiratory rate > 30 breaths/min, or lung infiltrates >50%) 2. Viral load D1, 5, 14 3. Symptoms D1, 5, 14 4. Adverse events Length of follow up: 14 days
21	Lim 2022 (I-TECH) Efficacy of Ivermectin Treatment on Disease Progression Among Adults With Mild to Moderate COVID-19 and Comorbidities: The I-TECH Randomized Clinical Trial	Malaysia	Open label RCT (N=500)	Mild to moderate COVID-19 50y or older with at least 1 comorbidity *2/3 – moderate disease	Ivermectin (0.4mg/kg) x 5 days + SC (n=250) High dose Ivermectin	Standard care (n=250)	1. Progression to severe disease 2. Time of progression to severe disease 3. All-cause mortality D28 4. Need for MV 5. ICU admission 6. Length of hospital stay
22	Manomaipiboon 2022 Efficacy and safety of ivermectin in the treatment of mild-to-moderate COVID-19 infection: A randomized, double blind, placebo, controlled trial	Thailand	Double-blind, RCT (N=74)	Mild to moderate COVID-19, within 72h of symptom/swab result Hospitalized patients Age 18-80 years	Ivermectin 12mg x 5 days + SC (n=37) Low dose Ivermectin	Standard care (n=37) (favipiravir, or andrographolide, CS, cetirizine, paracetamol)	1. Viral clearance D7 and D14 2. Duration of hospitalization 3. Frequency of clinical worsening 4. Need for MV 5. All-cause mortality D28 6. Adverse events Length of follow-up: 28 days
23	Mirahmadizadeh 2022 Efficacy of single-dose and double-dose ivermectin early treatment in preventing progression to hospitalization in mild COVID-19: A multi-arm, parallel-group randomized, double-blind, placebo-controlled trial	Iran	Double blind RCT (N=393)	Mild COVID-19 Age 18-80y with symptoms <48h	Low dose IVM: 12mg x.2 days High dose IVM: 24mg x 2 days	Placebo	1. Hospitalizations D28 2. Symptom resolution 3. Need for MV 4. Death D28 5. Time to resolution of symptoms 6. Adverse events 7. SAE Length of follow-up: 28 days

24	Naggie 2022 (ACTIV-6) Ivermectin for Treatment of Mild-to-Moderate COVID-19 in the Outpatient Setting: A Decentralized, Placebo-controlled, Randomized, Platform Clinical Trial	USA	Double blind RCT (N=1800)	Outpatients Age 30y and above Mild to moderate severity ≥2 symptoms for ≤7d	Ivermectin 400mcg/kg x 3d (n=919) High dose ivermectin	Placebo (n=881)	1. Time to sustained recovery (at least 3 days w/o symptoms) 2. Hospitalization or death D28 3. COVID Clinical Progression Scale on days 7, 14, and 28; 4. Mortality D28 5. hospitalization, urgent care visit, or emergency department visit D28 6. SAE, AE
25	Reis 2022 (TOGETHER) Effect of Early Treatment with Ivermectin among Patients with Covid-19	Brazil	Double blind RCT (N=1358)	Age 18 years and older At least 1 high-risk criterion for disease progression Outpatients	Ivermectin 0.4mg/kg x 3 days + SC (n=679) High dose Ivermectin	Placebo +SC (n=679)	1. Composite outcome of Hospitalization due to COVID-19 within 28 days OR ER visit due to clinical worsening of COVID-19 (requiring observation >6h) within 28 days 2. Viral clearance (D3, D7) 3. Time to hospitalization 4. Duration of hospitalization 5. Time to ER visit 6. Time to clinical recovery 7. All-cause mortality 8. Need for MV 9. Adverse events
26	Rezai 2022A (Outpatients) Non-effectiveness of Ivermectin on Inpatients and Outpatients With COVID-19; Results of Two Randomized, Double-Blinded, Placebo-Controlled Clinical Trial	Iran	Double blind RCT (N=582)	Mild COVID-19 Age ≥5y, weight ≥15kg	Ivermectin 0.4mg/kg x 3 days + SOC (N=282)_	Placebo + SOC (N=300)	1. Time to resolution of symptoms 2. Complete recovery (resolving main complaints at the sixth day) 3. Relative recovery (remaining main complaints at sixth day); 4. Clinical deterioration (needing hospitalization) 5. Viral clearance D5 6. Need for ICU admission 7. Adverse events

27	Rezai 2022B (Inpatients) Non-effectiveness of Ivermectin on Inpatients and Outpatients With COVID-19; Results of Two Randomized, Double-Blinded, Placebo-Controlled Clinical Trial	Iran	Double blind RCT (N=891)	Moderate to severe COVID-19 Age ≥18y	Ivermectin 0.4mg/kg x 3 days +SOC (N=447) *Remdesivir (98%), Dexamethasone (90.7%), Heparin and enoxaparin (85.1%)	Placebo + SOC (N=444)	1. Clinical improvement D? 2. Complete recovery ((resolving main complaints by discharge day) 3. Relative recovery (remaining main complaints at discharge day) 3. Clinical deterioration 4. Length of hospital stay 5. need for ICU 6. Need for MV 7. AE 8. Death

Appendix 4: Methodological Assessment of Included Studies

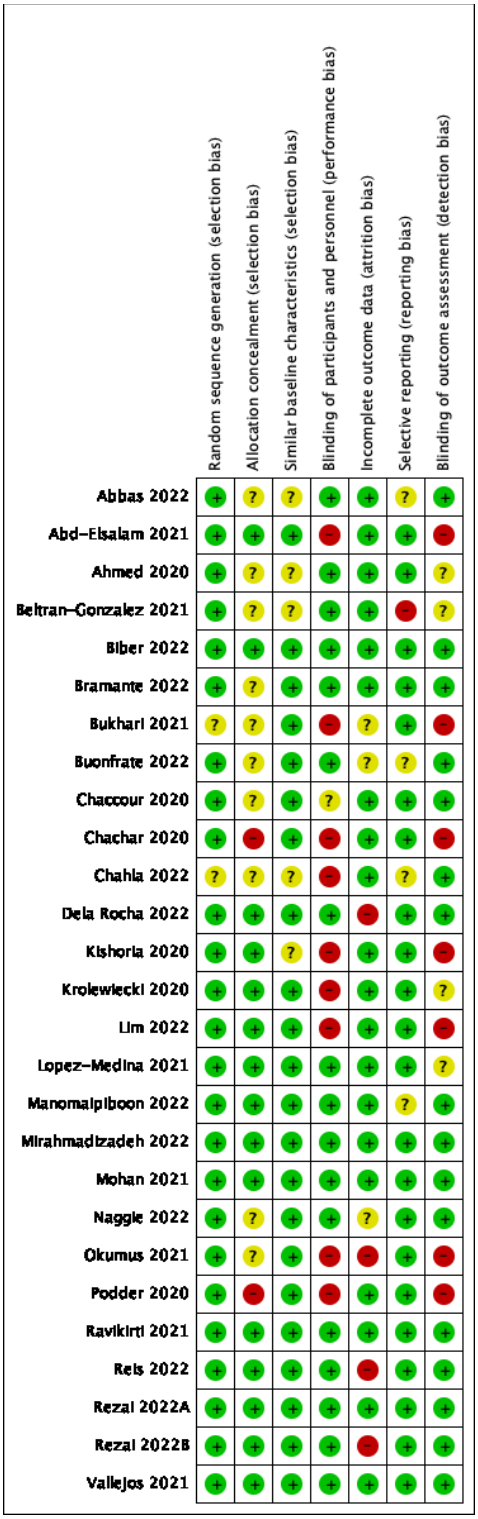

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Appendix 5: Grade Evidence Profile

Author(s): AP Zamora, N Esteban-Ipac
Question: Ivermectin compared to placebo or standard of care for COVID-19
Setting: Outpatient and hospitalized

