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REVIEW ARTICLE

RETRACTED: Meta-analysis of Randomized Trials of Ivermectin to Treat SARS-CoV-2 Infection

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Ivermectin is an antiparasitic drug being investigated for repurposing against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Ivermectin showed in vitro activity against SARS-COV-2, but only at high concentrations. This meta-analysis investigated ivermectin in 23 randomized clinical trials (3349 patients) identified through systematic searches of PUBMED, EMBASE, MedRxiv, and trial registries. The primary meta-analysis was carried out by excluding studies at a high risk of bias. Ivermectin did not show a statistically significant effect on survival (risk ratio [RR], 0.90; 95% CI, 0.57 to 1.42; P = .66) or hospitalizations (RR, 0.63; 95% CI, 0.36 to 1.11; P = .11). Ivermectin displayed a borderline significant effect on duration of hospitalization in comparison with standard of care (mean difference, −1.14 days; 95% CI, −2.27 to −0.00; P = .05). There was no significant effect of ivermectin on time to clinical recovery (mean difference, −0.57 days; 95% CI, −1.31 to 0.17; P = .13) or binary clinical recovery (RR, 1.19; 95% CI, 0.94 to 1.50; P = .15). Currently, the World Health Organization recommends the use of ivermectin only inside clinical trials. A network of large clinical trials is in progress to validate the results seen to date.

Keywords. COVID-19; ivermectin; repurposed; SARS-CoV-2.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to grow, with >550 000 new infections and >9000 deaths recorded worldwide daily in July 2021 [1]. Protective vaccines have been developed, but current supplies are too low to cover global demand in the coming months [2]. Researchers worldwide are urgently looking for interventions to prevent new infections, prevent disease progression, and lessen disease severity for those already infected.

While research on new therapeutic agents for coronavirus disease 2019 (COVID-19) is key, there is also great interest in evaluating the potential of already existing medicines against COVID-19, and many clinical trials are in progress to "repurpose" drugs normally indicated for other diseases. The known safety profiles, shortened development timelines, and well-established markets (with low price points and higher capacity to deliver at scale) for most of the already existing compounds proposed for COVID-19 are particularly advantageous compared with new drug discovery in a pandemic situation. Three repurposed anti-inflammatory drugs have shown significant survival benefits to date: the corticosteroid dexamethasone in the UK RECOVERY trial [3] and the interleukin-6 (IL-6) receptor antagonist drugs tocilizumab and sarilumab in the REMAP-CAP trial and the RECOVERY trial [4, 5]. Other repurposed treatments such as hydroxychloroquine, lopinavir/ritonavir, remdesivir, and interferon-beta have shown no significant survival benefit in large randomized trials [3, 6] despite initial reports of efficacy, underscoring the need for caution when interpreting early clinical trial data.

Dexamethasone is recommended for use by the World Health Organization (WHO) and has proven survival benefits for oxygen-dependent patients with COVID-19, while tocilizumab and sarilumab improve survival for patients in intensive care [3, 4]. Preliminary data suggest that nitazoxanide and budesonide may have a role in mild infection [7, 8]. However, there are no approved treatments for patients with mild SARS-CoV-2 infection, either to prevent disease progression or reduce viral transmission. Treatments increasing the viral clearance rate may reduce the risk of onward transmission, but this requires empirical demonstration.

Ivermectin is a well-established antiparasitic drug used worldwide for a broad number of parasites and also for topical use against rosacea. The antiviral activity of ivermectin has been demonstrated recently for SARS-CoV-2 in Vero/hSLAM cells [9]. However, the concentrations required to inhibit viral

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replication in vitro (EC_{50}, 2.2–2.8 μM; EC_{90}, 4.4 μM) are not achieved systemically after oral administration of the drug to humans at clinically approved doses [9, 10].

While ivermectin is estimated to accumulate in lung tissues (2.67 times more than plasma) [11], this is also unlikely to be sufficient to maintain target concentrations for pulmonary antiviral activity [10, 12]. Notwithstanding, ivermectin is usually present as a mixture of 2 agents and, although mainly excreted unchanged in humans, has 2 major metabolites [13]. Current data are insufficient to determine whether the minor form or a circulating metabolite has higher direct potency against SARS-CoV-2, but it seems likely that ivermectin would need to be profoundly more potent than the reported values.

Ivermectin has also demonstrated immunomodulatory and anti-inflammatory mechanisms of action in preclinical models of several other diseases. In-vitro studies have demonstrated that ivermectin suppresses production of the inflammatory mediators nitric oxide and prostaglandin E2 [14]. Furthermore, avermectin (from which ivermectin is derived) significantly impairs pro-inflammatory cytokine secretion (IL-1β and tumor necrosis factor [TNF]–α) and increases secretion of the immunoregulatory cytokine IL-10 [15]. Ivermectin also reduced TNF-α, IL-1, and IL-6 and improved survival in mice given a lethal dose of lipopolysaccharide [16]. Preclinical evidence to support these immunomodulatory and anti-inflammatory mechanisms of action have also been generated in other murine models [17, 18]. Finally, in Syrian golden hamsters infected with SARS-CoV-2, subcutaneous ivermectin demonstrated a reduction in the IL-6/IL-10 ratio in lung tissues and prevented pathological deterioration [19]. Ultimately, various potential mechanisms of action for ivermectin against COVID-19 exist and are undergoing further investigation, as recently summarized in a review article [20].

At standard doses of 0.2–0.4 mg/kg for 1–2 days, ivermectin has a good safety profile and has been distributed to billions of patients worldwide in mass drug administration programs. A recent meta-analysis found no significant difference in adverse events in those given higher doses of ivermectin, of up to 2 mg/kg, and those receiving longer courses, of up to 4 days, compared with those receiving standard doses [21]. Ivermectin is not licensed for pregnant or breast-feeding women or children <15 kg. The WHO Guidelines Group found that in 16 randomized controlled trials (RCTs) with 2407 participants ivermectin improved mortality outcomes compared with control but rated the quality of available evidence as low or very low [22]. Currently, the WHO does not recommend the use of ivermectin outside clinical trials.

The objective of this systematic review and meta-analysis was to combine available results from new published or unpublished randomized trials of ivermectin in SARS-CoV-2 infection to inform current guidelines.

METHODS

This systematic review and meta-analysis was conducted according to PRISMA guidelines. A systematic search of PUBMED and EMBASE was conducted to identify RCTs evaluating treatment with ivermectin for SARS-CoV-2-infected patients. Clinical trials with no control arm or those evaluating prevention of infection were excluded, alongside nonrandomized trials and case–control studies. Key data extracted included baseline characteristics (age, sex, weight, oxygen saturation, stage of infection), changes in inflammatory markers, viral suppression after treatment, clinical recovery, hospitalization, and survival. Data were extracted and cross-checked by 2 independent reviewers (H.W. and L.E.).

