Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection

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Abstract

Ivermectin is an antiparasitic drug being investigated for repurposing against SARS-CoV-2. Ivermectin showed in-vitro activity against SARS-COV-2 at high concentrations. This meta-analysis investigated ivermectin in 24 randomized clinical trials (3328 patients) identified through systematic searches of PUBMED, EMBASE, MedRxiv and trial registries. Ivermectin was associated with reduced inflammatory markers (C-Reactive Protein, d-dimer and ferritin) and faster viral clearance by PCR. Viral clearance was treatment dose- and duration-dependent. In 11 randomized trials of moderate/severe infection, there was a 56% reduction in mortality (Relative Risk 0.44 [95%CI 0.25-0.77]; p=0.004; 35/1064 (3%) deaths on ivermectin; 93/1063 (9%) deaths in controls) with favorable clinical recovery and reduced hospitalization. Many studies included were not peer reviewed and a wide range of doses were evaluated. Currently, WHO 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: SARS-CoV2, COVID-19, Ivermectin, Repurposed

Introduction

The SARS-CoV-2 pandemic continues to grow, with over 350,000 new infections and over 7,000 deaths recorded worldwide daily in May 2021 [1]. Protective vaccines have been developed, but current supplies are too low to cover worldwide demand in the coming months [2]. Researchers worldwide are urgently looking for interventions to prevent new infections, or prevent disease progression, and lessen disease severity for those already infected.

While research on new therapeutic agents for 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 ‗re-purpose' 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 to new drug discovery in a pandemic situation. Three re-purposed 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 RECOVERY trial [4,5]. Other re-purposed antimicrobials such as, hydroxychloroquine, lopinavir/ritonavir, remdesivir and interferon-beta, have shown no significant survival benefit in two 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 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 viral clearance rate may reduce the risk of onward transmission but this requires empirical demonstration.

Ivermectin is a well-established anti-parasitic drug used worldwide for a broad number of parasites and also for topical use against rosacea. Antiviral activity of ivermectin has been demonstrated recently for SARS-CoV-2 in Vero/hSLAM cells [9]. However, concentrations required to inhibit viral replication in-vitro (EC_{50}=2.2 - 2.8μM; EC_{90}=4.4μM) are not achieved systemically after oral administration of the drug to humans [9, 10].

The drug is estimated to accumulate in lung tissues (2.67 times that of plasma) [11], but 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 two agents and although mainly excreted unchanged in humans, has two 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 it 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 indications. *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 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 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. In this study, ivermectin also prevented pathological deterioration [19]. Ultimately, various potential mechanisms of action for ivermectin against COVID19 exist and are undergoing further investigation, as recently summarised in a review article [20].

At standard doses, of 0.2-0.4mg/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 2mg/kg, and those receiving longer courses, of up to 4 days, compared to those receiving standard doses [21]. Ivermectin is not licensed for pregnant or breast-feeding women, or children <15kg. The WHO Guidelines Group found that in 16 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

The systematic review and meta-analysis was conducted according to PRISMA guidelines. A systematic search of PUBMED and EMBASE was conducted to identify randomized control trials (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 non-randomized 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 two independent reviewers (HW and LE).

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. PRISMA checklist, PRISMA flow diagram, the search terms, and inclusion/exclusion criteria used are detailed in Supplementary Figure 1, Supplementary Tables 1, 2 and 3.

Registry databases were searched up until the 12th of May 2021. Clinicaltrials.gov [23] was searched using key words 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, non-randomised 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 May 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, PCR negativity at day 7, clinical recovery, time to clinical recovery, mechanical ventilation, duration of hospitalization and number of hospitalizations. Changes in inflammatory markers, viral suppression, clinical recovery and hospitalization were also summarized for individual trials where endpoints could not be combined.

Data analysis

Statistical analyses for all-cause mortality, time to viral clearance and clinical recovery were conducted using published data summaries. For the mortality outcome, clinical trials with at least one death reported were included in this analysis. Furthermore, any hospitalization within 12 hours of randomization was excluded. Treatment effects were expressed as risk ratios (RR) for binary outcomes and mean difference (MD) 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% (two-sided) and all analyses were conducted using Revman 5.3. A funnel plot for the mortality outcome was

created to assess publication bias and small study effects; the p-value was estimated from the regression-based Harbord test for small study effects.

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. Each study was assessed for risk of bias for the primary endpoint, viral load, and survival outcomes. The primary endpoint 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 endpoints including survival and viral load which are less likely to be influenced by this bias. Where information was not available in published papers, clinical trial investigators were proactively contacted to inform the risk bias analysis.

Results

24 RCTs involving a total of 3328 participants were included in this meta-analysis. The sample sizes of each trial ranged from 24 to 400 participants. Of the 24 included studies, eight were published papers, nine were available as pre-prints, six were unpublished results shared for this analysis, and one reported results via a trial registry website.

Overall, nine trials investigated ivermectin as a single dose (Table 1A) [27-35], 15 trials investigated multi-day dosing up to seven days (Table 1B) [36-50] , of which four trials were dose-ranging [28,39, 46, 48]. In the included trials, ivermectin was largely investigated in mild/moderate participants (15 trials). Overall, 18 trials were either single or double-blinded and six 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 endpoints, viral load, and survival. For the primary outcome assessment, 6/24 (25%) 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, 3/15 (20%) of the studies were assessed as high risk [Supplementary Table 3B]. In the survival assessment, 1/11 (9%) of the studies were assessed as high risk of. [Supplementary Table 3C].

Effects on Inflammatory Markers

Five trials provided results of the effect of ivermectin on inflammatory markers including C-reactive protein (CRP), ferritin and d-dimer (Table 2). Four of these trials demonstrated significant reductions in CRP compared to control. Furthermore, in the Elgazzar trial [36], ivermectin significantly reduced ferritin levels compared to control in the severe patient population while no significant difference was demonstrated in the mild/moderate population. The Okumus trial [47] showed significantly greater reductions in ferritin on day 10 of follow-up for ivermectin versus control. The Chaccour [35] and Ahmed [46] trials showed no significant difference in ferritin count between ivermectin and control. Elgazzar [36] showed significant differences in d-dimer between ivermectin and control in both the mild/moderate and severe populations. Okumus [47] showed significant differences in d-dimer on day 5 whilst Chaccour [35] found no significant differences in d-dimer between ivermectin and control, but with a smaller sample size.

Effects on Viral Clearance

Three different endpoints were used to analyze viral clearance: the percentage of patients undetectable on a set day (Table 3A), the number of days from randomization to negativity (Table 3B), and other measures such as cycle time (Ct) values and dose-response correlations (Table 3C). The Kirti [43] and Okumus [47] trials included viral load analysis only in a subset of patients. The effects of ivermectin on viral clearance were generally smaller when dosed on only one day. Several studies showed no statistically significant effect of ivermectin on viral clearance [28, 29, 34].