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivermectin	placebo or standard of care	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: range 7 days to 42 days)												
21	randomised trials	serious[a]	not serious	not serious	serious[b]	none	59/4462 (1.3%)	81/4238 (1.9%)	**RR 0.76** (0.55 to 1.05)	**5 fewer per 1,000** (from 9 fewer to 1 more)	⨁⨁◯◯ Low	CRITICAL
Clinical deterioration (follow-up: range 20 days to 30 days)												
7	randomised trials	serious[c]	not serious	not serious	serious[d]	publication bias strongly suspected[e]	72/766 (9.4%)	67/704 (9.5%)	**RR 1.03** (0.76 to 1.41)	**3 more per 1,000** (from 23 fewer to 39 more)	⨁◯◯◯ Very low	CRITICAL
Need for mechanical ventilation (follow-up: range 10 days to 42 days)												
10	randomised trials	serious[f]	not serious	not serious	serious[d]	publication bias strongly suspected[e]	288/2198 (13.1%)	319/1980 (16.1%)	**RR 0.91** (0.82 to 1.02)	**14 fewer per 1,000** (from 29 fewer to 3 more)	⨁◯◯◯ Very low	CRITICAL
ICU admission (follow-up: range 10 days to 28 days)												
5	randomised trials	serious[g]	not serious	not serious	serious[d]	none	40/1073 (3.7%)	47/1089 (4.3%)	**RR 0.85** (0.57 to 1.28)	**6 fewer per 1,000** (from 19 fewer to 12 more)	⨁⨁◯◯ Low	CRITICAL
Clinical improvement (follow-up: range 6 days to 90 days)												
9	randomised trials	very serious[h]	not serious	not serious	not serious	none	704/1133 (62.1%)	595/995 (59.8%)	**RR 1.01** (0.96 to 1.07)	**6 more per 1,000** (from 24 fewer to 42 more)	⨁⨁◯◯ Low	CRITICAL
Time to symptom resolution (follow-up: range 10 days to 28 days)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivermectin	placebo or standard of care	Relative (95% CI)	Absolute (95% CI)		
5	randomised trials	very serious[i]	not serious	not serious	serious[d]	none	**Pooled mean difference (Mohan 2020, Podder 2020)**: MD -0.53 days [95% CI -1.50, 0.44] **Lopez-Medina 2021:** Ivermectin group 10 days (IQR, 9-13) compared with 12 days (IQR, 9-13) in placebo group. Hazard Ratio 1.07 [95%CI, 0.87 to 1.32]; *p* = .53 by log-rank test. **Manomaipiboon 2022:** Ivermectin group median 8 days (IQR 3.5-14) compared with 8 days (IQR 5-14) in the placebo group (HR 1.18 95% CI 0.67 to 2.08) **Naggie 2022:** Ivermectin group median 12 days (IQR, 11-13) in the ivermectin group compared with 13 days (IQR, 12-14) in the placebo group (HR 1.07, 95% Ci 0.96 to 1.17)				⨁◯◯◯ Very low	CRITICAL
Hospitalization (follow-up: range 14 days to 42 days)												
6	randomised trials	not serious	not serious	not serious	serious[d]	publication bias strongly suspected[e]	135/1601 (8.4%)	142/1452 (9.8%)	**RR 0.91** (0.65 to 1.28)	**9 fewer per 1,000** (from 34 fewer to 27 more)	⨁⨁◯◯ Low	CRITICAL
Duration of hospitalization (follow-up: range 28 days to 30 days)												
5	randomised trials	serious[i]	serious[k]	not serious	serious[d]	none	Mean difference -0.13 days [95% CI -0.79, 1.04]				⨁◯◯◯ Very low	IMPORTANT
Virologic clearance (follow-up: range 6 days to 30 days)												
13	randomised trials	serious[i]	serious[d]	not serious	serious[m]	none	316/806 (39.2%)	255/726 (35.1%)	**RR 1.15** (0.94 to 1.42)	**53 more per 1,000** (from 21 fewer to 148 more)	⨁◯◯◯ Very low	IMPORTANT
Adverse events (follow-up: range 7 days to 90 days)												
18	randomised trials	very serious[n]	serious[o]	not serious	serious[d]	publication bias strongly suspected[e]	463/3784 (12.2%)	457/3561 (12.8%)	**RR 1.07** (0.86 to 1.34)	**9 more per 1,000** (from 18 fewer to 44 more)	⨁◯◯◯ Very low	CRITICAL
Serious adverse events (follow-up: range 7 days to 90 days)												
15	randomised trials	very serious[p]	not serious[q]	not serious	serious[d]	publication bias strongly suspected[e]	24/2542 (0.9%)	12/2390 (0.5%)	**RR 1.49** (0.75 to 2.94)	**2 more per 1,000** (from 1 fewer to 10 more)	⨁◯◯◯ Very low	CRITICAL

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

Explanations

a. Issues on attrition (Okumus 2021, Reis 2022, Rezai 2022B) and reporting (Beltran-Gonzales 2021) biases
b. Wide confidence interval
c. Issues on performance bias (Krolewcki 2020, Lim 2022)
d. Wide confidence interval
e. Asymmetric funnel plot
f. Issues on performance (Abd-Elsalam 2021, Krolewcki 2020, Lim 2022) and attrition bias (Ravikirti 2022, Reis 2022)
g. Issues on performance (Lim 2022) and attrition bias (Ravikirti 2021)
h. Issues on selection (Chachar 2020) and performance bias (Chachar 2020, Chahla 2022, Kishoria 2020, Okumus 2021). 4 out of 7 studies were unblinded, hence assessed to have very serious risk of bias for this subjective outcome.
i. Issues on selection and performance bias (Podder 2020)
j. Issues in performance bias (Abd Elsalam 2021, Lim 2022), reporting bias (Beltran Gonzales 2021) and attrition bias (Rezai 2022B)
k. High degree of heterogeneity (I2 = 68%)
l. Issues in selection bias (Chachar 2020, Ravikirti 2021), performance and detection bias (Chachar 2020, Kishoria 2020), Bukhari 2021, Podder 2020, Okumus 2021). and attrition bias (Okumus 2021)
m. High degree of heterogeneity (I2 = 83%)
n. Issues in selection (Chachar 2020), performance and detection bias (Abd Elsalam 2021, Bukhari 2021, Chachar 2020, Lim 2022 , Okumus 2021), performance bias (Krolewcki 2020) and attrition bias (Okumus 2021, Reis 2022, Rezai 2022B)
o. High degree of heterogeneity (I2 = 57%)
p. Issues in selection bias (Chachar 2020), performance bias (Krolewcki 2020), performance and detection bias (Bukhari 2021, Chachar 2020, Lim 2022, Okumus 2021), and attrition bias (Dela Rocha 2022, Okumus 2021)
q. High degree of heterogeneity (I2 = 76%)

