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

Authors: Andrew Hill on behalf of the International Ivermectin Project Team*

International Ivermectin Project Team

Ahmed S. Abdulamir[1], Sabeena Ahmed[2], Asma Asghar[3], Olufemi Emmanuel Babalola[4], Rabia Basri[5], , Aijaz Zeeshan Khan Chachar[5], Abu Taiub Mohammed Mohiuddin Chowdhury[7], Ahmed Elgazzar[8], Leah Ellis[9], Jonathan Falconer[10], Anna Garratt[11], Basma M Hany[8], Hashim A. Hashim[12], Wasim Md Mohosin Ul Haque[13], Arshad Hayat[3], Shuixiang He[7], Ramin Jamshidian[14], Wasif Ali Khan[2], Ravi Kirti[15], Alejandro Krolewiecki[16], Carlos Lanusse[17], Jacob Levi[18], Reaz Mahmud[19], Sermand Ahmed Mangat[3], Kaitlyn McCann[9], Anant Mohan[20], Morteza Shakhsi Niaee[21], Nurullah Okumuş[22], Victoria Pilkington[23], Chinmay Saha Podder[24], Ambar Qavi[9], Houssam Raad[25], Ali Samaha[25], Hussein Mouawia[25], Mohammad Sadegh Rezai[26], Surapaneni Sasank[27], Veerapaneni Spoorthi[28], Tejas Suri[20], Junzheng Wang[9], Hannah Wentzel[9] , Andrew Hill[29]

1. College of Medicine, Alnahrain University, Alkadymia, Baghdad, Iraq
2. International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh
3. Department of Medicine, Combined Military Hospital, Lahore, Pakistan
4. Bingham University/Lagos University, Nigeria
5. Fatima Memorial Hospital, Lahore, Pakistan
6. Barcelona Institute for Global Health, Clinica Universidad de Navarra, Universidad de Navarra, Spain
7. Xi'an Jiaotong University Medical College First Affiliated Hospital, Shaanxi, China
8. Faculty of Medicine, Benha University, Banha, Egypt
9. Faculty of Medicine, Imperial College London, UK
10. Department of Infectious Diseases, Chelsea and Westminster Hospital, Imperial NHS Trust, London, UK
11. Department of Infectious Diseases, University Hospital of Wales, Cardiff and Vale University Health Board, UK
12. Alkarkh Hospital, Alatefiya, Baghdad, Iraq
13. Department of Nephrology, BIRDEM General Hospital, Dhaka, Bangladesh
14. Jundishapur University of Medical Sciences, Ahvaz, Iran
15. Department of General Medicine, All India Institute of Medical Sciences, Patna, India
16. Instituto de Investigaciones de Enfermedades Tropicales (IIET-CONICET), Sede Regional Orán, Universidad Nacional de Salta, Argentina
17. Laboratorio de Farmacología, Centro de Investigación Veterinaria de Tandil (CIVETAN), CONICET-CICPBA-UNCPBA, Facultad de Ciencias Veterinarias, Universidad Nacional del Centro de la Provincia de Buenos Aires, Tandil, Argentina
18. Department of Intensive Care, University College London Hospital, ULCH NHS Trust, London, UK

19. Department of Neurology, Dhaka Medical College, Dhaka, Bangladesh
20. Department of Pulmonary Critical Care & Sleep Medicine, All India Institute of Medical Sciences, New Delhi, India
21. Qazvin Science & Technology Park, Qazvin, Iran
22. Department of Neonatology, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey
23. Oxford University Clinical Academic Graduate School, University of Oxford, UK
24. Debidwar Upazila Health Complex, Debidwar, Comilla, Bangladesh
25. Biotherapies de Maldies Genetiques et Cancer, Universite Bordeaux Segalen, Bordeaux, France
26. Pediatric Infectious Diseases Research Center, Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran
27. Gandhi Hospital, Andhra Pradesh, India
28. Apollo Medical College, Hyderabad, India
29. Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, L7 3NY, UK

Funding: Unitaid

Conflicts of Interest: None of the authors has declared a conflict of interest

Corresponding author:

Dr Andrew Hill PhD

Department of Pharmacology and Therapeutics

University of Liverpool,

70 Pembroke Place

Liverpool L69 3GF, UK

Email: microhaart@aol.com

Abstract

Introduction: Ivermectin is a well-established antiparasitic drug licensed since 1981, more recently approved for its anti-inflammatory effects against rosacea. It is being investigated for repurposing against SARS-CoV-2. In-vitro, ivermectin showed some antiviral activity but at higher concentrations than achieved in human plasma after normal oral dosing. An animal model demonstrated pathological benefits in COVID-19 but no effect on viral RNA. We aimed to assess the available global data from randomized controlled trials (RCTs) of ivermectin in COVID-19.

Methods: We conducted a systematic search of PUBMED, EMBASE, MedRxiv and trial registries. We excluded prevention studies and non-randomized or case-controlled studies. We identified and included 18 RCTs. Data were combined from 2282 patients into a systematic review and meta-analysis.