Search Strategy and Selection Criteria

RCTs were eligible for inclusion if they compared an ivermectin-based regimen with a comparator or standard of care (SOC) for the treatment of SARS-CoV-2 infection. The PRISMA checklist, PRISMA flow diagram, the search terms, and inclusion/exclusion criteria used are detailed in Supplementary Figure 1 and Supplementary Tables 1, 2, and 3.

Registry databases were searched through July 20, 2021. ClinicalTrials.gov [23] was searched using the keywords

Table 1. Trial Summaries. Ivermectin Trials With Dosing on Day 1 Only

Study	Country	Sample Size	Daily Dose	Duration	Patients	Ivermectin Arm	Comparator Arm
Mahmud et al. [28][a]	Bangladesh	363	12 mg	1 day (DB)	Mild/moderate	Ivermectin + doxycycline + SOC	Placebo + SOC
Mohan et al. [29][a]	India	125	0.2–0.4 mg/kg (elixir)	1 d (DB)	Mild/moderate	Ivermectin + SOC	Placebo
SAINT [30][a]	Spain	24	0.4 mg/kg	1 d (DB)	Mild/moderate	Ivermectin	Placebo
Gonzalez [31][a]	Mexico	106	12 mg	1 d (DB)	Severe	Ivermectin	Placebo
Rezai et al. [32][a]	Iran	69	0.2 mg/kg	1 d (DB)	Moderate/severe	Ivermectin + SOC	SOC
Podder et al. [33][b]	Bangladesh	62	0.2 mg/kg	1 d (OL)	Mild	Ivermectin + SOC	SOC
Asghar et al. [34][b]	Pakistan	86	12 mg	1 d (OL)	Mild/moderate	Ivermectin + SOC	SOC
Chowdhury [35][b]	Bangladesh	116	0.2 mg/kg	1 d (OL)	PCR positive	Ivermectin + doxycycline	HCQ + azithromycin

Abbreviations: DB, double-blind; HCQ, hydroxychloroquine; OL, open-label; PCR, polymerase chain reaction; SB, single-blind; SOC, standard of care.
[a]Studies were evaluated as having fair or good overall quality of evidence using the Cochrane Risk of Bias Tool. See Supplementary Table 3 for further details.
[b]Studies were evaluated as having limited overall quality of evidence using the Cochrane Risk of Bias Tool. See Supplementary Table 3 for further details.

"COVID," "SARS-CoV-2," and "ivermectin" to identify studies. The WHO International Clinical Trials Registry Platform (ICTRP) was accessed via the COVID-NMA Initiative's mapping tool [24] and Stanford University's Coronavirus Antiviral Research Database (CoV-RDB) [25] to identify additional trials listed on other national and international registries. Literature searches via PubMed, Embase, and the preprint servers medRxiv and ResearchSquare were conducted to identify published studies. Duplicate registrations, nonrandomized studies, and prevention studies were excluded following discussion between the authors.

Additionally, the research teams conducting unpublished clinical trials were contacted and requested to join regular international team meetings from December 2020 to July 2021. All results available from eligible unpublished studies were also included in this systematic review.

All of the clinical trials included in this meta-analysis were approved by local ethics committees, and all patients gave informed consent.

The primary outcome was all-cause mortality from randomization to the end of follow-up. Secondary outcomes included time to viral clearance, polymerase chain reaction (PCR) negativity at day 7, clinical recovery, time to clinical recovery, mechanic[illegible] ventilation, duration of hospitalization, and number of hospitalizations. Changes in inflammatory markers, viral sup[illegible]ion, clinical recovery, and hospitalization were also sum[illegible]arize[illegible] for individual trials where end points could not be com[illegible]ed.

We did include studies that were preprints (not yet pu[illegible]lished in peer-reviewed journals) after completin[illegible] ri[illegible] of bias assessment and discussions with the investiga[illegible]rs. Howe[illegible] 2 studies that were initially included were late[illegible] removed due to concerns about the quality of data.

Data Analysis

Statistical analyses for al[illegible]-cause [illegible]ort[illegible]y, time to viral clearance, and clinical recovery [illegible]re conducted using published data summaries. For the morta[illegible]y outcome, clinical trials with at least 1 death reported were included in this analysis. Furthermore, any hospitalization within 12 hours of randomization was excluded. Treatment effects were expressed as risk ratios (RRs) for binary outcomes and mean differences (MDs) for continuous outcomes. For each outcome, we pooled the individual trial statistics using the random-effects inverse variance model; a continuity correction of 0.5 was applied to treatment arms with no deaths. Heterogeneity was evaluated by I^2. The significance threshold was set at 5% (2-sided), and all analyses were conducted using Revman 5.3.

All studies included in this analysis were assessed for risk of bias using the Cochrane Collaboration Risk of Bias standardized assessment tool [26]. The outcome of this assessment is given in Supplementary Table 3. The results from this assessment were compared with the risk of bias evaluation from

Table 2. Trial Summaries. Ivermectin Trials With Multiday Dosing

Study	Country	Sample Size	Daily Dose	Duration	[illegible]tien	Ivermectin Arm	Comparator Arm
Zoni et al. (IVERCOR) [36][a]	Argentina	501	12–24 mg	2 d (DB)	Mild/[illegible]derate	Iver[illegible]tin	Placebo
Lopez-Medina et al. [37][a]	Colombia	398	0.3 mg/kg	5 d (DB)	Mild	Iv[illegible]rect.	Placebo
Krolewiecki et al. [38][a]	Argentina	45	0.6 mg/kg	5 d (OL)	Mild to moderate	[illegible]ermectin [illegible]OC	SOC
Babalola et al. [39][a]	Nigeria	60	0.1–0.2 mg/kg	2/wk (DB)	Mild	Ivermec[illegible] + SOC	Placebo + LPV/r (SOC)
Fonseca et al. [40][a]	Brazil	168	14 mg	3 d (DB)	Severe	Iverm[illegible]in	Hydroxychloroquine or chloroquine
Abd-Elsalam et al. [41][a]	Egypt	164	12 mg	3 d (OL)	PCR Positive	Ive[illegible]ctin +SC	SOC
Kirti et al. [42][a]	India	112	12 mg	2 d (DB)	Mild/moderate	Iverme[illegible] + SOC	SOC + placebo
Petkov et al. [43][a]	Bulgaria	100	0.4 mg/kg	3 d (DB)	Mild/moderate	Ivermectin	Placebo
Schwartz et al. [44][a]	Israel	94	12-15mg	3 d (DB)	Mild/moderate	Ivermectin	Placebo
Ahmed et al. [45][a]	Bangladesh	72	0.2 mg/kg	5 d (DB)	Mild	Ivermectin + SOC	SOC + placebo
Okumus et al. [46][b]	Turkey	60	0.2 mg/kg	5 d (DB)	Severe	Ivermectin + SOC	FAVI/HQ/AZI (SOC)
Hashim et al. [47][b]	Iraq	140	0.2 mg/kg	2–3 d (SB)	Symptomatic	Ivermectin + doxycycline + SOC	SOC
Chachar et al. [48][b]	Pakistan	50	0.2 mg/kg	2 d (OL)	Mild	Ivermectin + SOC	SOC
Niaee et al. [27][b]	Iran	180	0.2–0.4 mg/kg	1–3 d (DB)	Mild/moderate	Ivermectin + SOC	SOC + placebo
Chahla et al. [49][b]	Argentina	254	24 mg	1/wk for 4 wk (OL)	Mild	Ivermectin + SOC	SOC

Abbreviations: DB, double-blind; FAVI/HQ/AZI, favipiravir/hydroxychloroquine/azithromycin; LPV/r, lopinavir/ritonavir; OL, open-label; PCR, polymerase chain reaction; SB, single-blind; SOC, standard of care.