Appendix 6: Forest Plots

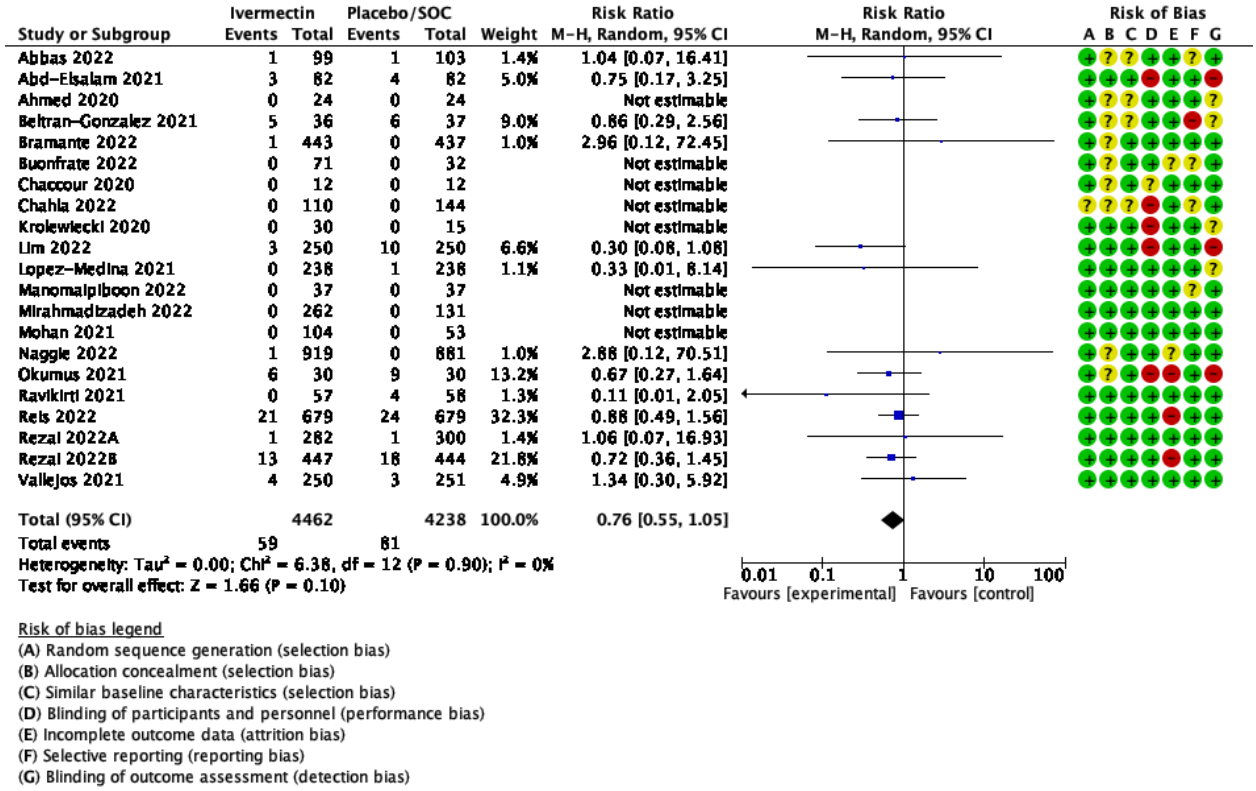

Figure 2. All-cause mortality

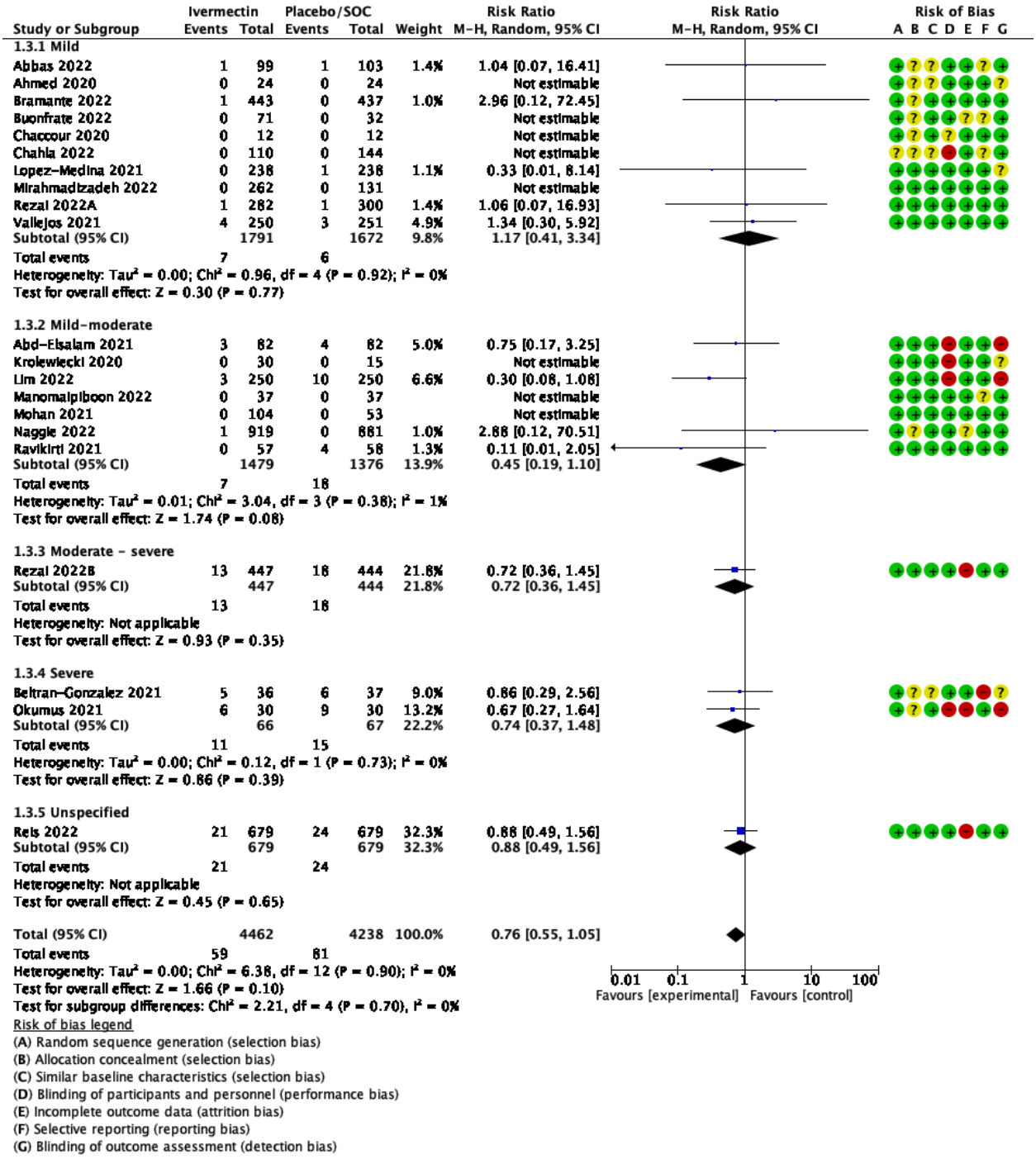

Figure 3. All-cause mortality_Subgroup analysis by disease severity

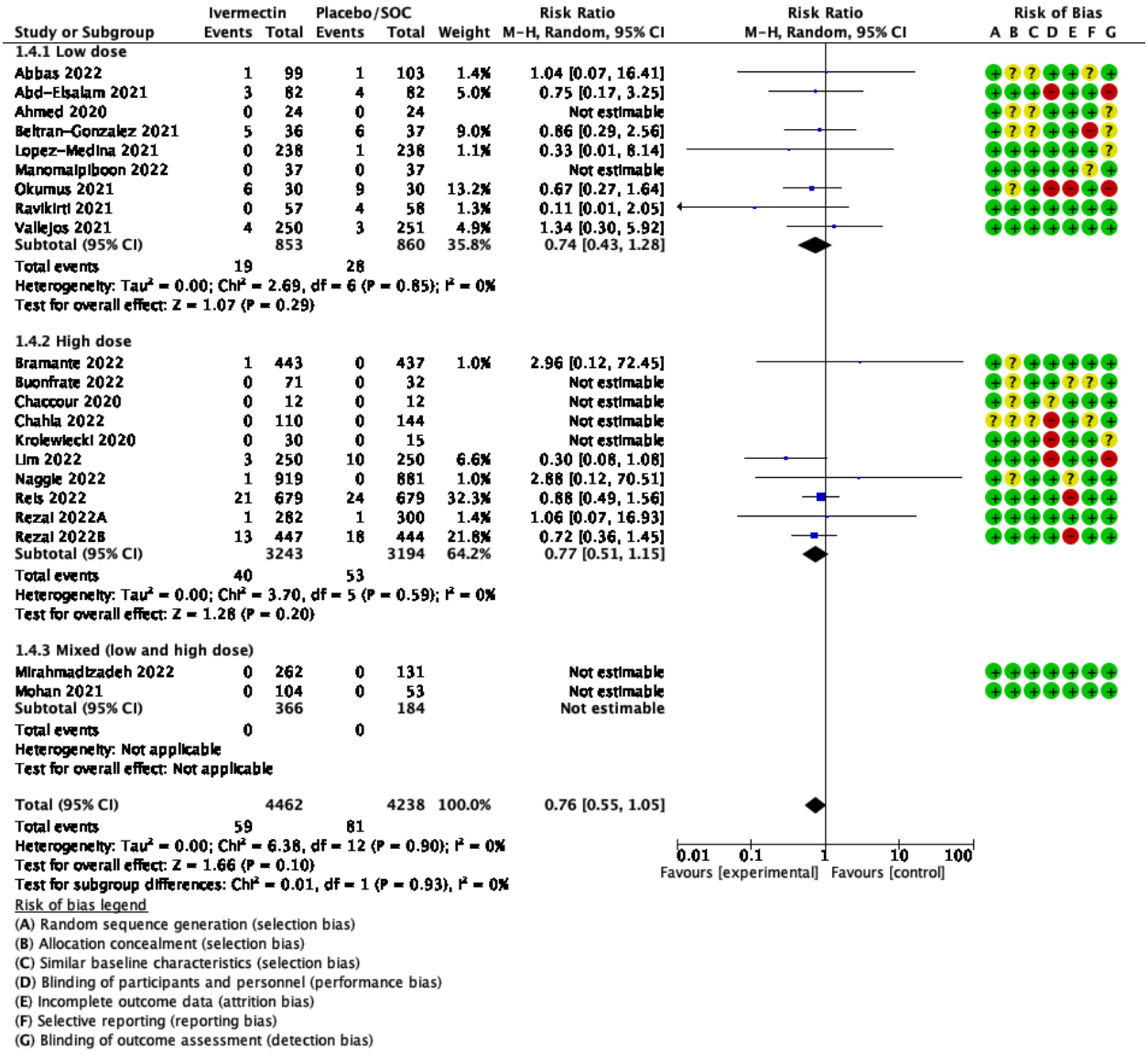

Figure 4. All-cause mortality_Subgroup analysis by dose of ivermectin

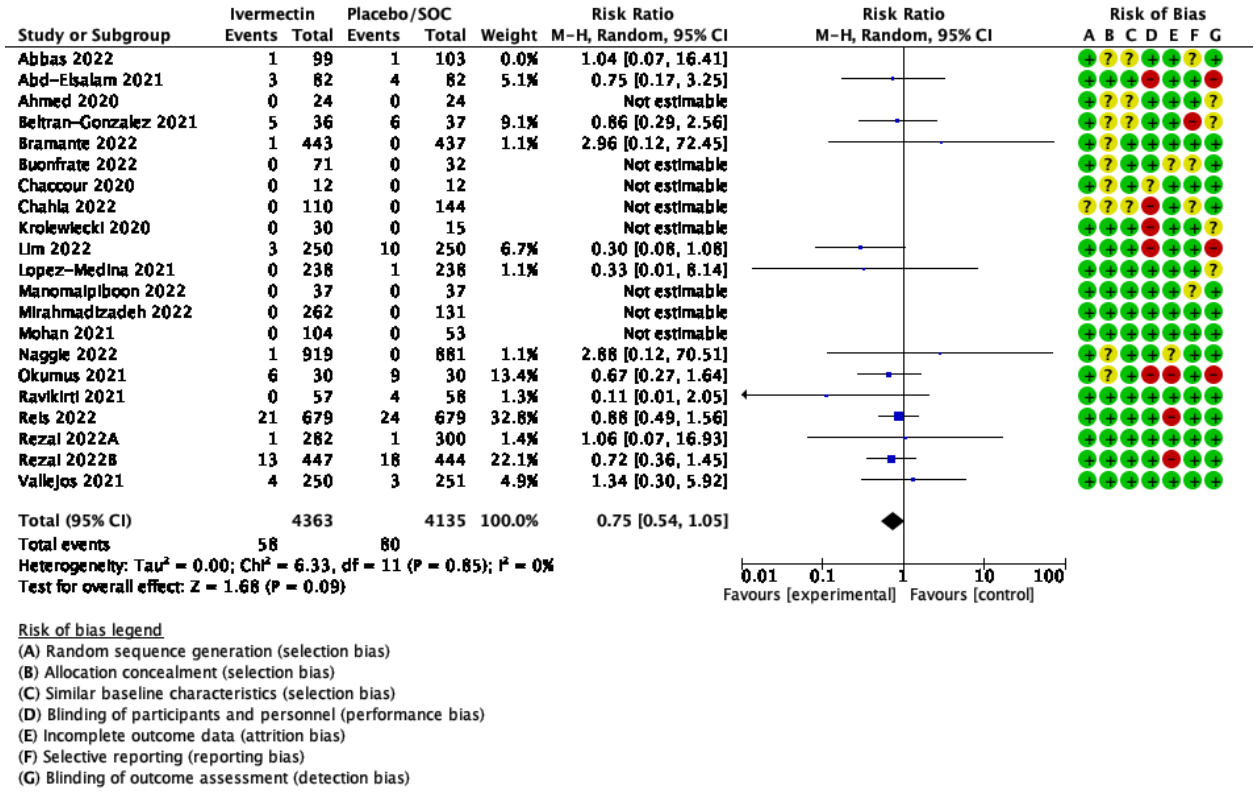

Figure 5. All-cause mortality, excluding short communication (Abbas 2022)