Results: 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. Ivermectin showed significantly shorter duration of hospitalization compared to control. In six RCTs of moderate or severe infection, there was a 75% reduction in mortality (Relative Risk=0.25 [95%CI 0.12-0.52]; p=0.0002); 14/650 (2.1%) deaths on ivermectin; 57/597 (9.5%) deaths in controls) with favorable clinical recovery and reduced hospitalization.

Discussion: Many studies that were included were not yet published or peer-reviewed and meta-analyses are prone to confounding issues. Furthermore, there was a wide variation in standards of care across trials, and ivermectin dose and duration of treatment was heterogeneous. Ivermectin should be validated in larger, appropriately controlled randomized trials before the results are sufficient for review by regulatory authorities.

Keywords: SARS-CoV2, COVID-19, Ivermectin, repurposed

Introduction

The pandemic of SARS-CoV-2 continues to grow, with 650,000 new infections and over 11,000 deaths recorded worldwide daily in January 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 on evaluating the potential use against COVID-19 of already existing medicines, 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 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 [4]. 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, 5] 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 improves survival for patients in intensive care [3, 4]. 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 lower 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 for SARS-CoV-2 in Vero/hSLAM cells [IB6]. However, concentrations required to inhibit viral replication in vitro (EC_{50}=2.8μM; EC_{90}=4.4μM) are not achieved systemically after oral administration of the drug to humans [6, 7]. The drug is estimated to accumulate in lung tissues (2.67 times that of plasma) [8], but this is also unlikely to be sufficient to maintain target concentrations for pulmonary antiviral activity [7, 9]. Current data suggest that the dosages of ivermectin used in human trials are unlikely to provide systemic or pulmonary concentrations necessary to exert meaningful direct antiviral activity. Notwithstanding, ivermectin is usually present as a mixture of two agents and although mainly excreted unchanged in humans, has two major metabolites [10]. 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 [11]. 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 [12]. Ivermectin also reduced TNF-α, IL-1, and IL-6, and improved survival in mice given a lethal dose of lipopolysaccharide [13]. Preclinical evidence to support these immunomodulatory and anti-inflammatory mechanisms of action have also been generated in murine models of atopic dermatitis and allergic asthma [14, 15]. 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 [16]. The impact of ivermectin in this model appeared to be gender specific, appearing more active in females than in males. Irrespective of gender, no impact of ivermectin on viral titers in lung or nasal turbinate was observed in this model, supporting a mechanism of action not relating to direct antiviral activity.

In pharmacokinetic studies, the Area Under the Curve (AUC) and maximum concentration (Cmax) of ivermectin are generally dose proportional, and bioavailability of ivermectin increases 2.57-fold in the fed state [8]. Increasing the frequency or dose of ivermectin does increase the Cmax and AUC of total drug, but not sufficiently to reach the published EC_{50} against SARS-CoV-2 in monkey Vero/hSLAM cells [8]. Ivermectin has approximately twice the systemic availability when given as an oral solution compared to solid forms (tablets or capsules) [10].

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 [17]. Ivermectin is not licensed for pregnant or breast-feeding women, or children <15kg.

The objective of this systematic review and meta-analysis was to combine available results from published or unpublished randomized trials of ivermectin in SARS-CoV-2 infection.Limitations of current analysis is important as it is being performed with secondary data from a wide variety of different trials in many different parts of the world with designs that were not originally meant to be compatible. Further refined analysis, including direct data examination, are warranted.

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 (RCT) 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 COVID-19. Clinicaltrials.gov [18] was searched on 14th December 2020 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, updated to 9th December 2020, [19] and Stamford University's Coronavirus Antiviral Research Database (CoV-RDB), updated to 15th December 2020, [20] to identify additional trials listed on other national, and international registries.

Additionally, literature searches via PubMed, and the preprint server MedRxiv were conducted to identify published studies not prospectively or retrospectively registered in a trial registry. Duplicate registrations, non-controlled studies and prevention studies were excluded following discussion between the authors.

In a third stage of data collection, the research teams conducting unpublished clinical trials were contacted and requested to join regular international team meetings in December 2020 and January 2021. All results available from 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 signed informed consent.

The primary outcome was all-cause mortality from randomization to the end of follow-up. Changes in inflammatory markers, viral suppression, clinical recovery and hospitalization were measured in different ways between trials and were summarized for individual clinical trials where endpoints could not be combined.

Data analysis

Statistical analyses for all-cause mortality were conducted with summary published data, on the intention-to-treat population, including all randomized patients. Clinical trials with at least two deaths reported were included in this analysis. Treatment effects were expressed as risk ratios (RR) for binary 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.

All studies included in this analysis were assessed for risk of bias using the Cochrane Collaboration risk of bias standardized assessment tool [21] and the outcome of this assessment is given in supplementary table 1.

Results

In this meta-analysis, 18 RCTs involving a total of 2282 participants were included. The sample sizes of each trial ranged from 24 to 400 participants. Of the 18 included studies, five were published papers, six were available as pre-prints, six were unpublished results shared for this analysis; one reported results via a trial registry website.