[a]Studies were evaluated as having fair or good overall quality of evidence using the Cochrane Risk of Bias Tool. See Supplementary Table 3 for further details.

[b]Studies were evaluated as having limited overall quality of evidence using the Cochrane Risk of Bias Tool. See Supplementary Table 3 for further details.

other meta-analyses. Each study was assessed for risk of bias for the primary end point, viral load, and survival outcomes. The primary end point in the trials tended to be clinical recovery, which is more subjective and likely to be influenced by knowledge of treatment arms. An assessment was also carried out on more objective end points including survival and viral load, which are less likely to be influenced by this bias. The baseline characteristics of participants were evaluated with chi-square tests to check for imbalances between the treatment arms due to ineffective randomization. Where information was not available in published papers, clinical trial investigators were proactively contacted to inform the risk of bias analysis. The primary meta-analysis was performed by excluding studies at a high risk of bias, consistent with methods used in other similar meta-analyses. Eight high-risk studies were excluded, for example, the Niaee et al. [27] study, which had significant imbalances in baseline characteristics between treatment arms. A supplementary analysis including studies at high risk of bias is provided in the Supplementary Data (Supplementary Figure 2A–H).

RESULTS

Twenty-three RCTs involving a total of 3349 participants were included in this meta-analysis. The sample sizes of each trial ranged from 24 to 501 participants. Of the 23 included studies, 14 were published papers, 8 were available as preprints, and 1 reported results via a clinical trial report.

Overall, 9 trials investigated ivermectin as a single dose (Table 1) [28–35], 15 trials investigated multiday dosing up to 7 days (Table 2) [27, 36–49], of which 4 trials were dose-ranging [27, 36, 39, 44]. In the included trials, ivermectin was largely investigated in mild/moderate participants. Overall, 16 trials were either single or double-blinded and 7 were open-label.

Evaluation of Studies

An evaluation of the quality of the studies included in this meta-analysis was conducted according to the Cochrane Collaboration tool to assess the risk of bias across the following outcomes: primary end points, viral load, and survival. For the primary outcome assessment, 8/23 (34.8%) studies were assessed as high risk of bias (Supplementary Table 3A). However, in assessments of more objective outcomes, including viral load and mortality, the number of high-risk studies was lower. In the PCR assessment, 4/14 (28.6%) of the studies were assessed as high risk (Supplementary Table 3B). In the survival assessment, 3/11 (27.3%) of the studies were assessed as high risk of bias (Supplementary Table 3C).

A study in Egypt [50] reported significant improvement in clinical recovery and mortality following treatment with ivermectin and has been cited in multiple meta-analyses. However, on July 15, 2021, the Elgazzar et al. paper was retracted from the preprint server ResearchSquare due to "ethical concerns." There was evidence reported showing that instances of plagiarism and serious data inconsistencies were discovered in their paper. The most significant flaw detected was that the data for ~79 participants were nearly identical to the data of other participants. These concerns resulted in the exclusion of the Elgazzar paper from this meta-analysis. Similarly, a published study conducted in Lebanon by Raad et al [51], which reported significant effects of ivermectin on hospitalisation and viral load is currently being investigated. An analysis of their raw database suggested that data for multiple participants were duplicates. As a result of these inconsistencies the Raad study was also excluded from this meta-analysis.

Effects on Inflammatory Markers

Three trials provided results of the effect of ivermectin on inflammatory markers including C-reactive protein (CRP), ferritin, and d-dimer (Table 3). Two of these trials demonstrated significant reductions in CRP compared with control. However, these significant changes in inflammatory markers were mainly seen in studies at high risk of bias.

Effects on Viral Clearance

Three different end points were used to analyze viral clearance: the percentage of patients undetectable on a set day (Table 4), the number of days from randomization to negativity (Table 5), and other measures such as cycle time (Ct) values and dose–response correlations (Table 6). The Kirti [43] and Okumus [47] trials included viral load analysis only in a subset of patients. The effect of ivermectin on viral clearance was most pronounced in the randomized trials evaluating doses of up to 5 days of ivermectin using doses of 0.4 mg/kg. Several studies showed no statistically significant effect of ivermectin on viral clearance [29, 34, 36]. There were inconsistent conclusions on viral clearance.

In a meta-analysis of viral clearance with subgroups of dose duration, there were significant differences in time to viral clearance in favor of ivermectin (mean difference, −1.98 days; 95% CI, −3.41 to −0.55; P = .007) (Figure 1A). In an overall analysis including studies at high risk of bias, similar effects of ivermectin on time to viral clearance were seen (Supplementary Figure 2A). However, in another analysis, ivermectin did not have a statistically significant effect on viral clearance at day 3 (RR, 0.99; 95% CI, 0.84 to 1.15; P = .86) (Figure 1B), day 7 (RR, 1.19; 95% CI, 0.93 to 1.51; P = .16) (Figure 1C), or day 10 (RR, 1.23; 95% CI, 0.89 to 1.70; P = .21) (Figure 1D). On including studies at a high risk of bias, ivermectin had a borderline significant effect on viral clearance at day 7 (RR, 1.33; 95% CI, 1.01 to 1.74; P = .04) (Supplementary Figure 2C), but not at days 3 and 10 (Supplementary Figures 2B and 2D).