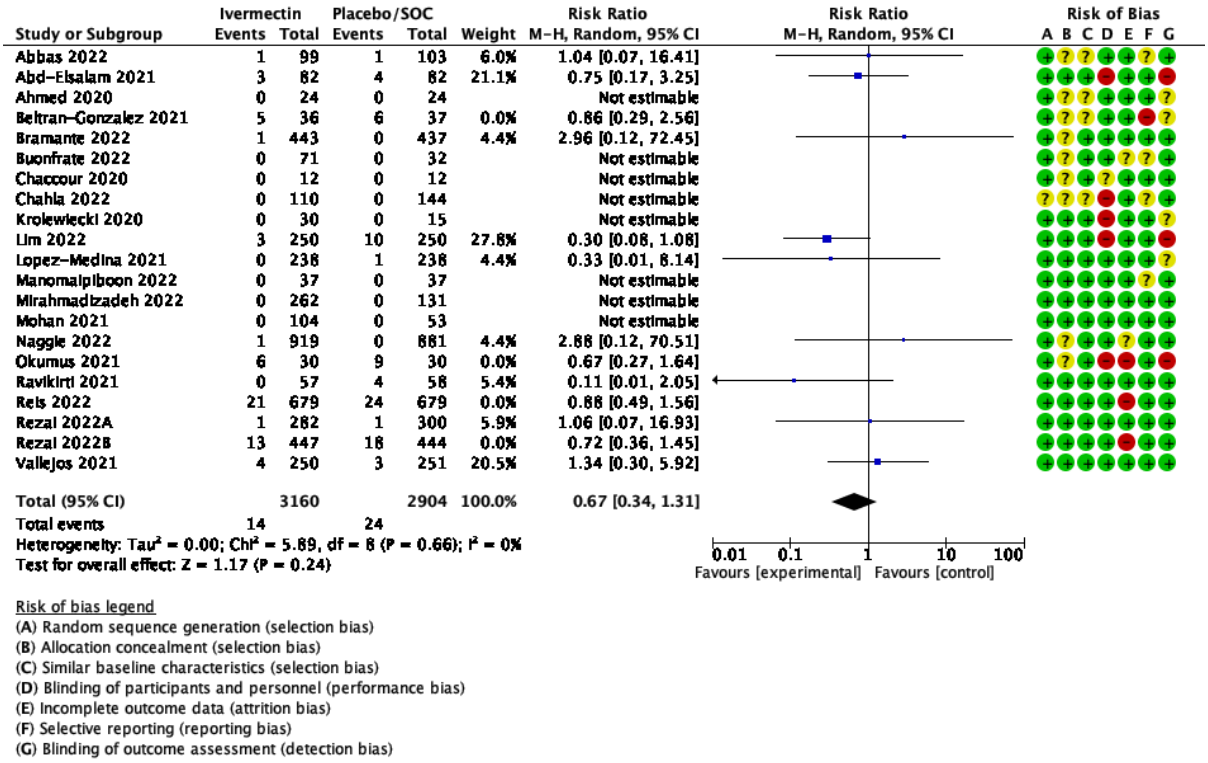

Figure 6. All-cause mortality, excluding studies with high risk of bias (Beltran-Gonzalez 2021, Chahla 2022, Okumus 2021, Reis 2022, Rezai 2022B)

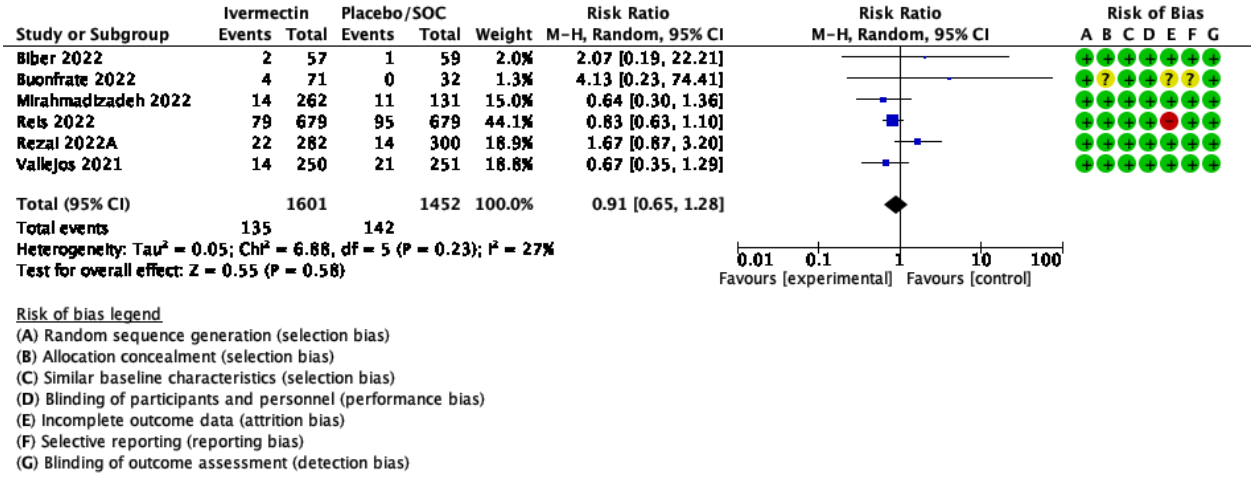

Figure 7. Need for Hospitalization

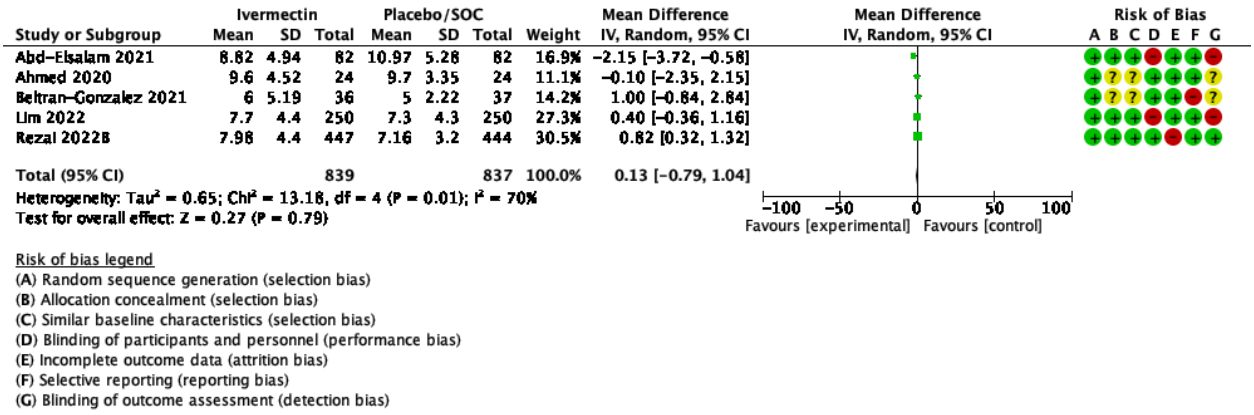

Figure 8. Duration of hospitalization (days)