The three studies randomizing patients to different doses or durations of ivermectin showed apparent dose-dependent effects on viral clearance. First, in the Babalola trial (n=60) [48], the 0.4mg/kg dose showed trends for faster viral clearance than the 0.2mg/kg dose. Second, in the Mohan trial (n=125) [28], the 0.4 mg/kg dose of ivermectin led to a numerically higher

percentage of patients with viral clearance by day five than the 0.2mg/kg dose. Third, in the Ahmed trial (n=72) [46], ivermectin treatment for five days led to a higher percentage of patients with viral clearance at day 13 compared with one day of treatment. Finally, in Krolewiecki (n=45) [50], PK/PD correlations showed significantly faster viral clearance for patients with PK exposures above 160ng/mL.

The effect of ivermectin on viral clearance was most pronounced in the randomized trials evaluating doses of up to five days of ivermectin using doses of 0.4mg/kg. At these doses, there were statistically significant effects on viral clearance in all four randomized trials. In a meta-analysis of viral clearance with subgroups of dose duration, there were significant differences in time to viral clearance in favour of ivermectin (Mean Difference -3.00 days [95%CI -4.96, -1.03]; p=0.003, Figure 1A]. In a sensitivity analysis excluding high risk of bias studies, similar effects of ivermectin on time to viral clearance were seen [Supplementary Figure 2]. Furthermore, in another analysis, ivermectin showed improved viral clearance at day 7 (Relative Risk 1.35 [95%CI 1.05-1.75]; p=0.02, Figure 1B].

Effects on Clinical Recovery and Duration of Hospitalization

Definitions of clinical recovery varied across trials, as shown in Table 4. In Table 4A, three of the six trials showed significantly faster time to clinical recovery on ivermectin compared to control. In four trials, ivermectin showed significantly shorter duration of hospitalization compared to control (Table 4B).

In a meta-analysis of clinical recovery with subgroups of dose duration, there were significant differences in time to clinical recovery in favour of ivermectin (Mean Difference -1.58 days [95%CI -2.80, -0.35]; p=0.01, Figure 1C]. Additionally, ivermectin showed a 29% improvement in clinical recovery in an analysis with subgroups of dose duration (RR 1.29 [95%CI 1.12-1.47]; p=0.0003, Figure 1D].

Ivermectin demonstrated a shorter duration of hospitalization compared to control (Mean Difference -4.27 days [95%CI -8.60-0.06]; p=0.05, Figure 1E). Ivermectin was not associated with a lower risk of hospitalization compared to control (RR 0.40 [95%CI 0.14-1.08]; p=0.07, Figure 1F). However, this analysis involved only four trials in 704 participants. In a sensitivity

analysis including any hospitalization within 12 hours of randomization, there were significantly fewer hospitalisations compared to control (RR 0.32 [95%CI 0.13-0.80]; p=0.01, Supplementary Figure 3).

Effects on Survival

11 randomized trials reported that at least one person had died post-randomization and were included in the analysis (Table 5). Across these 11 trials in 2127 patients, there were 35/1064 (3%) deaths in the ivermectin arms, versus 93/1063 (9%) deaths in the control arms. In a combined analysis using inverse variance weighting, ivermectin showed a 56% reduction in mortality (RR 0.44 [95%CI 0.25-0.77]; p=0.004, Figure 1G). Heterogeneity was moderate, I^2 = 43%. There was a 70% improvement in survival in the subgroup of mild/moderate participants (RR 0.30 [95%CI 0.15-0.58]; p=0.0004). The total number of deaths was small, the analysis was based on 128 deaths and there was no significant difference between ivermectin and control in the severe subgroup (0.58 [95%CI 0.25-1.32]; p=0.19).

Consistent results were observed in an analysis excluding high risk of bias studies (RR 0.45 (95%CI 0.24-0.82); p=0.01, Supplementary Figure 4). When only low risk of bias studies were included this result was also maintained (RR 0.31 [95%CI 0.10-0.90]; p=0.03, Supplementary Figure 5).

Additional subgroup analysis of the mortality outcome with trials separated by dose-duration, blinding and control group showed consistent survival benefit and no significant subgroup differences were found (Supplementary Figures 6, 7 and 8).

A leave-one-out sensitivity analysis was performed and no single study had a substantial effect on the overall effect size (Supplementary Table 4).

A funnel plot for the mortality outcome showed no significant effects of publication bias: the treatment effects were similar in studies of different sizes, p= 0.618 (Supplementary Figure 9).

Ivermectin was not associated with lower risk of mechanical ventilation (RR 0.97 [95%CI 0.57-1.67]; p=0.92, Figure 1H]. However, this estimate was based on five studies in 641 participants including only 49 events.

Discussion

This systematic review and meta-analysis of 24 RCTs (n = 3328) showed ivermectin treatment reduces inflammatory markers, achieves viral clearance more quickly and improves survival compared with SOC. The effects of ivermectin on viral clearance were stronger for higher doses and longer durations of treatment. These effects were seen across a wide range of RCTs conducted in several different countries.

The results from this analysis have emerged from the International Ivermectin Project Team meetings between December 2020 and May 2021. Independent research teams were conducting the trials across 16 countries and agreed to share their data, which was 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 Polymerase Chain Reaction (PCR) assays in all the studies. We have only included randomized clinical trials in this meta-analysis. The 24 RCTs included were designed and conducted independently, with results combined in May 2021. However each individual trial was small and a wide range of population types included. Clinical recovery definitions differed between trials and there were no significant differences on survival in severe participants.

Secondary Endpoints

Secondary endpoints for some RCTs included biomarkers of disease severity. Some of these provide evidence for an anti-inflammatory mechanism of action of ivermectin in SARS-CoV-2 infected patients. Previous meta-analyses have demonstrated that high levels of CRP, ferritin, d-dimer and lymphocytopenia are related to COVID-19 severity and hyper-inflammation [51, 52]. Studies of IL-6 receptor antagonists have been shown to reduce CRP and d-dimer levels in patients with COVID-19 [5].

Ivermectin may also have a role in short-term prevention of SARS-CoV-2 infection, suggested by pilot studies [53, 54]. This potential benefit also needs to be validated in larger randomized trials.

Mechanism of action

At the time of writing, knowledge gaps prevent a robust conclusion about the mechanism of action of ivermectin. Ivermectin‘s broad-spectrum anti-viral 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 also prevent viral replication.

As discussed in the introduction, the current *in-vitro* EC_{50} estimates (2.2μ, 2.4μM and 2.8μM depending on gene assay analyzed by RT-qPCR) are still 35 times higher than plasma concentrations following normal oral dosing. Even doses 8.5x fold the FDA recommended 200μg/kg of 1.7mg/kg only reach plasma concentrations of 0.28μM [55]. The increased bioavailability in the fed state and higher concentrations seen in lung tissue compared to plasma is still below the current published EC_{50} results.

However, EC_{50} results can vary greatly depending on lab methodology; cell lineage, viral quantification methods, the strain of the virus cultured and the Multiplicity of infection used. This is an established phenomenon: viral polymorphisms of influenza demonstrated a 5-fold variation in EC_{50} of different neuraminidase assays that looked at the susceptibility of field isolates of influenza virus against oseltamivir [56]. Specifically in SARS-CoV-2, EC_{50}s for previously repurposed drugs have varied significantly. Remdesivir, now licensed for SARS-CoV-2, performed >10 fold better in hACE2 augmented A549 cells (0.115 μM) than Vero E6 (1.28μM) [57]. whereas other examples of repurposed drugs like sofosbuvir demonstrated over 10-fold variation in EC_{50} when used in Vero E6 cells versus HUH7 [58]. Consequently, the EC_{50} so far demonstrated for ivermectin against SARS-CoV-2 should be interpreted with caution as it is unlikely to be one set value and liable to change depending on the lab

methodology used. In vitro assays for ivermectin should be repeated for different cell types using different measures of activity.