Table 3. Changes in Inflammatory Markers

	CRP, mg/L			Ferritin, µg/L			D-dimer, mg/L		
	Ivermectin	Control	P Value	Ivermectin	Control	P Value	Ivermectin	Control	P Value
Okumus, Turkey (n = 60)[a]									
Baseline	340.3	215.0		683	747		1.3	1.3	
Day 5	51.8	194.3	<.01	875	1028	0.12	5.9	3.6	0.22
Day 10	36.1	92.4	<.05	495	1207	<.01	0.7	1.5	<.05
Chaccour, Spain (n = 24)[b]									
Baseline	3.5	3.0		165	156		0.3	0.3	
Day 7	1.0	1.1	n.s.[c]	125	199	n.s.[c]	0.3	0.3	n.s.[c]
Day 14	0.8	0.6	n.s.[c]	152	145	n.s.[c]	0.3	0.3	n.s.[c]
Ahmed, Bangladesh (n = 45, ivermectin 5 d)									
Baseline	22.0	29.0		269	222		-	-	
Day 7	3.0	14.0	<.05*	211	218	0.[illegible]*	-	-	
Ahmed, Bangladesh (n = 46, ivermectin 1 d)									
Baseline	26.0	29.0		259	222		-	-	
Day 7	11.0	14.0	0.07*	213	218	0.17	-	-	

Normal ranges: CRP (<10 mg/L), ferritin (11–336 µg/L), d-dimer (<0.5 mg/L).

Abbreviation: CRP, C-reactive protein.

*P value compares within-group changes from baseline to end point of ivermectin group.

**P value shows significance of total changes from baseline. All other P values compare ivermectin vs control.

[a]Studies were evaluated as having limited overall quality of evidence using the Cochrane Risk of Bias Tool. See Supplementary Table 3 for further details.

[b]Median presented; all other data mean.

[c]"n.s." was used when no statistically significant difference was found but the actual P value was reported by individual authors and could not be calculated by the current authors.

Effects on Clinical Recovery and Duration of Hospitalization

Definitions of clinical recovery varied across trials, as shown in Table 7, 8 and 9. In Table 7, 3 of the 6 trials showed significantly faster time to clinical recovery on ivermectin compared with control. In 3 trials, ivermectin showed significantly shorter duration of hospitalization compared with control (Table 8).

In a meta-analysis of clinical recovery with subgroups of dose duration, ivermectin had no significant effect on time to clinical recovery (mean difference, [illegible] days; 95% CI, −1.31 to 0.17; P = .13) (Figure 1E). Additionally, there was no significant difference in binary clinical recovery in an analysis with subgroups of dose duration (RR, 1.19; 95% CI, 0.94 to 1.50; P = .15) (Figure 1F). However, in the supplementary analysis including studies at a high risk of bias, ivermectin showed a significant improvement in time to clinical recovery (mean difference, −1.58; 95% CI, −2.80 to −0.35; P = .01) (Supplementary Figure 2E) and binary clinical recovery (RR, 1.14; 95% CI, 1.04 to 1.25; P = .006) (Supplementary Figure 2F).

Ivermectin demonstrated a borderline significant effect on duration of hospitalization, in comparison with control (mean difference, −1.14 days; 95% CI, −2.27 to −0.00; P = .05) (Figure 1G). Ivermectin did not have a statistically significant effect on risk of hospitalization compared to control (RR, 0.63; 95%

Table 4. Effects of Ivermectin on Viral Clearance

Study	Country, No.	Daily Dose	Duration	Viral Load End Point	Result IVM vs Control, %	P Value
No. detectable or undetectable (%)						
Mahmud et al.	Bangladesh, n = 363	12 mg	1 d (DB)	Undetectable day 14	92 vs 80	<.001
Mohan et al.	India, n = 125	0.2 mg/kg Elixir	1 d	Undetectable day 5	35 vs 31	.3
Mohan et al.	India, n = 125	0.4 mg/kg Elixir	1 d	Undetectable day 5	48 vs 31	.3
Kirti et al.	India, n = 112	12 mg	2 d	Undetectable day 6	24 vs 32	.35
Schwartz et al.	Israel, n = 100	12–15 mg	3 d (DB)	Day 10 PCR neg Ct >30	85 vs 69	.02
Zoni et al. (IVERCOR)	Argentina, n = 501	12–24 mg	2 d (DB)	Day 3 (±1) PCR neg	47.08 vs 49.79	.55
Zoni et al. (IVERCOR)	Argentina, n = 501	12–24 mg	2 d (DB)	Day 12 (±2) PCR neg	89.08 vs 92.47	.29
Podder et al.[a]	Bangladesh, n = 62	0.2 mg/kg	1 d (OL)	Day 10 PCR neg	90 vs 95	>.05
Asghar et al.[a]	Pakistan, n = 86	0.2 mg/kg	1 d	Undetectable day 7	90 vs 44	<.001

Abbreviations: Ct, cycle threshold; DB, double-blind; IVM, ivermectin; OL, open-label; PCR, polymerase chain reaction.

[a]Studies were evaluated as having limited overall quality of evidence using the Cochrane Risk of Bias Tool. See Supplementary Table 3 for further details.

Table 5. Effects of Ivermectin on Viral Clearance. Effects of Ivermectin on Time to Viral Clearance

Study	Country, No.	Daily Dose	Duration	Viral Load End Point	Result IVM vs Control	P Value
Time to viral clearance, d						
Babaloa et al.[a]	Nigeria, n = 60	0.1 mg/kg	2/wk (DB)	Time to PCR neg	6 vs 9.2 d	.003
Babaloa et al.[a]	Nigeria, n = 60	0.2 mg/kg	2/wk (DB)	Time to PCR neg	4.7 vs 9.2 d	.003
Ahmed et al.[a]	Bangladesh, n = 72	0.2 mg/kg	5 d (DB)	Time to PCR neg	9.7 vs 12.7 d	.02
Ahmed et al.[a]	Bangladesh, n = 72	0.2 mg/kg	1 d (DB)	Time to PCR neg	11.5 vs 12.7 d	.27
Petkov et al.	Bulgaria, n = 100	0.4 mg/kg	3 d (DB)	Time to PCR neg	4.52 vs 5.06	.341
Zoni et al. (IVERCOR)	Argentina, n = 501	12–24 mg	2 d (DB)	Time to PCR neg	3 d vs 3 d	.55
Chowdhury[b]	Bangladesh, n = 112	0.2 mg/kg	1 d (OL)	Time to PCR neg	9 vs 9.3 d	.23

Abbreviations: DB, double-blind; IVM, ivermectin; OL, open-label; PCR, polymerase chain reaction.

[a]Dose–response effect seen.

[b]Studies were evaluated as having limited overall quality of evidence using the Cochrane Risk of Bias Tool. See Supplementary Table 3 for further details.

CI, 0.36 to 1.11; $P = .11$, Figure 1H). However, this analysis involved only 3 trials in 993 participants. On including studies at a high risk of bias, ivermectin did not have a significant effect on hospitalizations (RR, 0.60; 95% CI, 0.34 to 1.05; $P = .08$, Supplementary Figure 2G). A leave-1-out sensitivity analysis was performed, and no single study had a substantial impact on the overall effect size (Supplementary Table 5). In a sensitivity analysis including any hospitalization within 12 hours of randomization, there were significantly fewer hospitalizations in the ivermectin group compared to control (RR, 0.57; 95% CI, 0.33 to 0.98; $P = .04$, Supplementary Figure 3). However, this significant effect was dependent on the inclusion of 1 study at a low risk of bias (Supplementary Table 6).