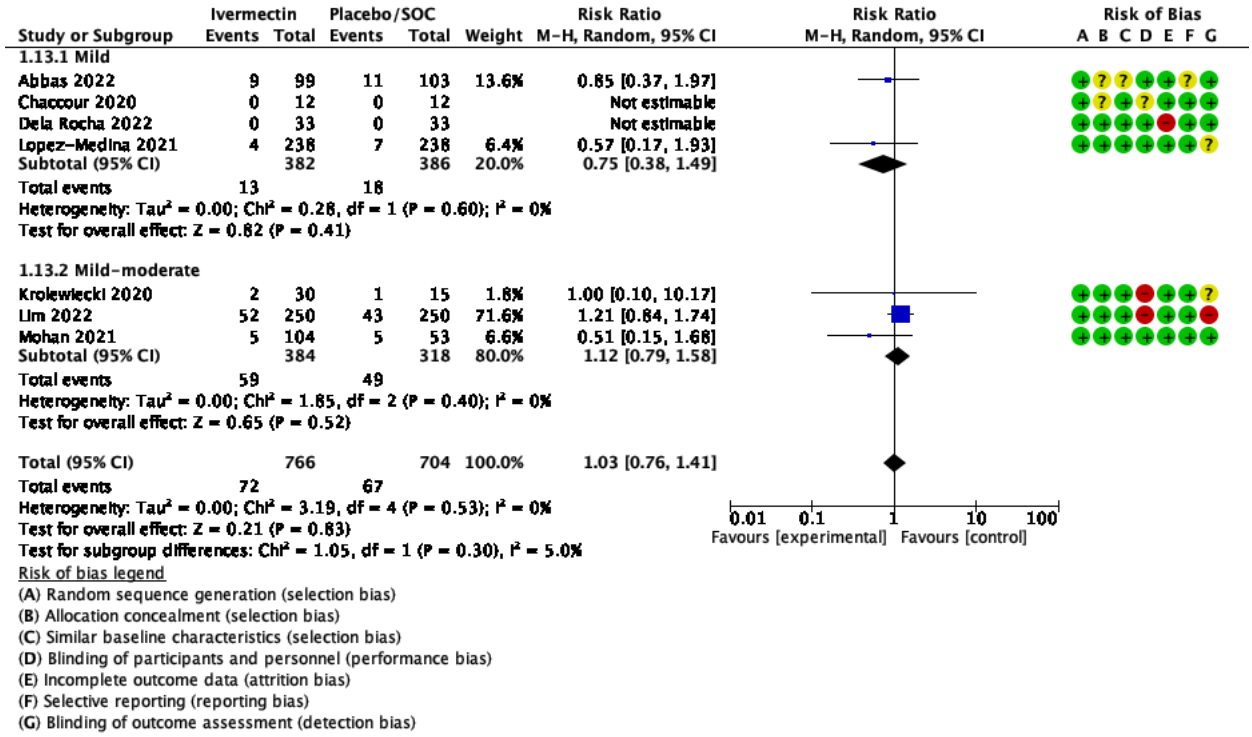

Figure 9. Clinical deterioration

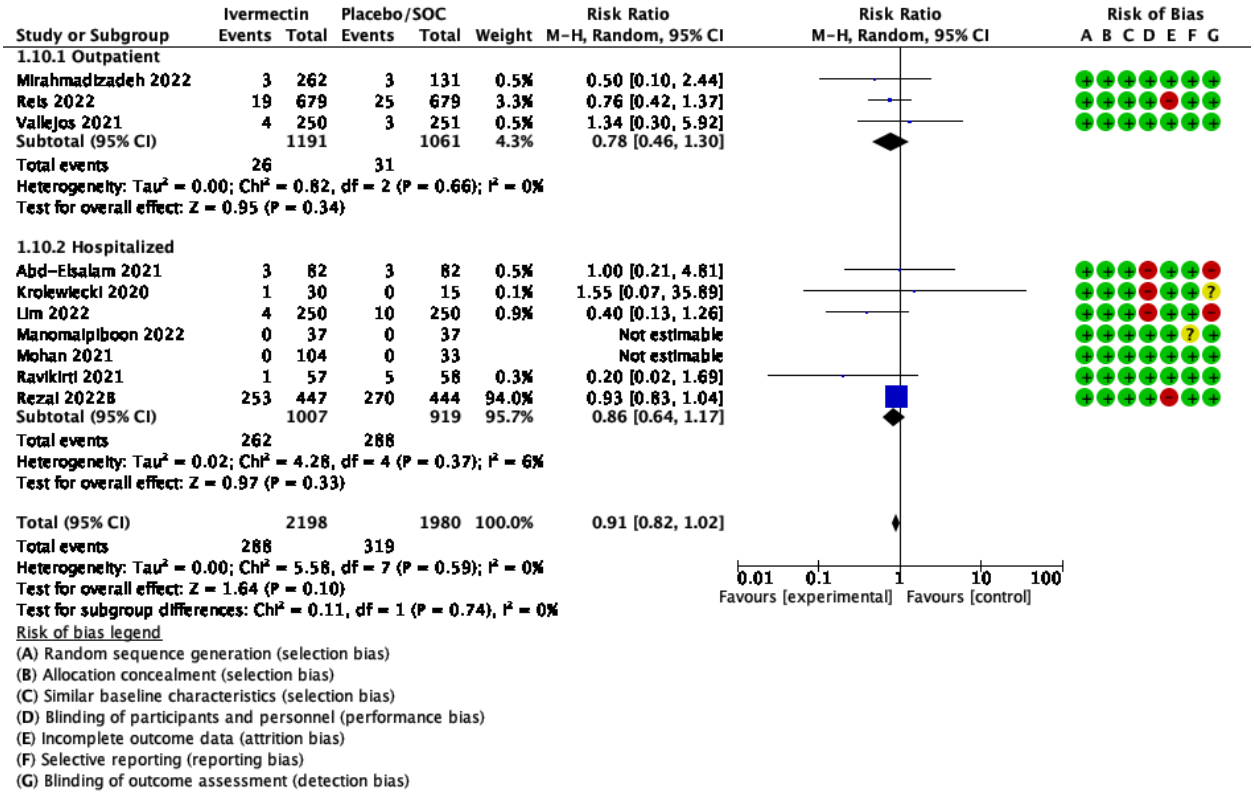

Figure 10. Need for mechanical ventilation

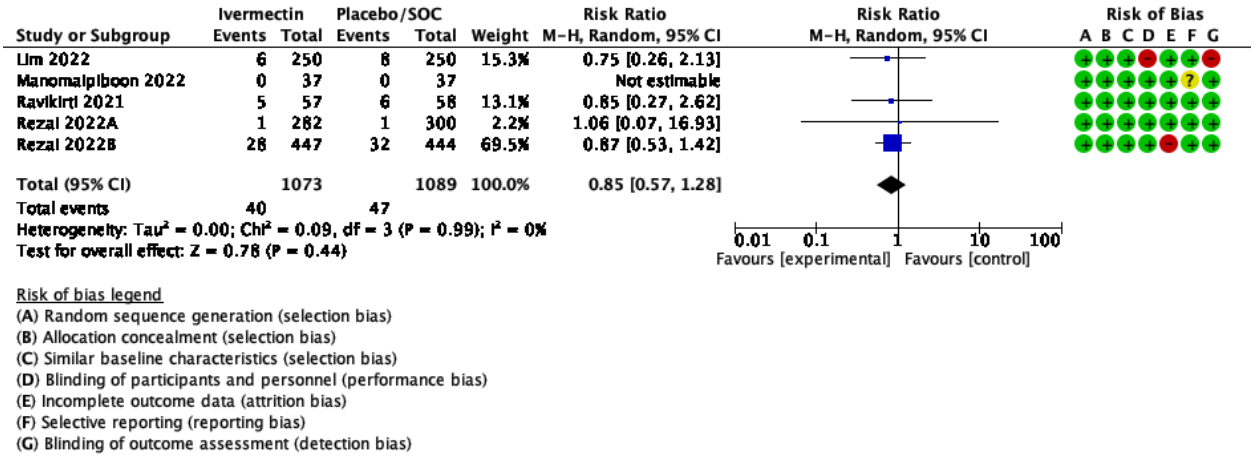

Figure 11. Need for ICU admission

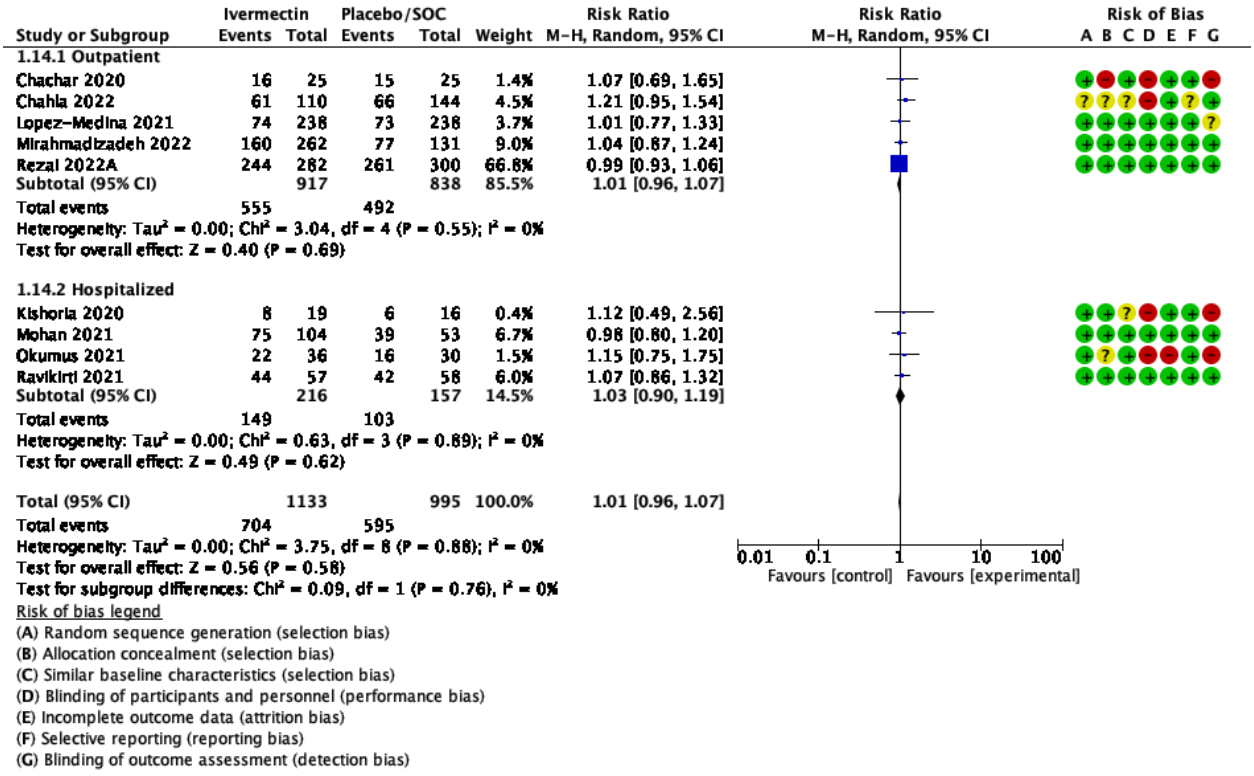

Figure 12. Clinical Improvement (Day 6-10)