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 together with those that used placebo or standard care. However, lopinavir/ritonavir and hydroxychloroquine have shown no overall benefit or harm in large randomized trials and meta-analyses. [7, 59-61] Furthermore, additional analyses in this paper separating trials by subgroups of standard care/ placebo and active control showed no significant difference between groups.

Another limitation is that ivermectin was given in combination with doxycycline in three trials. Individual trials may not have power to detect treatment effects on rare endpoints such as survival. Outcome measures were not standardized; viral clearance was measured in most trials, but at different time points and with different PCR cycle thresholds. The reliability of PCR tests for quantification purposes has been the subject of substantive debate. Most studies were conducted in populations with only mild/moderate infection and some trials excluded patients with multiple comorbidities.

For open label studies, there is a risk of bias in the evaluation of subjective endpoints such as clinical recovery and hospital discharge. However, the risk is lower for objective endpoints such as viral clearance and survival. We have attempted to control for publication bias by contacting each research team conducting the trials directly. This has generated more results than would be apparent from a survey of published clinical trials only but means that many of the included trials have not been peer-reviewed. Review and publication of RCTs generally takes three to six months. It has become common practice for clinical trials of key COVID-19 treatments to be evaluated from pre-prints, such as for the WHO SOLIDARITY, RECOVERY and REMAP-CAP trials [4,5,7].

These RCTs have been conducted in a wide range of countries, often in low-resource conditions and overburdened healthcare 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 5).

Despite limitations, this analysis suggests a dose and duration-dependent impact of ivermectin on rate of viral clearance. These trials evaluated a wide range of ivermectin dosing, from 0.2mg/kg for 1 day to 0.6mg/kg for 5 days. This wide range of doses allowed an estimation of dose-dependency on viral clearance but reduces the number of patients included that were consistently administered the same dose for the same duration. The maximum effective dose of ivermectin is not yet clear and new clinical trials are evaluating higher doses, up to 1.2mg/kg for 5 days.

The 56% survival benefit seen in this meta-analysis is based on 128 deaths, in 11 different clinical trials. This is a smaller total number of deaths than the RECOVERY trial, which led to the approval of dexamethasone and is based on 1592 deaths. However, the observed survival benefit of 56% in ivermectin is stronger than for other repurposed drugs, requiring a smaller sample size to be demonstrated. Emerging mortality results from larger studies of ivermectin will require careful evaluation and may change the conclusions from the current analysis.

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 24 RCTs in 3328 patients showed a 56% improvement in survival, faster time to clinical recovery and signs of a dose-dependent effect of viral clearance for patients given ivermectin versus control treatment. This benefit needs to be validated in larger confirmatory trials.

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Table 1: Trial Summaries

Table 1A: Ivermectin trials with Dosing on day 1 only

Study	Country	Sample Size	Daily dose	Duration	Patients	Ivermectin Arm	Comparator Arm
Mahmud et a l [25] †	Bangladesh	363	12 mg	1 day (DB)	Mild/ moderate	Ivermectin + Doxycycline + SOC	SOC
Mohan et al [26] †	India	125	0.2-0.4 mg/kg (elixir)	1 day (DB)	Mild / moderate	Ivermectin + SOC	Placebo + SOC
Chowdhury [27] †	Bangladesh	116	0.2 mg/kg	1 day (DB)	PCR positive	Ivermectin + Doxycycline	HCQ + Azithromycin
Gonzalez [28] †	Mexico	106	12 mg	1 day (DB)	Severe	Ivermectin	Placebo
Raad et al [29] †	Lebanon	100	0.2 mg/kg	1 day (SB)	Mild	Ivermectin + SOC	SOC

Asghar et al [32] †	Pakistan	86	0.2 mg/kg	1 day (OL)	Mild / moderate	Ivermectin + SOC	SOC
Rezai et al [31] *	Iran	69	0.2 mg/kg	1 day (DB)	Moderate / severe	Ivermectin + SOC	SOC
Podder et al [32] †	Bangladesh	62	0.2 mg/kg	1 day (OL)	Mild	Ivermectin + SOC	SOC
SAINT [33] *	Spain	24	0.4 mg/kg	1 day (DB)	Moderate	Ivermectin	Placebo

SOC = Standard of care; OL= open label; SB= single-blind; DB= double-blind

Table 1B: Ivermectin trials with multi-day dosing

Study	Country	Sample Size	Daily dose	Duration	Patients	Ivermectin Arm	Comparator Arm
Elgazzar et al [36] †	Egypt	400	0.4 mg/kg	5 days (DB)	Mild to severe	Ivermectin + SOC	HCQ + SOC
Lopez-Medina et al [37]*	Colombia	398	0.3 mg/kg	5 days (DB)	Mild	Ivermectin	Placebo
Chahla et al [38] †	Argentina	254	24mg	1 / week for 4 weeks (OL)	Mild	Ivermectin + SOC	SOC
Niaee et al [39] *	Iran	180	0.2 - 0.4 mg/kg	1-3 days (DB)	Mild / moderate	Ivermectin + SOC	SOC + Placebo
Fonseca et al [40]*	Brazil	168	14mg	3 days (DB)	Severe	Ivermectin	Hydroxychloroquine or Chloroquine
Abd-Elsalam et al [41] †	Egypt	164	12 mg	3 days (OL)	PCR Positive	Ivermectin +SOC	SOC
Hashim et al [42] †	Iraq	140	0.2 mg/kg	2-3 days (SB)	Symptomatic	Ivermectin + Doxycycline + SOC	SOC

Kirti et al [43] *	India	112	12 mg	2 days (DB)	Mild / moderate	Ivermectin + SOC	SOC + Placebo
Petkov et al [44] *	Bulgaria	100	0.4 mg/kg	3 days (DB)	Mild/ moderate	Ivermectin	Placebo
Schwartz et al [45] †	Israel	94	12-15mg	3 days (DB)	Mild/moderate	Ivermectin	Placebo
Ahmed et al [46] *	Bangladesh	72	0.2 mg/kg	5 days (DB)	Mild	Ivermectin + SOC	SOC + Placebo
Okumus et al [47] †	Turkey	60	0.2 mg/kg	5 days (DB)	Severe	Ivermectin + SOC	FAVI/HQ/AZI (SOC)
Babalola et al [48] *	Nigeria	60	0.1-0.2 mg/kg	2 / week (DB)	Mild	Ivermectin + SOC	Placebo + LPV/r (SOC)
Chachar et al [49] †	Pakistan	50	0.2 mg/kg	2 days (OL)	Mild	Ivermectin + SOC	SOC
Krolewiecki et al [50] †	Argentina	45	0.6 mg/kg	5 days (OL)	Mild to moderate	Ivermectin + SOC	SOC

* Denoted 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.