Effects on Survival

Eleven randomized trials reported that at least 1 person had died postrandomization, and 8 of these trials which were not at a high risk of bias were included in the primary analysis (Table 10). Across these 8 trials in 1848 patients, there were 25/894 (2.8%) deaths in the ivermectin arms, 45/954 (4.8%) deaths in the control arms. In a combined analysis using inverse variance weighting, ivermectin did not show a significant effect on mortality (RR, 0.90; 95% CI, 0.57 to 1.42; $P = .66$) (Figure 1I). Heterogeneity was absent ($I^2 = 0\%$). There was no significant effect on survival in both subgroups of mild/moderate participants (RR, 0.70; 95% CI, 0.29 to 1.65; $P = .41$) and severe participants (RR, 0.99; 95% CI, 0.59 to 1.69; $P = .98$). However, this analysis was small and based on 71 deaths. In the supplementary analysis, including studies at a high risk of bias, a borderline significant effect on survival was observed (RR, 0.62; 95% CI, 0.39 to 0.99; $P = .05$) (Supplementary Figure 2H). In this analysis, a significant improvement in survival was observed for patients with mild/moderate disease (RR, 0.42; 95% CI, 0.21 to 0.83; $P = .01$) (Supplementary Figure 2H) in comparison with those with severe disease (RR, 0.90; 95% CI, 0.57 to 1.42; $P = .64$) (Supplementary Figure 2H). However, this was dependent on the inclusion of 1 study (Niaee et al. [27]) at a high risk of bias.

Additional subgroup analysis of the mortality outcome with trials separated by dose duration, blinding, and control group showed consistent absence of survival benefit, and no significant subgroup differences were found (Supplementary Figures 4, 5, and 6). A leave-1-out sensitivity analysis was performed, including studies at high risk of bias. By excluding the Niaee et al. [27] study, which is at a high risk of bias, the effect of ivermectin on survival becomes nonsignificant (Supplementary Table 4).

Ivermectin was not associated with lower risk of mechanical ventilation (RR, 1.04; 95% CI, 0.63 to 1.71; $P = .87$) (Figure 1J). However, this estimate was based on 6 studies in 1059 participants including only 59 events.

DISCUSSION

This systematic review and meta-analysis evaluated ivermectin for the treatment of SARS-CoV-2 infection in 23 RCTs (n = 3349). The primary analysis was carried out by excluding studies at a high risk of bias, consistent with other similar meta-analyses. Ivermectin did not show a statistically significant effect on survival (RR, 0.90; 95% CI, 0.57 to 1.42; $P = .66$) (Figure 1I) or hospitalizations (RR, 0.63; 95% CI, 0.36 to 1.11; $P = .11$) (Figure 1H). Ivermectin displayed a borderline significant effect on the duration of hospitalization in comparison with SOC (mean difference,

Table 6. Effects of Ivermectin on Viral Clearance. Effect of Ivermectin on Other Measures of Viral Clearance

Study	Country, No.	Daily Dose	Duration	Viral Load End Point	Result IVM vs Control	P Value
Other measures of viral clearance						
Krolewiecki et al.[a]	Argentina, n = 45	0.6 mg/kg	5 d	PK/PD	Dose-related	.02

Abbreviations: IVM, ivermectin; PK/PD, pharmacokinetic/pharmacodynamic.

[a]Dose–response effect seen.