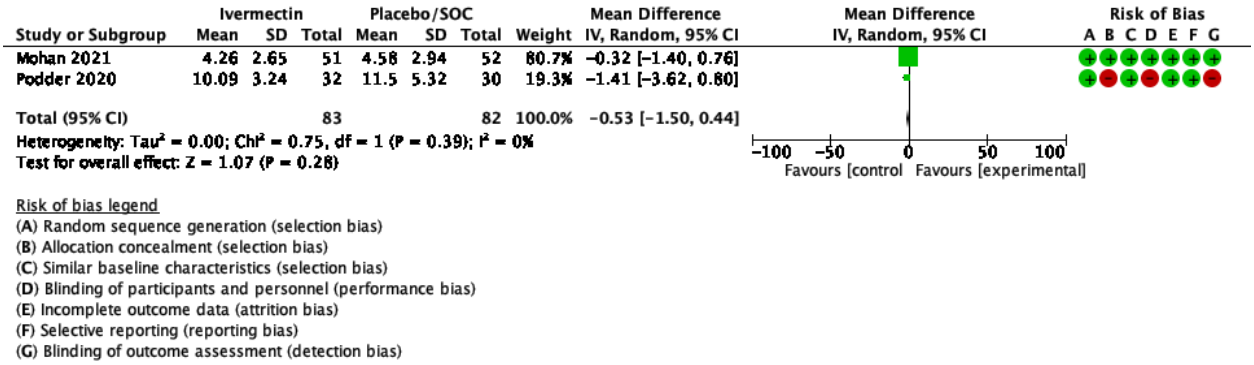

Figure 13. Time to symptom resolution (days)