† Denoted studies were evaluated as having limited overall quality of evidence using the Cochrane Risk of Bias Tool. See Supplementary Table 3 for further details.

SOC = Standard of care

Table 2: 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
Elgazzar, Egypt (n=200, mild/moderate COVID-19)									
Baseline	48.4	50.6		168	172		4.8	5.4	
Day 7	4.8	8.3	p<0.001	95	98	0.62	0.5	0.7	p<0.001
Elgazzar, Egypt (n=200, severe COVID-19)									
Baseline	64.8	68.2		420	334		8.2	8.6	
Day 7	28.6	58.6	p<0.001	104	294	p<0.001	0.7	1.9	p<0.001
Okumus, Turkey (n=60)									
Baseline	340.3	215.0		683	747		1.3	1.3	
Day 5	51.8	194.3	p<0.01	875	1028	0.12	5.9	3.6	0.22
Day 10	36.1	92.4	p<0.05	495	1207	p<0.01	0.7	1.5	p<0.05
Chaccour, Spain (n=24)*									

Baseline	3.5	3.0		165	156		0.3	0.3	
Day 7	1.0	1.1	n.s**	125	199	n.s**	0.3	0.3	n.s**
Day 14	0.8	0.6	n.s**	152	145	n.s**	0.3	0.3	n.s**
Ahmed, Bangladesh (n=45, Ivermectin 5 days)									
Baseline	22.0	29.0		269	222		-	-	
Day 7	3.0	14.0	p<0.05+	211	218	0.06+	-	-	
Ahmed, Bangladesh (n= 46, Ivermectin 1 day)									
Baseline	26.0	29.0		259	222		-	-	
Day 7	11.0	14.0	0.07+	213	218	0.17+	-	-	
Iran Niaee (n=60, Ivermectin- 0.2 mg)*									
Baseline	200.0	270.0		-	-		-	-	
Day 5	85.0	245.0	p<0.001++	-	-		-	-	
Iran Niaee (n=60, Ivermectin- 0.2, 0.2, 0.2 mg)*									
Baseline	390.0	270.0		-	-		-	-	
Day 5	200.0	245.0	p<0.001++	-	-		-	-	
Iran Niaee (n=60, Ivermectin- 0.4 mg)*									
Baseline	250.0	270.0		-	-		-	-	

Day 5	80.0	245.0	p<0.001++	-	-	-	-
Iran Niaee (n=60, Ivermectin- 0.4, 0.2, 0.2 mg)*							
Baseline	340.0	270.0		-	-	-	-
Day 5	170.0	245.0	p<0.001++	-	-	-	-

*Median presented, all other data mean.

** 'n.s.' was used when no statistically significant difference was found, but the actual p-value was ot reported by the individual authors and could not be calculated by current authors

+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

*Normal ranges: CRP(<10mg/L), Ferritin(***11-336µg/L)** *D-dimer(<0.5mg/L).*

Table 3: Effects of ivermectin on viral clearance

Table 3A:

Study	Country (n)	Daily dose	Duration	Viral load endpoint	Result IVM vs Control	P value
Number Detectable or Undetectable (%)						
Mahmud et al	Bangladesh, n=363	12 mg	1 day (DB)	Undetectable Day 14	92% vs 80%	p < 0.001
Asghar et al	Pakistan, n=86	0.2 mg/kg	1 day	Undetectable Day 7	90% vs 44%	p < 0.001
Mohan et al	India, n=125	0.2mg/kg Elixir	1 day	Undetectable Day 5	35% vs 31%	p = 0.3
Mohan et al	India, n=125	0.4mg/kg Elixir	1 day	Undetectable Day 5	48% vs 31%	p = 0.3
Kirti et al	India, n=112	12 mg	2 days	Undetectable Day 6	24% vs. 32%	p = 0.35

Podder et al	Bangladesh, n=62	0.2 mg/kg	1 day (OL)	Day 10 PCR neg	90% vs 95%	p > 0.05
Okumus et al	Turkey, n=60	0.2 mg/kg	5 days (DB)	Day 10 PCR Neg	88% vs 38%	p = 0.01
Schwartz et al	Israel n=100	12-15mg	3 days (DB)	Day 10 PCR Neg Ct>30	81% vs 60%	p=0.02

Table 3B: Effects of Ivermectin on Time to Viral Clearance

Study	Country (n)	Daily dose	Duration	Viral load endpoint	Result IVM vs Control	P value
Time to Viral Clearance (Days)						
Chowdhury	Bangladesh, n=112	0.2 mg/kg	1 day (DB)	Time to PCR neg	9 vs 9.3 days	p = 0.23
Elgazzar et al Mild/Moderate	Egypt, n=200	0.4 mg/kg	5 days (OL)	Days detectable	5 vs 10 days	p < 0.001
Elgazzar et al Severe	Egypt, n=200	0.4 mg/kg	5 days (OL)	Days detectable	6 vs 12 days	p < 0.001
Babaloa et al *	Nigeria, n=60	0.1 mg/kg	2 / week (DB)	Time to PCR neg	6 vs 9 days	p = 0.003
Babaloa et al *	Nigeria, n=60	0.2 mg/kg	2 / week (DB)	Time to PCR neg	4.7 vs 9 days	p = 0.003

Ahmed et al *	Bangladesh, n=72	0.2 mg/kg	5 days (DB)	Time to PCR neg	10 vs 13 days	p = 0.02
Ahmed et al *	Bangladesh, n=72	0.2 mg/kg	1 days (DB)	Time to PCR neg	11.5 vs 13 days	p = 0.27
Petkov et al	Bulgaria n=100	0.4 mg/kg	3 days (DB)	Time to PCR neg	4.52 vs 5.06	p=0.341

Table 3C: Effect of ivermectin on other measures of viral clearance.

Study	Country (n)	Daily dose	Duration	Viral load endpoint	Result IVM vs Control	P value
Other Measures of Viral clearance						
Raad et al	Lebanon, n=100	0.2 mg/kg	1 day	Day 3	Ct values 30.1 ± 6.22 vs. 18.96 ± 3.26	p = 0.01
Krolewiecki et al*	Argentina, n=45	0.6 mg/kg	5 days	PK/PD	Dose-related	p = 0.02

***Dose-response effect seen**

Table 4: Effects on of ivermectin on clinical recovery and hospitalization

Table 4A: Time to clinical recovery

Study	Country	Daily dose	Duration	Endpoint	Results IVM vs control	P value
Time to clinical recovery						
Mohan et al	India n=125	0.2 mg/kg Elixir	1 day (SB)	Time to clinical recovery	4.8 vs 4.6 days	p = 0.77
Mohan et al	India n=125	0.4 mg/kg Elixir	1 day (SB)	Time to clinical recovery	4.3 vs 4.6 days	p = 0.77
Hashim et al	Iraq n=140	0.2 mg/kg	2-3 days (SB)	Time to clinical recovery	10.6 vs 17.9 days	p < 0.001
Chowdhury et al	Bangladesh n=116	0.2 mg/kg	1 day (DB)	Time to clinical recovery	5.9 vs 6.9 days	p = 0.071