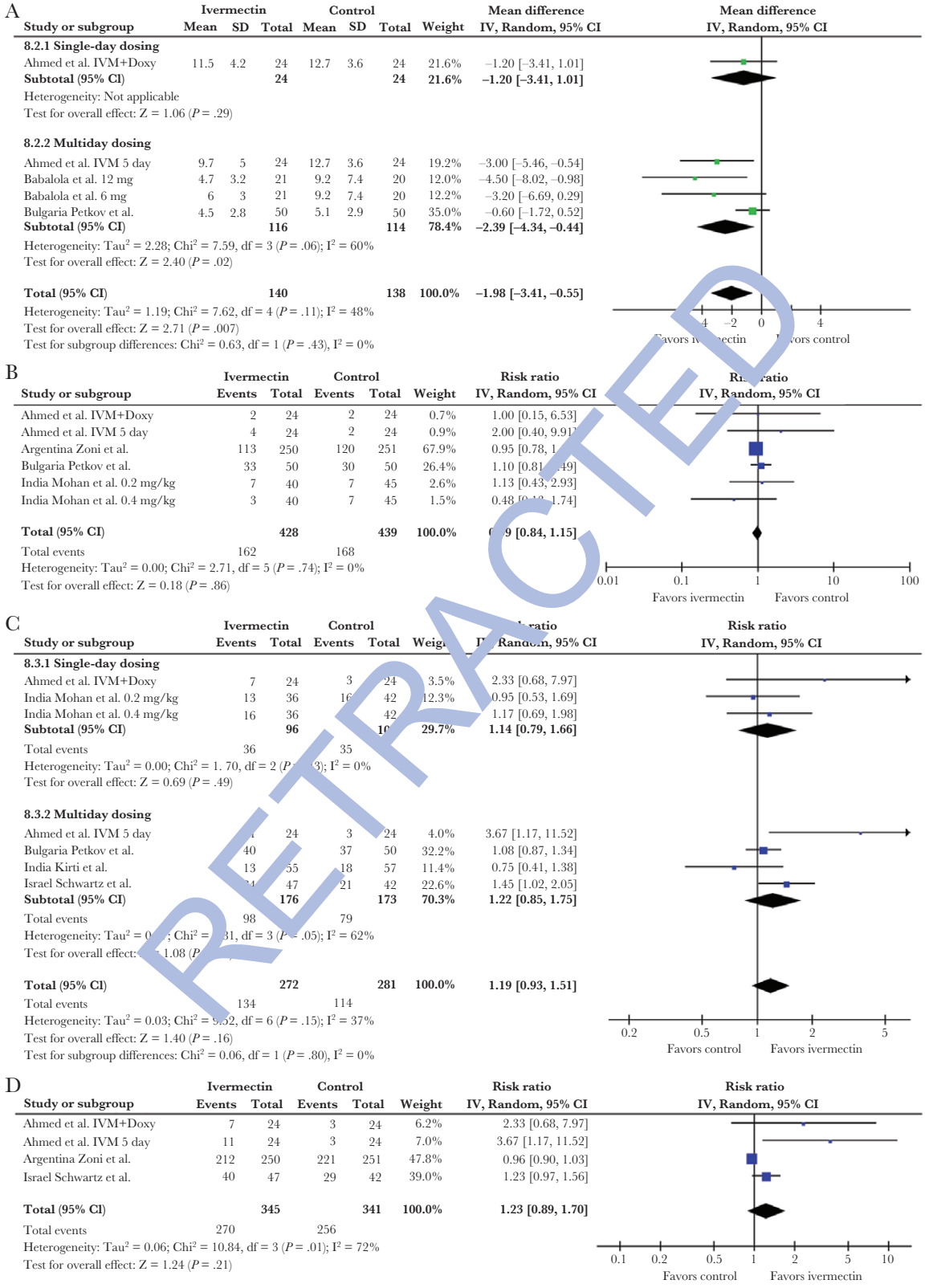

Figure 1. A, Forest plot of time to viral clearance by dose duration, excluding high risk of bias studies. B, Forest plot of PCR negativity at day 3, excluding high risk of bias studies. C, Forest plot of PCR negativity at day 7 (Kirti et al. and Schwartz et al. measured at day 6, excluding high risk of bias studies). D, Forest plot of PCR negativity at day 10, excluding high risk of bias studies. E, Forest plot of time to clinical recovery by dose duration, excluding high risk of bias studies. F, Forest plot of clinical recovery (binary) by dose duration, excluding high risk of bias studies. G, Forest plot of duration of hospitalization by dose, excluding high risk of bias studies. H, Forest plot of new hospitalizations in trials on outpatients, excluding high risk of bias studies. I, Forest plot of survival by severity, excluding high risk of bias studies. J, Forest plot of mechanical ventilation, excluding high risk of bias studies. Abbreviation: PCR, polymerase chain reaction.

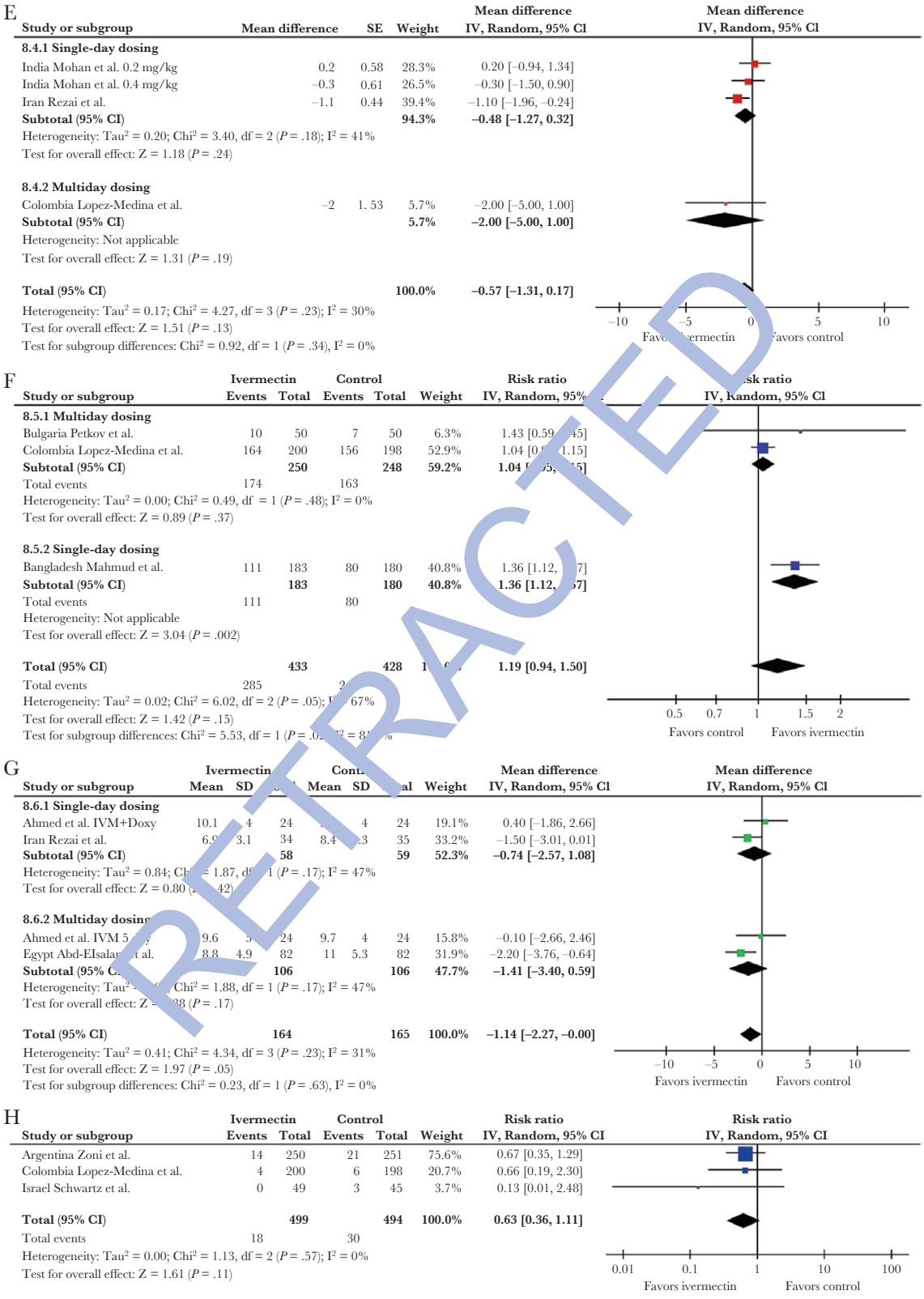

Figure 1. Continued.