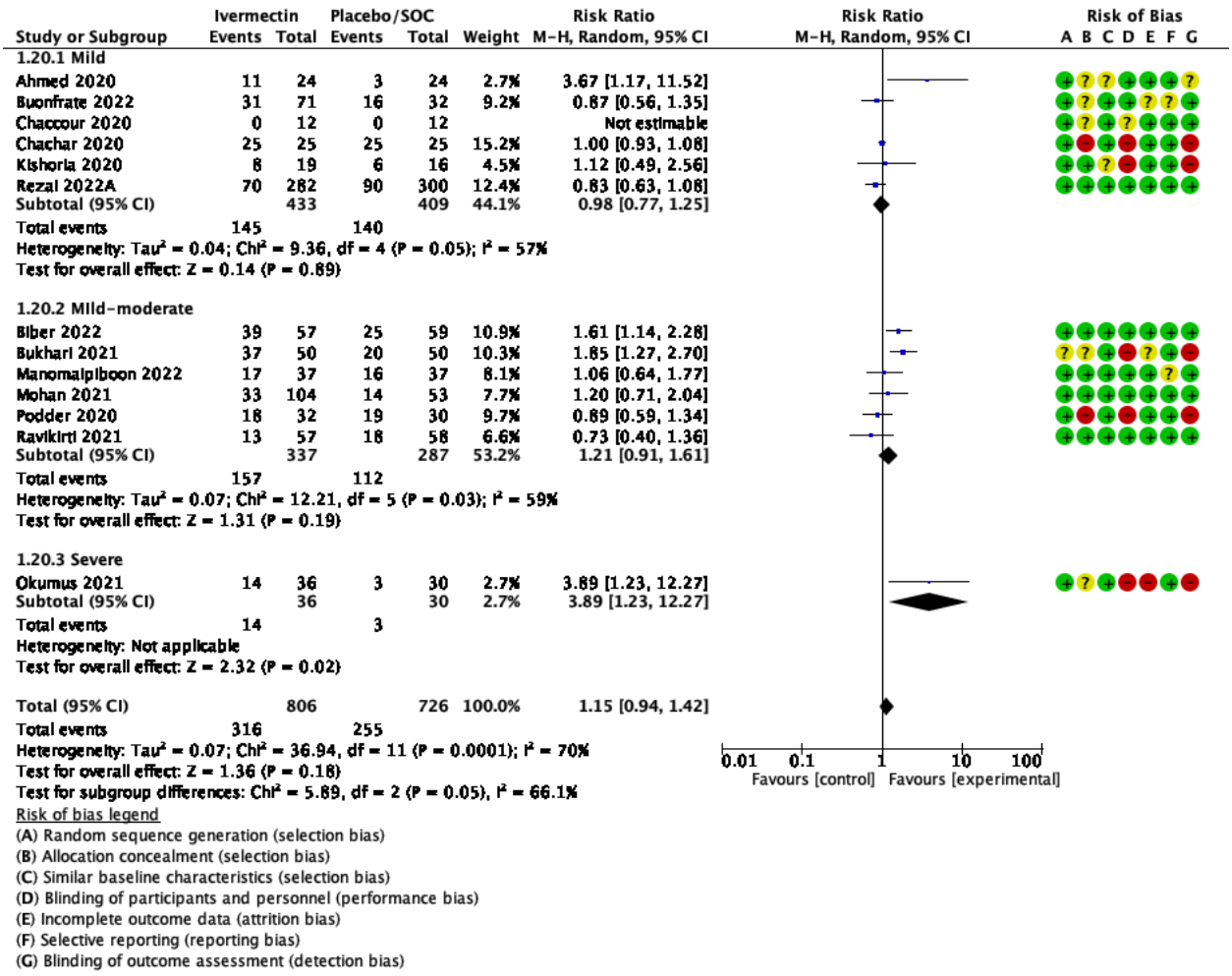

Figure 14. Virologic clearance, subgroup by disease severity

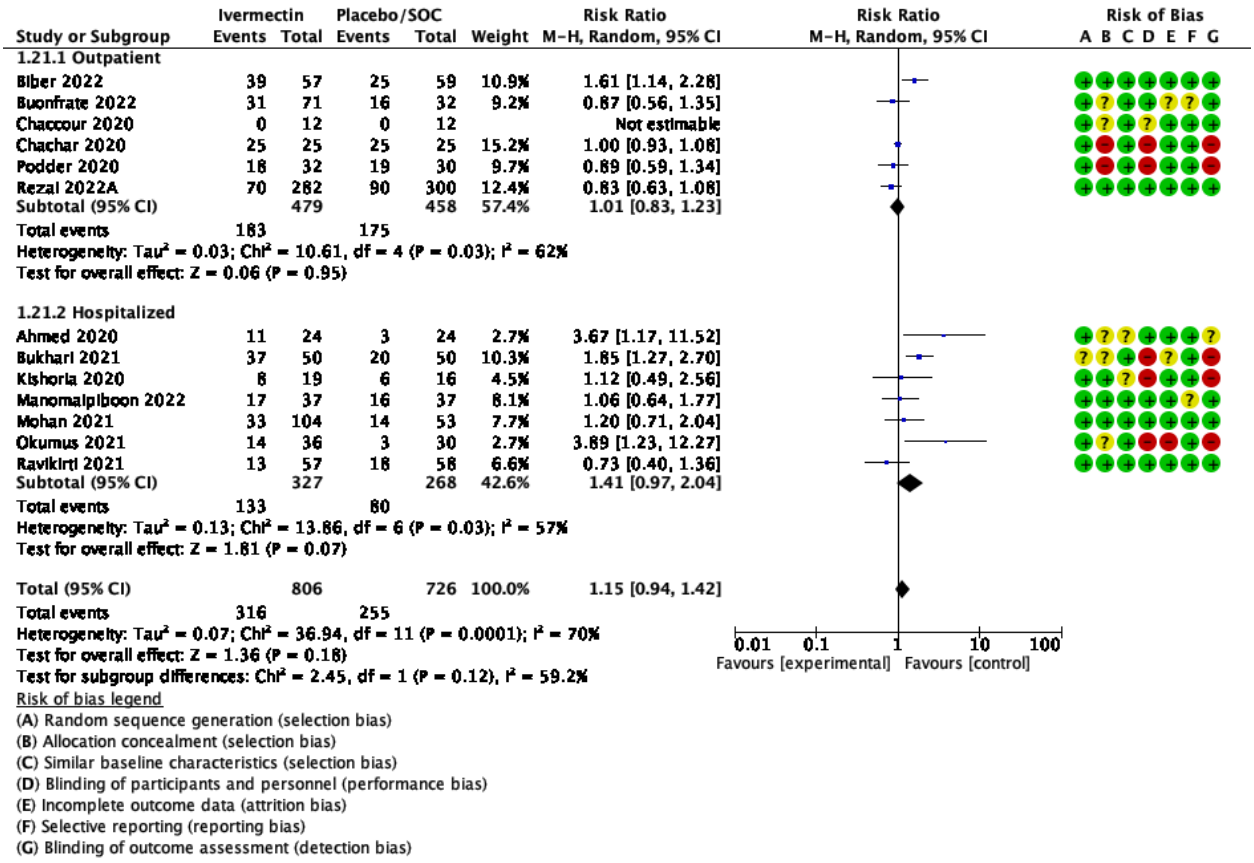

Figure 15. Virologic clearance, by hospitalization status

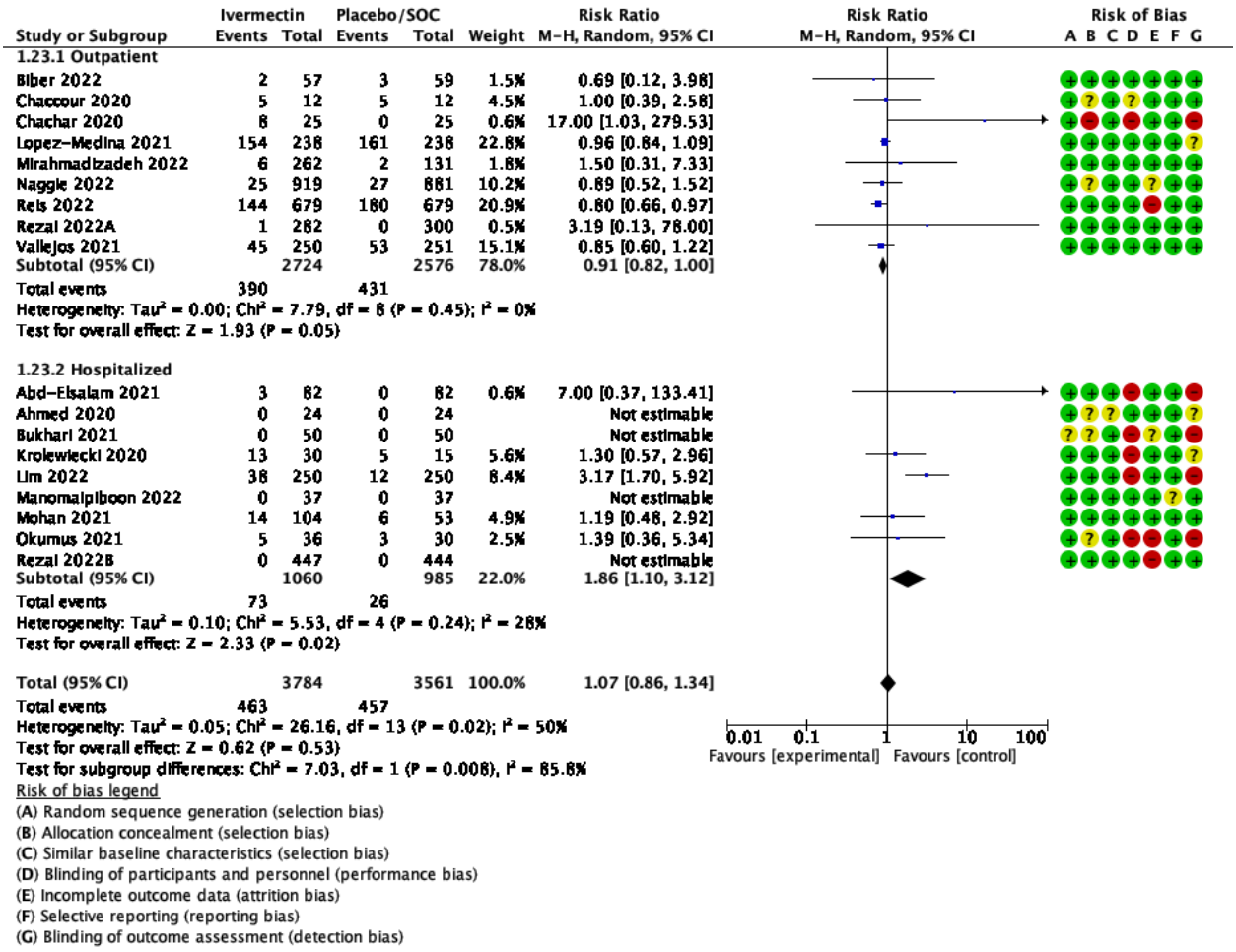

Figure 16. Adverse events

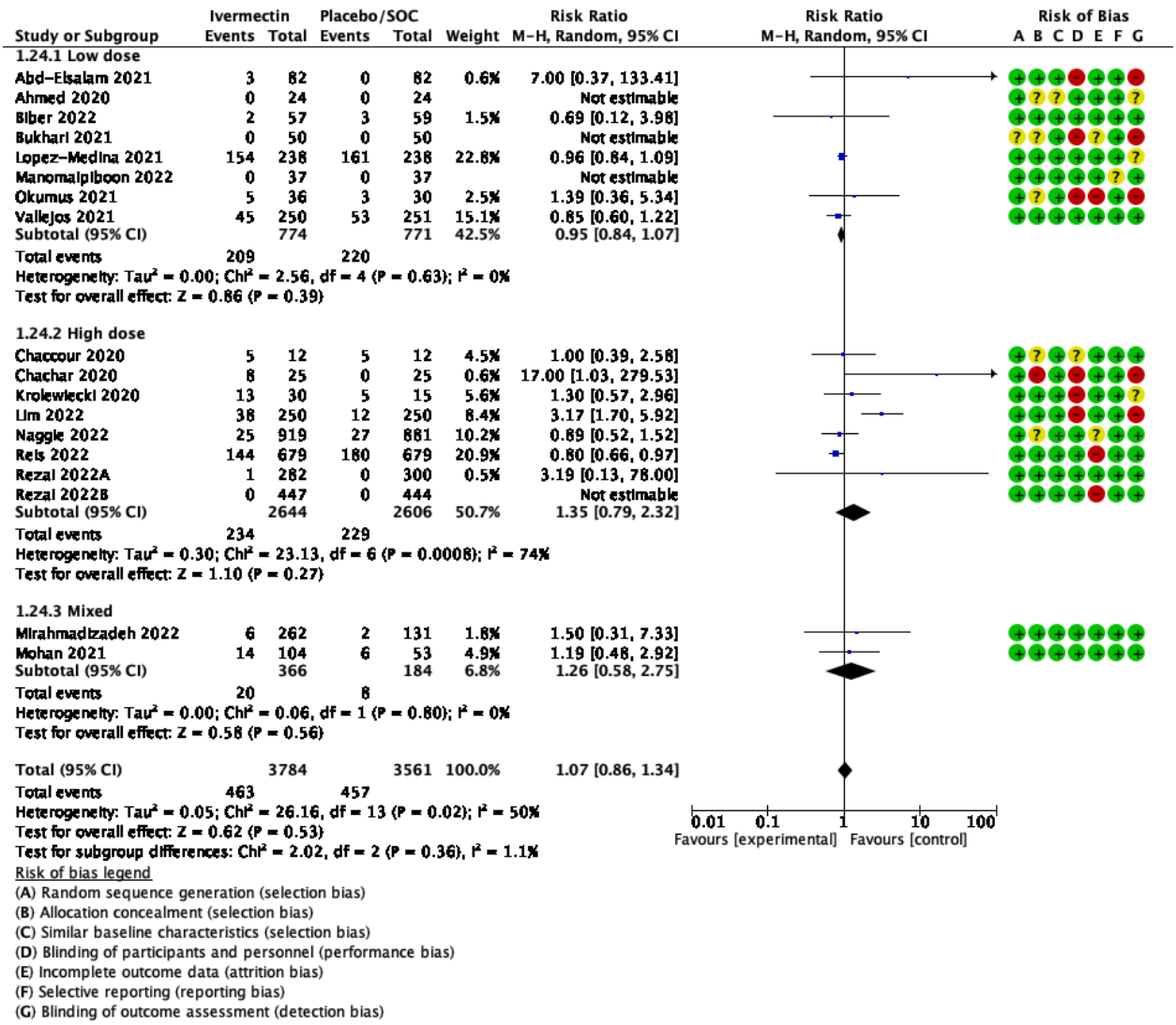

Figure 17. Adverse events_Subgroup analysis by dose of ivermectin

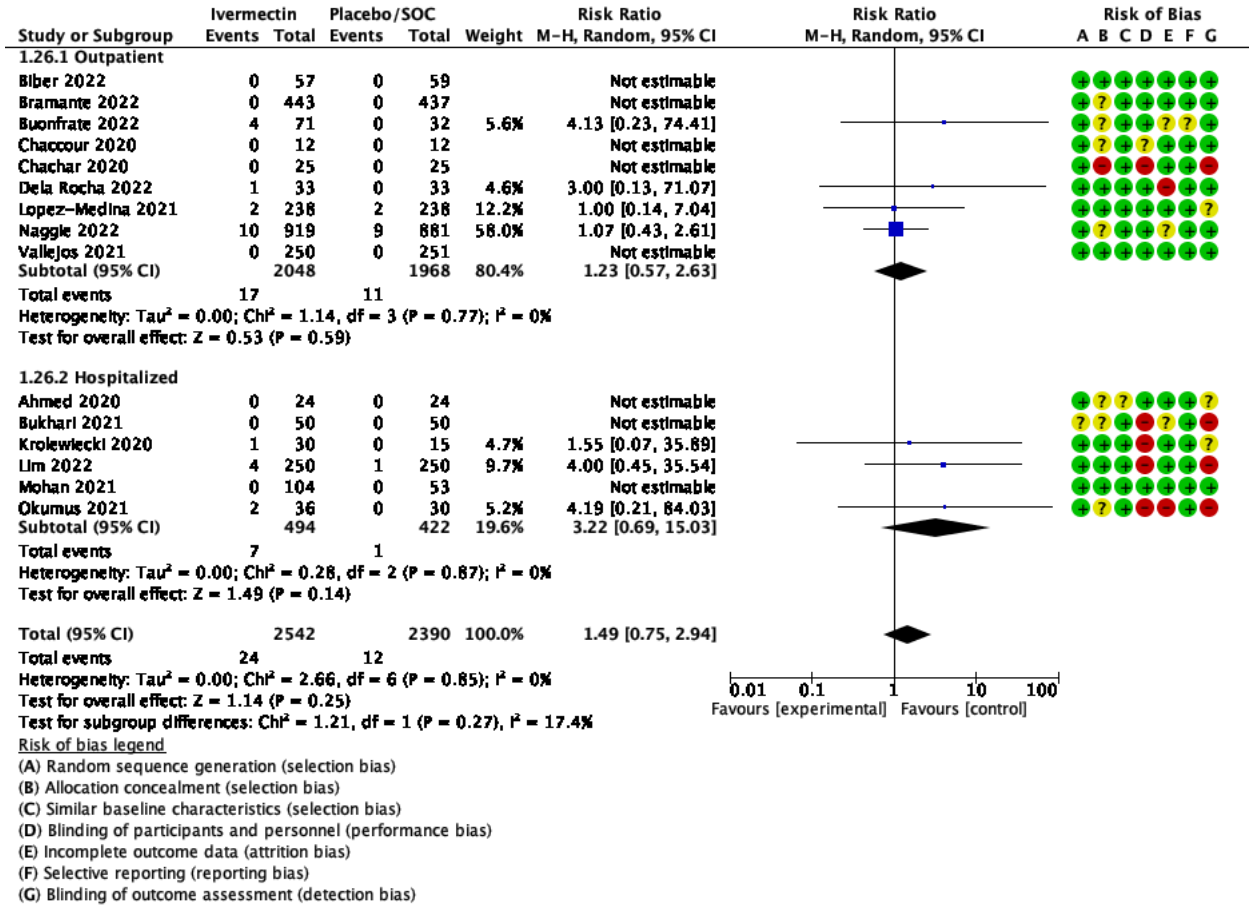

Figure 18. Serious adverse events

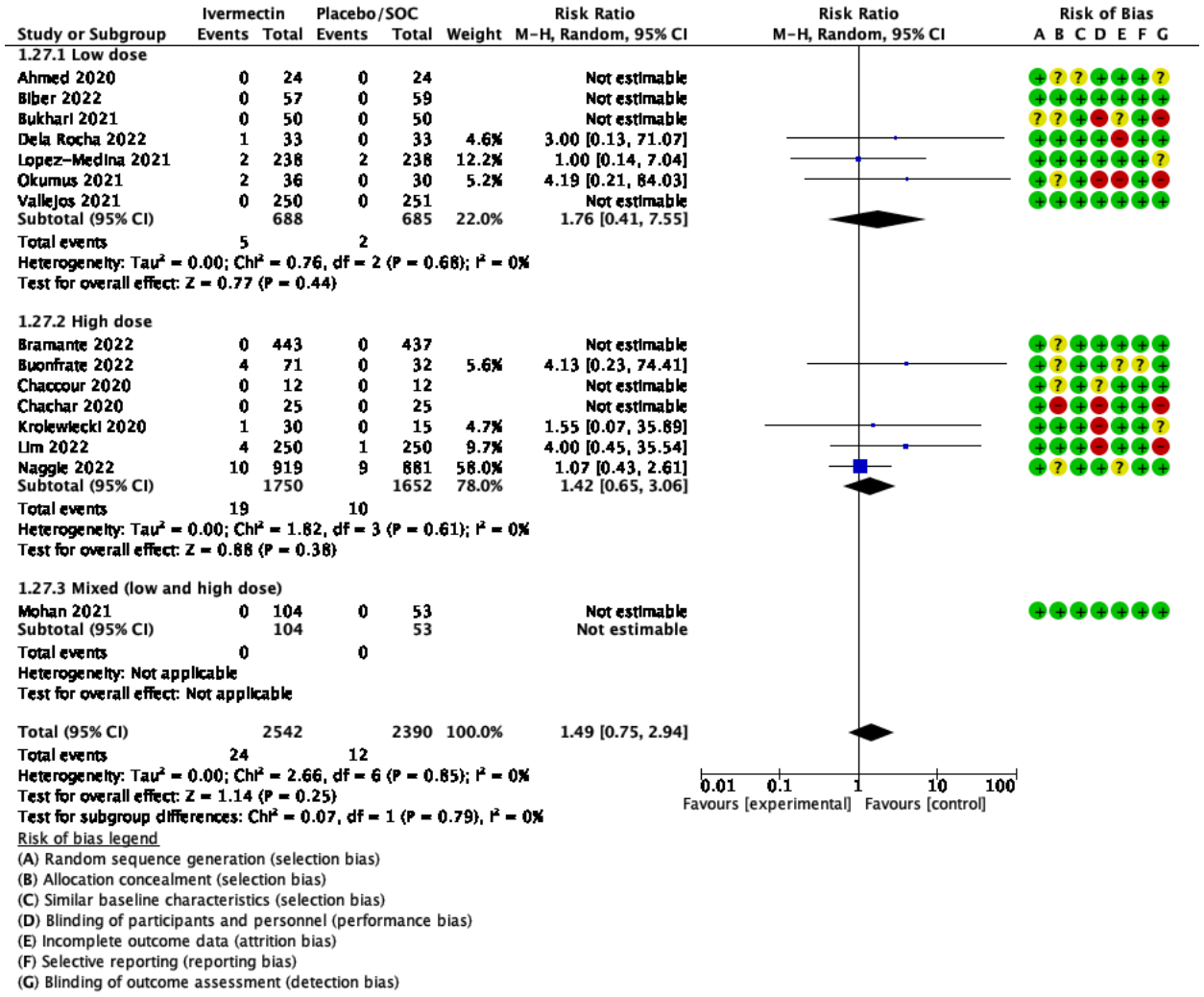

Figure 19. Serious adverse events_Subgroup analysis by dose of ivermectin

Appendix 7: Summary of Results of the Cochrane Review
(*Popp et al, 2022*)

Mild (out-patient)	RCTs	Ivermectin vs. placebo/SOC	
All-cause mortality (28 days)	6 RCTs (N=2860)	RR 0.77 [0.47, 1.25]	⊕⊕⊕◯ Moderate
Worsening of clinical status: admission to hospital or death (28 days)	2 RCTs (N=590)	RR 1.09 (0.20, 6.02)	⊕⊕◯◯ Low