Podder et al	Bangladesh n=62	0.2 mg/kg	1 day (OL)	Time to clinical recovery	5.3 vs 6.3 days	p > 0.05
Rezai et al	Iran n=69	0.2 mg/kg	1 days (OL)	Time to clinical recovery	4.1 vs 5.2 days	p = 0.018
Lopez-Medina et al	Colombia n=398	0.3 mg/kg	5 days (DB)	Time to clinical recovery	10 vs 12 days	p=0.53

Table 4B: Effect of Ivermectin on duration of hospitalization

Study	Country	Daily dose	Duration	Endpoint	Results IVM vs control	P value
Duration of hospitalization						
Rezai et al	Iran n=69	0.2 mg/kg	1 days (OL)	Days in hospital	6.9 vs 8.4 days	p = 0.01
Raad et al	Lebanon n=100	0.2 mg/kg	1 day (OL)	Hospitalization	0% vs 6%	p = 0.00
Niaee et al	Iran n=165	0.2 - 0.4 mg/kg	1-3 days (DB)	Days in hospital	6.5 vs 7.5 days	p = 0.006
Elgazzar et al Mild/moderate	Egypt n=200	0.4 mg/kg	5 days (OL)	Days in hospital	5 vs 15 days	p < 0.001
Elgazzar et al	Egypt	0.4 mg/kg	5 days (OL)	Days in hospital	6 vs 18 days	p < 0.001

Severe	n=200					
Ahmed et al	Bangladesh, n=72	0.2 mg/kg	5 days (DB)	Days in hospital	9.6 vs 9.7	p=0.93
Ahmed et al	Bangladesh, n=72	0.2 mg/kg	1 days (DB)	Days in hospital	10.1 vs 9.7	p=0.93
Abd El-Salam et al	Egypt n=164	12 mg	3 days	Days in hospital	8.82 vs. 10.97	p=0.09
Gonzalez et al	Mexico n=106	12 mg	1 day	Days in hospital	6 vs 5	p=0.45

Table 4C: Number of Participants with clinical recovery by Day 7 to 10 post-randomization

Study	Country	Daily dose	Duration	Endpoint	Results IVM vs control	P value
Number of Participants Recovered (%)						
Chachar et al	Pakistan n=50	0.2 mg/kg	2 days (OL)	Day 7 Clinical recovery	64% vs 60%	p = 0.5
Okumus et al	Turkey n=60	0.2 mg/kg	5 days (DB)	Day 10 Clinical improvement	73% vs 53%	p = 0.10
Mahmud et al	Bangladesh n=363	12 mg	1 day (DB)	Day 7 Clinical recovery	61% vs 44%	p <0.03
Petkov et al	Bulgaria n=100	0.4 mg/kg	3 days (DB)	Day 7 Clinical recovery	20% vs 14%	n/a
Elgazzar et al Mild/Moderate	Egypt, n=200	0.4 mg/kg	5 days (OL)	Clinical improvement	99% vs 74%	p<0.001

Elgazzar et al Severe	Egypt, n=200	0.4 mg/kg	5 days (OL)	Clinical improvement	94% vs 50%	p<0.001
Chahla et al	Argentina n=254	24 mg	1/ week for 4 weeks (OL)	Clinical improvement	98% vs 87%	p=0.0007

Table 5: Effects of ivermectin on survival

Trial	Country	Dosing	Ivermectin	Control
Mahmud et al	Bangladesh	0.2 mg/kg, 1 day	0/183	3/180
Niaee et al	Iran	0.2 mg/kg 1-3 days	4/120	11/60
Hashim et al	Iraq	0.2-0.4 mg/kg 2-3 days	2/70	6/70
Elgazzar et al	Egypt	0.4 mg/kg 5 days	2/200	24/200
Okumus et al	Turkey	0.2 mg/kg, 5 days	6/30	9/30
Kirti et al	India	12 mg, 5 days	0/55	4/57
Rezai et al	Iran	0.2 mg/kg, 1 day	1/35	0/34
Abd-Elsalam	Egypt	0.2 mg/kg, 3 days	3/82	4/82
Gonzalez	Mexico	0.2 mg/kg, 1 day	5/36	6/37

Lopez-Medina	Colombia	0.3 mg/kg 5 days	0/200	1/198
Fonseca	Brazil	14mg 3 days	12/53	25/115
Total			**35/1064 (3%)**	**93/1063 (8.7%)**