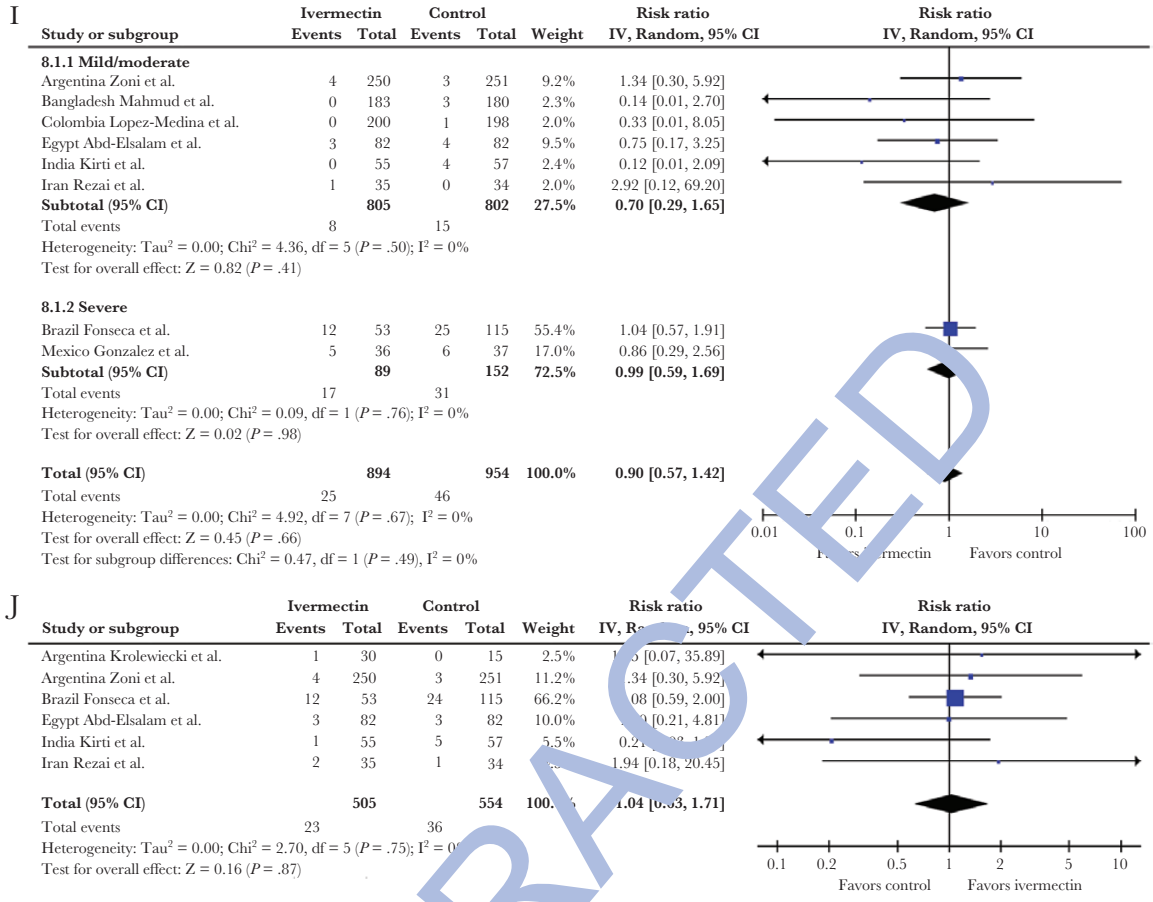

Figure 1. Continued.

–1.14 days; 95% CI, –2.27 to –0.00; P = .05) (Figure 1G). There was no significant effect on time to clinical recovery (mean difference, –0.57 days; 95% CI, –1.57 to 0.13; P = .13) (Figure 1E). Ivermectin showed a significant effect in achieving viral clearance more quickly compared with SOC. However, no significant effect was observed on PCR negativity at days 3, 7, and 10. Ivermectin did not have a significant effect on the risk of mechanical ventilation. A supplementary analysis was performed by including studies at a high risk of bias. Ivermectin displayed a borderline significant effect on survival. Time to clinical recovery and binary clinical recovery showed significant improvement with ivermectin in comparison with SOC. Furthermore, ivermectin had a borderline significant effect on viral clearance at day 7, but not days 3 and 10. Ivermectin had a significant effect on reducing inflammatory markers, mainly seen in studies at a high risk of bias. However, these results need to be treated with caution.

Table 7. Effects on of Ivermectin on Clinical Recovery and Hospitalization. Time to Clinical Recovery

Study	Country	Daily Dose	Duration	End Point	Results IVM vs Control	P Value
Time to clinical recovery						
Mohan et al.	India, n = 125	0.2 mg/kg elixir	1 d (SB)	Time to clinical recovery	4.8 vs 4.6 d	.77
Mohan et al.	India, n = 125	0.4 mg/kg elixir	1 d (SB)	Time to clinical recovery	4.3 vs 4.6 d	.77
Rezai et al.	Iran, n = 69	0.2 mg/kg	1 d (OL)	Time to clinical recovery	4.1 vs 5.2 d	.018
Lopez-Medina et al.	Colombia, n = 398	0.3 mg/kg	5 d (DB)	Time to clinical recovery	10 vs 12 d	.53
Hashim et al.[a]	Iraq, n = 140	0.2 mg/kg	2–3 d (SB)	Time to clinical recovery	10.6 vs 17.9 d	<.001
Podder et al.[a]	Bangladesh, n = 62	0.2 mg/kg	1 d (OL)	Time to clinical recovery	5.3 vs 6.3 d	>.05
Chowdhury et al.[a]	Bangladesh, n = 116	0.2 mg/kg	1 d (OL)	Time to clinical recovery	5.9 vs 6.9 d	.071

Abbreviations: DB, double-blind; IVM, ivermectin; OL, open-label; SB, single-blind.

[a]Studies were evaluated as having limited overall quality of evidence using the Cochrane Risk of Bias Tool. See Supplementary Table 3 for further details.

Table 8. Effects on of Ivermectin on Clinical Recovery and Hospitalization. Effect of Ivermectin on Duration of Hospitalization

Study	Country	Daily Dose	Duration	End Point	Results IVM vs Control	P Value
Duration of hospitalization						
Rezai et al.	Iran, n = 69	0.2 mg/kg	1 d (OL)	Days in hospital	6.9 vs 8.4 d	.01
Ahmed et al.	Bangladesh, n = 72	0.2 mg/kg	5 d (DB)	Days in hospital	9.6 vs 9.7 d	.93
Ahmed et al.	Bangladesh, n = 72	0.2 mg/kg	1 d (DB)	Days in hospital	10.1 vs 9.7 d	.93
Abd El-Salam et al.	Egypt, n = 164	12 mg	3 d	Days in hospital	8.82 vs 10.97 d	.09
Gonzalez et al.	Mexico, n = 106	12 mg	1 d	Days in hospital	6 vs 5 d	.45
Niaee et al.[a]	Iran, n = 165	0.2–0.4 mg/kg	1–3 d (DB)	Days in hospital	6.5 vs 7.5 d	.006

Abbreviations: DB, double-blind; IVM, ivermectin; OL, open-label.

[a]Studies were evaluated as having limited overall quality of evidence using the Cochrane Risk of Bias Tool. See Supplementary Table [illegible] for further details.

The results from this meta-analysis had to be revised after 2 of the original trials (Elgazzar, Egypt [50] and Raad, Lebanon [51]) were found to be unreliable, based on analysis of the raw database. Other trials at high risk of bias have also been removed from the primary analysis. There have also been suggestions that several clinical trials of other repurposed trials are unreliable and cannot be included in the evidence base. A previous study of hydroxychloroquine for COVID-19 was retracted from *The Lancet* [52], leading to changes in procedures for publication in *The Lancet* [53]. Furthermore, there have been concerns that a recent randomized trial of the anti-androgen drug proxalutamide, reporting a 77% survival benefit, cannot be verified [54]. In addition, results from nonrandomized studies can be overinterpreted. For example, a case–control study of remdesivir in hospitalized patients suggested a [illegible]% survival benefit, which was widely reported [55]. This apparent benefit was not confirmed when the large randomized SOLIDARITY trial results were reported. This series of examples underscores the need for large prospective randomized trials to confirm any preliminary benefits claimed for new treatments for COVID-19. Review of the data by stringent regulatory authorities will be needed to determine whether clinical trial results are valid and could support approval for routine [illegible].