Improvement of clinical status: all initial symptoms resolved (14 days)	2 RCTs (N=478)	RR 0.90 (0.60, 1.36)	⊕⊕◯◯ Low
Adverse events during the trial period	5 RCTs (N=1502)	RR 1.24 [0.87, 1.76)	⊕⊕◯◯ Low
Serious adverse events during the trial period	5 RCTs (N=1502)	RR 2.27 (0.62, 8.31)	⊕⊕◯◯ Low
Viral clearance at D7	2 RCTs (N=331)	RR 1.01 [0.69, 1.48)	⊕⊕◯◯ Low
Moderate to Severe (in patient)	**RCTs**	**Ivermectin vs. placebo/SOC**	
All-cause mortality (28 days)	3 RCTs (N=230)	RR 0.60 [0.14, 2.51]	⊕◯◯◯ Very low
Clinical worsening: Need for invasive ventilation (28 days)	2 RCTs (N=118)	RR 0.82 [0.33, 2.04]	⊕◯◯◯ Very low
Clinical improvement: participants discharged alive at D28	1 RCT (N=73)	RR 1.03 [0.78, 1.35]	⊕⊕◯◯ Low
Adverse events during the trial period	3 RCTs (N=228)	RR 1.04 [0.61, 1.79]	⊕⊕◯◯ Low
Serious adverse events during the trial period	2 RCTs (N=197)	RR 1.55 (0.07 to 35.89)	⊕◯◯◯ Very low
Viral clearance at D7	3 RCTs (N=231)	RR 1.12 [0.80,1.58]	⊕⊕◯◯ Low