Figure1A

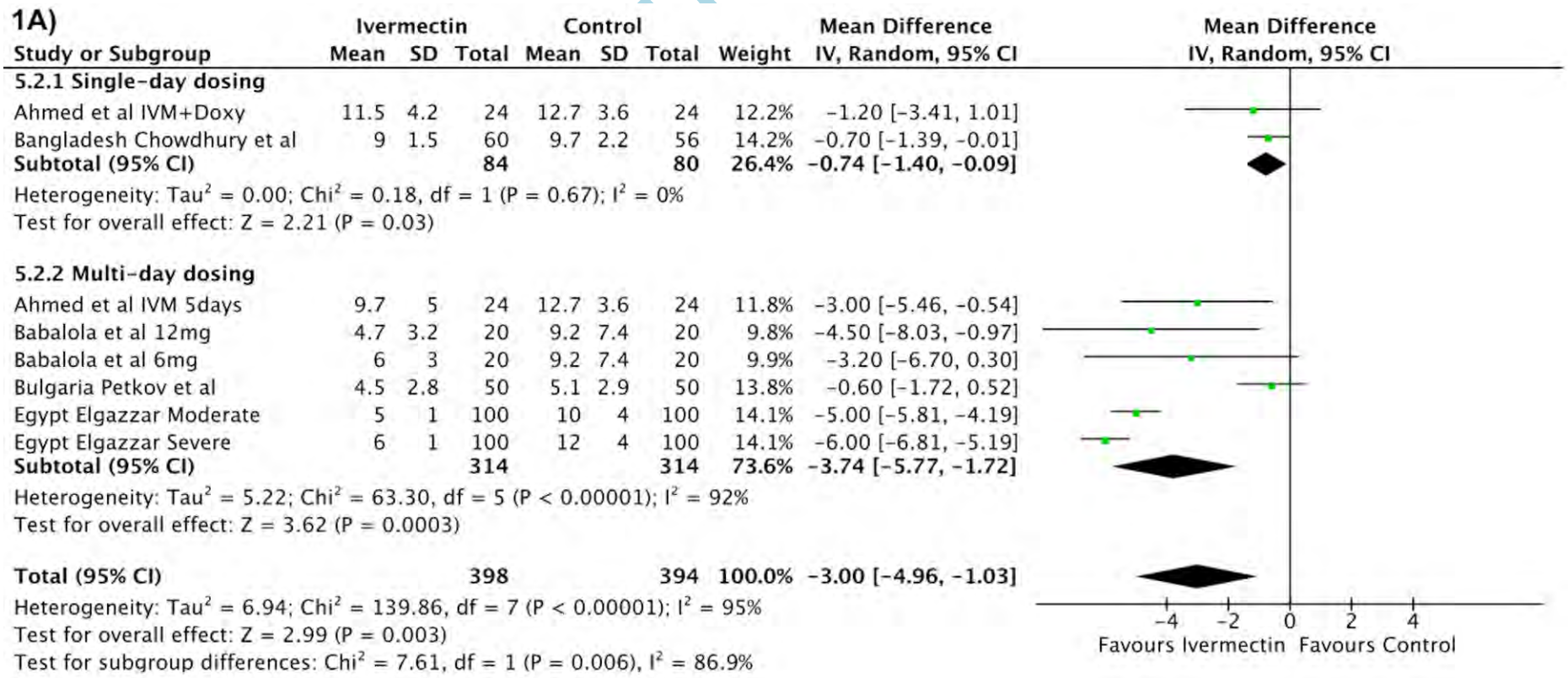

Figure 1B

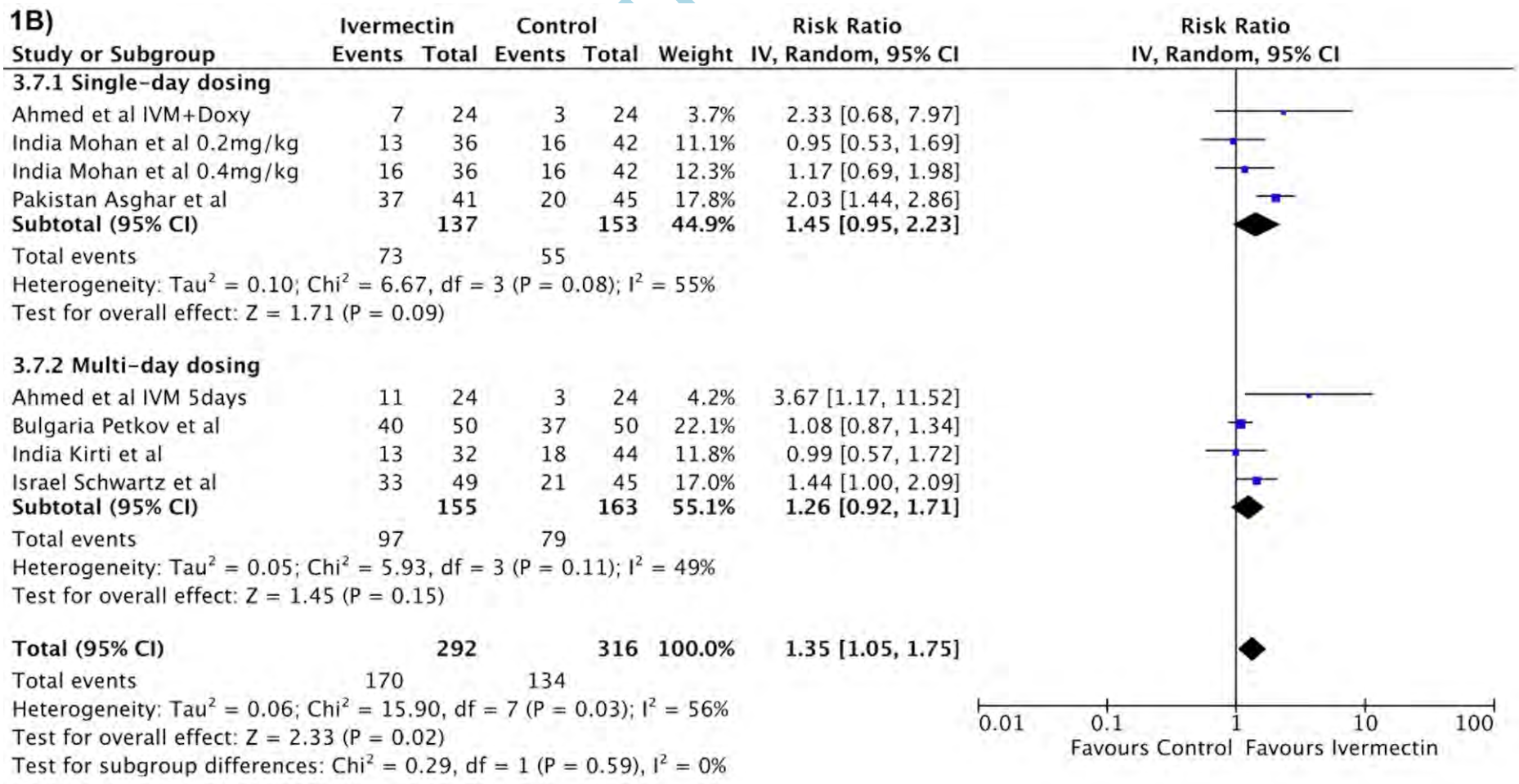

Figure 1C

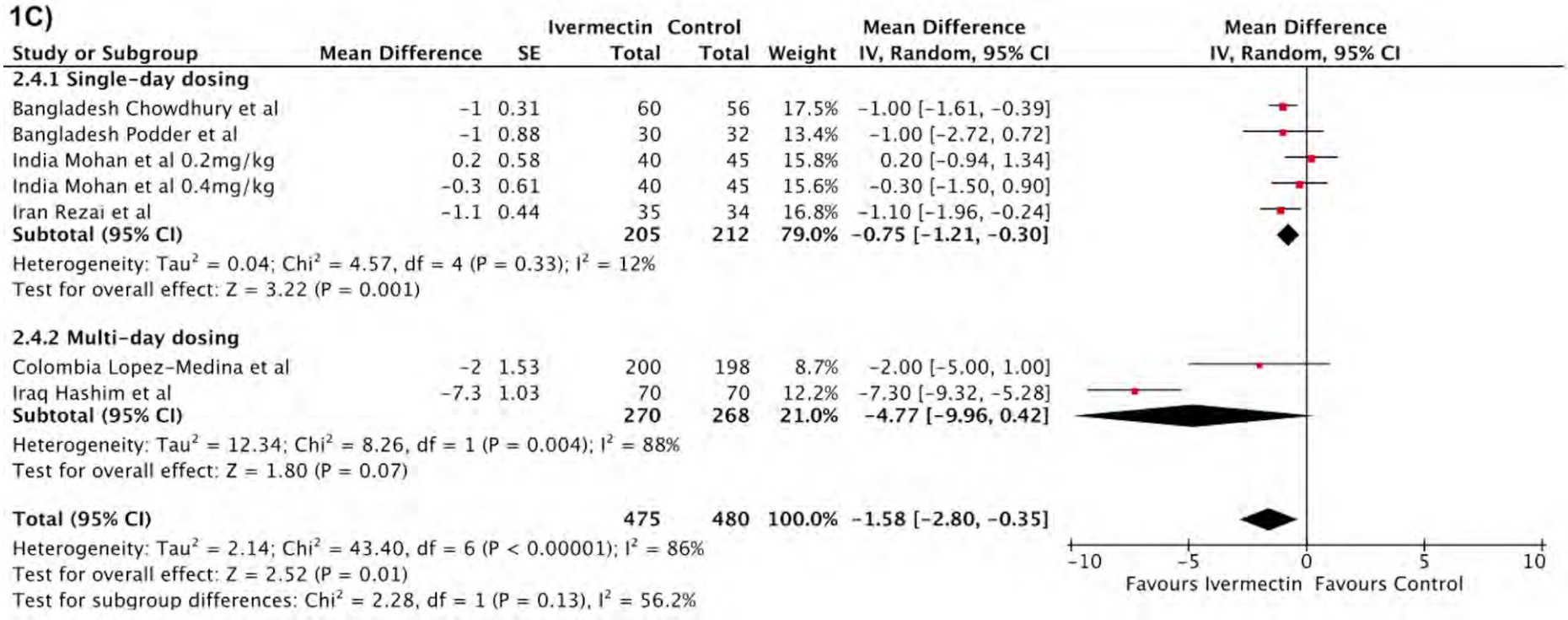

Figure 1D

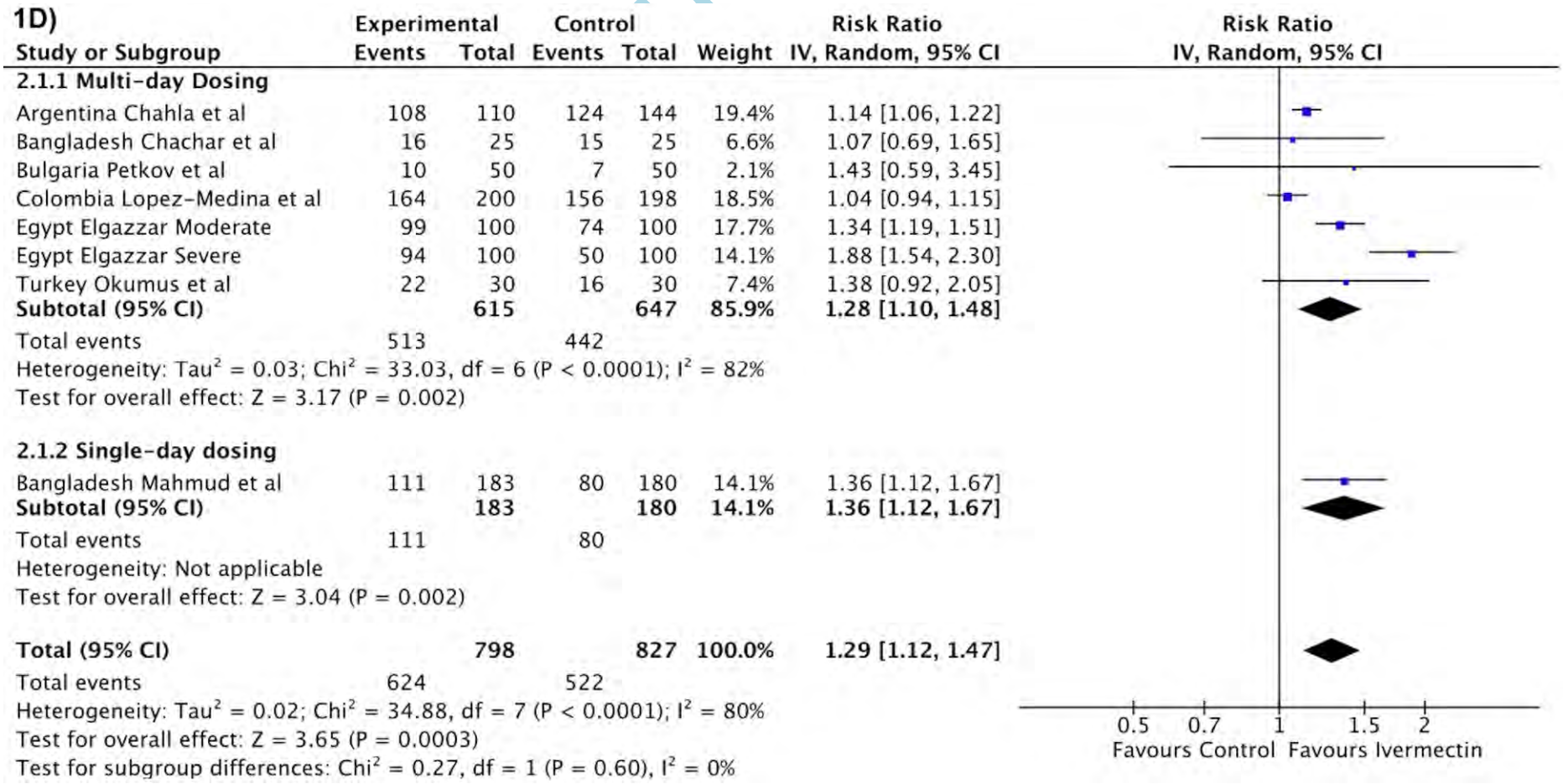

Figure 1E

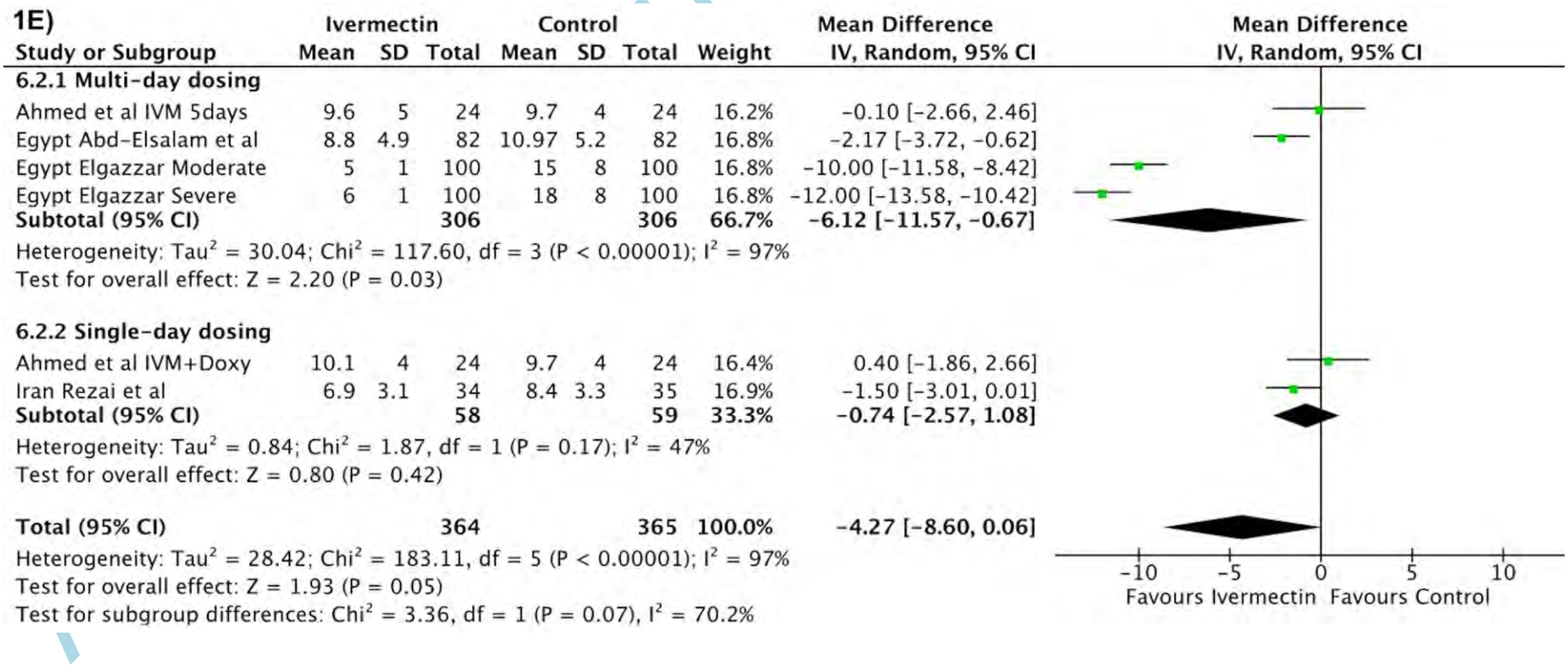

Figure 1F

1F)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Bangladesh Chowdhury et al	0	60	2	56	11.2%	0.19 [0.01, 3.81]
Colombia Lopez-Medina et al	4	200	6	198	65.2%	0.66 [0.19, 2.30]