The results from this analysis have emerged from the International Ivermectin Project Team meetings between December 2020 and July 2021. Independent research teams were conducting the trials across 16 countries and agreed to share their data, which were often unpublished, to accelerate the speed of reporting and to ensure their fragmented research, widespread across the world, could contribute to global learning. Viral clearance was evaluated by PCR assays in all the studies. We have only included randomized clinical trials in this meta-analysis. The 23 RCTs included were designed and conducted independently, with results combined in September 2021. However, each individual trial was small, and a wide range of population types were included. Clinical recovery definitions differed between trials, and there were no significant differences in terms of survival.

Mechanism of Action

At the time of writing, knowledge gaps prevent a robust conclusion about the potential mechanisms of action of ivermectin. Ivermectin's broad-spectrum antiviral effects have been proposed to be related to its impact on the NF-κB pathway and via binding to the host cell importin α/β1 heterodimer, nuclear transport proteins responsible for nuclear entry of cargoes, and these effects in turn may prevent viral replication. The current in-vitro EC_{50} estimates (2.2 μ, 2.4 μM, and 2.8 μM depending on gene assay analyzed by reverse transcription quantitative PCR) are still 35× higher than plasma concentrations following normal oral dosing. Even doses 8.5× the FDA-recommended 200 μg/kg of 1.7 mg/kg only reach plasma concentrations of 0.28 μM [56]. The increased bioavailability in the fed state and higher concentrations seen in lung tissue compared with plasma are still below the current published EC_{50} results.

Table 9. Effects on of Ivermectin on Clinical Recovery and Hospitalization. Number of Participants With Clinical Recovery by Days 7 to 10 Postrandomization

Study	Country	Daily Dose	Duration	End Point	Results IVM vs Control, %	P Value
No. of participants recovered (%)						
Petkov et al.	Bulgaria, n = 100	0.4 mg/kg	3 d (DB)	Day 7 clinical recovery	20 vs 14	n/a
Mahmud et al.	Bangladesh, n = 363	12 mg	1 d (DB)	Day 7 clinical recovery	61 vs 44	<.03
Okumus et al.[a]	Turkey, n = 60	0.2 mg/kg	5 d (DB)	Day 10 clinical improvement	73 vs 53	.10
Chahla et al.[a]	Argentina, n = 254	24 mg	1/wk for 4 wk (OL)	Clinical improvement	98 vs 87	.0007
Chachar et al.[a]	Pakistan, n = 50	0.2 mg/kg	2 d (OL)	Day 7 clinical recovery	64 vs 60	.5

Abbreviations: DB, double-blind; IVM, ivermectin; OL, open-label.

[a]Studies were evaluated as having limited overall quality of evidence using the Cochrane Risk of Bias Tool. See Supplementary Table 3 for further details.

Table 10. Effects of Ivermectin on Survival

Trial	Country	Dosing	Ivermectin	Control
Mahmud et al.	Bangladesh	0.2 mg/kg, 1 d	0/183	3/180
Lopez-Medina	Colombia	0.3 mg/kg 5 d	0/200	1/198
Zoni et al.	Argentina	12–24 mg, 2 d	4/250	3/251
Fonseca	Brazil	14 mg 3 d	12/53	25/115
Kirti et al.	India	12 mg, 5 d	0/55	4/57
Rezai et al.	Iran	0.2 mg/kg, 1 d	1/35	0/34
Abd-Elsalam	Egypt	0.2 mg/kg, 3 d	3/82	4/82
Gonzalez	Mexico	0.2 mg/kg, 1 d	5/36	6/37
Niaee et al.[a]	Iran	0.2 mg/kg 1–3 d	[illegible]	11/60
Hashim et al.[a]	Iraq	0.2–0.4 mg/kg 2–3 d	2/70	6/70
Okumus et al.[a]	Turkey	0.2 mg/kg, 5 d	6/30	9/30
Total			[illegible]/1114 (3[illegible]%)	72/1114 (6.5%)

[a]Studies were evaluated as having limited overall quality of evidence using the Cochrane Risk of Bias Tool. See Supplemen[illegible]ary Table[illegible] for further details.

Limitations

A key limitation to this meta-analysis is the comparability of the data, with studies differing in dosage, treatment duration, and inclusion criteria. Furthermore, the standard of care used in the control arm differed between trials. In this meta-analysis, trials that used active controls such as hydroxychloroquine or lopinavir/ritonavir were combined with those that us[illegible] placebo or standard care. However, lopinavir/ritonavir and hydroxychloroquine have shown no overall benefit or harm in large randomized trials and meta-analyses [, 57–9]. Furthermore, additional analyses in this pape[illegible] separating trials by subgroups of standard care/placebo a[illegible]d activ[illegible]ontrol showed no significant difference between g[illegible]s.

Another limitation is that ivermectin was given in combination with doxycycline in 3 trials. Indi[illegible]dual trials may not have power to detect treatment effects o[illegible]are en[illegible] points such as survival. Outcome measures were not st[illegible]rdized [illegible]iral clearance was measured in most trials [illegible]ut at dif[illegible]en[illegible] time points and with different PCR cycle th[illegible]eshold[illegible] The reliability of PCR tests for quantification purposes [illegible]as been the subject of substantive debate. Most studies were cond[illegible]ted in populations with only mild/moderate infection, and some trials excluded patients with multiple comorbidities.

These RCTs have been conducted in a wide range of countries, often in low-resource conditions and overburdened health care systems. Larger RCTs are currently underway in Spain, South America, Africa, and North America, with results from an additional 5000 participants expected in Summer 2021 (Supplementary Table 7).

Several other repurposed medications have shown promise in early smaller trials, for example, sofosbuvir/daclatasvir, colchicine, and remdesivir, but the benefit was not seen later in larger trials. This meta-analysis of 23 RCTs in 3349 patients showed that ivermectin had a significant effect on faster viral clearance and a borderline significant effect on duration of hospitalization. In the primary analysis, excluding studies at a high risk of bias, there was no signific[illegible]t effect of [illegible]rmectin on survival or hospitalisations. Recentl[illegible] the p[illegible]liminary results from the TOGETHER trial were presented. In this [illegible]ndomised, placebo-controlled study of ivermectin in over 1200 outpatients, there was no significant effect of i[illegible]rmectin o[illegible] hospitalisation or survival [60]. These results need to [illegible] validat[illegible]d in larger confirmatory trials.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. All of the clinical trials included in this meta-analysis were approved by local ethics committees, and all patients signed informed consent.

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