Israel Schwartz et al	0	49	3	45	11.8%	0.13 [0.01, 2.48]
Lebanon Raad et al	0	50	3	50	11.8%	0.14 [0.01, 2.70]
Total (95% CI)		**359**		**349**	**100.0%**	**0.40 [0.14, 1.08]**
Total events	4		14			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.88$, df = 3 (P = 0.60); $I^2 = 0\%$

Test for overall effect: Z = 1.80 (P = 0.07)

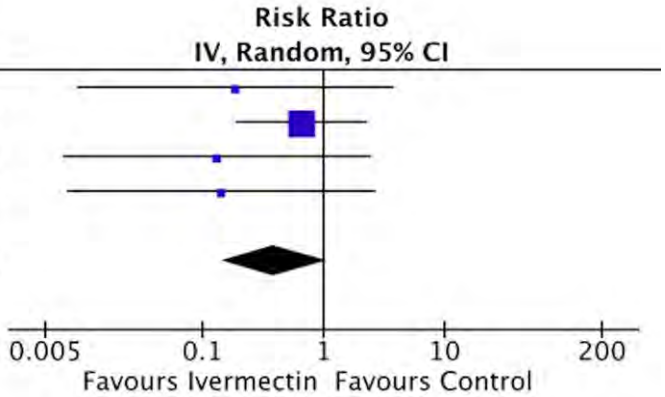

Figure 1G

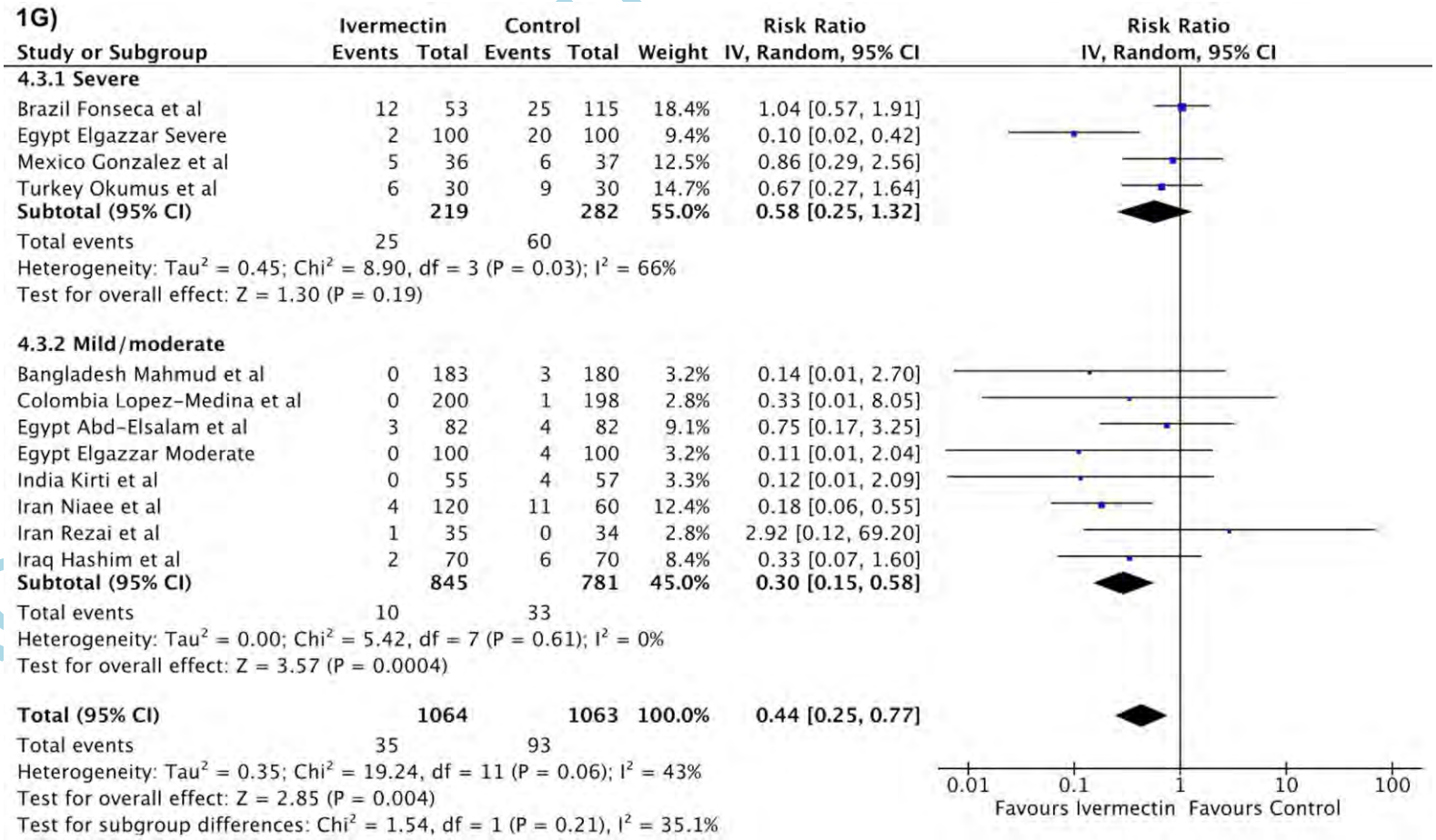

Figure 1H

1H)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Argentina Krolewiecki et al	1	30	0	15	3.0%	1.55 [0.07, 35.89]
Brazil Fonseca et al	12	53	24	115	78.5%	1.08 [0.59, 2.00]
Egypt Abd-Elsalam et al	3	82	3	82	11.9%	1.00 [0.21, 4.81]
India Kirti et al	1	55	5	57	6.6%	0.21 [0.03, 1.72]
India Mohan et al	0	100	0	52		Not estimable
Total (95% CI)		**320**		**321**	**100.0%**	**0.97 [0.57, 1.67]**
Total events	17		32			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.26$, df = 3 (P = 0.52); $I^2 = 0\%$

Test for overall effect: Z = 0.10 (P = 0.92)