Overall, nine trials investigated ivermectin as a single dose (Table 1A), nine trials investigated multi-day dosing up to seven days (Table 1B), of which three trials were dose-ranging. In this meta-analysis, ivermectin was largely investigated in mild/moderate participants (11 trials). Overall, 12 trials were either single or double-blinded and six were open-label.

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 [22], 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 [23] showed significantly greater reductions in in ferritin on day 10 of follow-up for ivermectin versus control. The Chaccour [24] and Ahmed [25] trials showed no significant difference in ferritin count between ivermectin and control. Elgazzar [22] showed significant differences in d-dimer between ivermectin and control in both the mild/moderate and severe populations. Okumus [23] showed significant differences in d-dimer on day 5 whilst Chaccour [24] found no differences 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 [26] and Okumus [23] 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 [27, 28, 29].

The three studies randomizing patients to different doses or durations of ivermectin showed apparent dose-dependent effects on viral clearance. Firstly, in the Babalola trial [30], the 0.4mg/kg dose showed trends for faster viral clearance than the 0.2mg/kg dose. Secondly, in the Mohan trial [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. Thirdly, in the Ahmed trial [25], 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 [31], 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 treatment, using doses of 0.4mg/kg (Figure 1). At these doses, there were statistically significant effects on viral clearance in all four randomized trials.

Effects on Clinical Recovery and Duration of Hospitalization

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

Effects on Survival

Six randomized trials reported that at least two people had died post-randomization and were included in the analysis (Table 5). Across these six trials in 1255 patients, there were 14/658 (2.1%) deaths in the ivermectin arms, versus 57/597 (9.5%) deaths in the control arms. In a combined analysis using inverse variance weighting ivermectin showed a 75% improvement in survival (RR 0.25 [95%CI 0.12-0.52]; p=0.0002, Figure 2). Heterogeneity was moderate, I^2 = 34%.

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. Of the 18 trials, 11 were of poor quality and seven of fair or high quality. Further evaluation with access to original data from the trials is warranted to increase quality of evidence. [Supplementary table 1]

Discussion

This systematic review of 18 RCTs (n = 2282) 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. However, the data should be interpreted carefully in the context that meta-analyses are highly prone to confounding bias, and current viral PCR assays have several important limitations. Many of the studies assessed have not been peer-reviewed. Larger, appropriately controlled randomized trials are needed before rigorous evaluation of the clinical benefits of ivermectin can be undertaken.

The results from this analysis have emerged from the International Ivermectin Project Team meetings in December 2020 and January 2021. Independent research teams were conducting the trials across 12 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 18 RCTs included were designed and conducted independently, with results combined in December 2020.

Limitations

Key limitations to this meta-analysis include the comparability of the data, with studies differing in dosage, treatment duration, and inclusion criteria. Furthermore, the SOC used in the background treatment differed between different trials. Additionally, ivermectin was often given in combination with doxycycline or other antimicrobials. 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 co-morbidities.

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 [3, 4, 5].

These RCTs have been conducted in a wide range of countries, often in low-resource conditions and overburdened healthcare systems. The evidence from this first set of studies will require validation in larger RCTs evaluating fixed dosing schedules, preferably using higher doses for between 3-5 days. Larger RCTs are currently underway in Mexico, South America and Egypt, with results expected in February and March 2021.

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 75% survival benefit seen in this meta-analysis is based only on 71 deaths, in six different clinical trials. This is a smaller total number of deaths than in either the RECOVERY or REMAP-CAP trials, which led to the approval of dexamethasone, tocilizumab and sarilumab. However, the observed survival benefit of 75% is stronger than for the other re-purposed drugs. Emerging mortality results from larger

studies of ivermectin will require careful evaluation and may change the conclusions from the current analysis.

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 [32, 33]. Studies of IL-6 receptor antagonists have been shown to reduce CRP and d-dimer levels in patients with COVID-19 [4].

Across three studies, in a cumulative 683 patients, we found a slight increase in lymphocyte counts [22, 34, 35] following ivermectin administration. CRP, a marker of infection and inflammation, were reduced following ivermectin administration across four trials [22, 23, 25, 34]. D-dimer is a fibrin degradation product, often raised in severe COVID-19 due to thrombus formation. Ferritin can also be raised in severe COVID-19 due to the cytokine storm and hyperinflammation. Levels of both d-dimer and ferritin following one week of ivermectin treatment in severe COVID-19 cases were reduced to levels less than half of those receiving SOC [22]. These reductions in D-dimer and ferritin were more significant in patients with severe disease compared to those with mild/moderate disease at baseline. Furthermore, erythrocyte sedimentation rate and lactate dehydrogenase, non-specific markers of inflammation and tissue damage, respectively, were both reduced slightly following ivermectin administration in two separate studies of patients with COVID-19 [34, 36].

A key component of SARS-CoV-2 pathogenesis is its pro-thrombotic effect, leading to blood clots in the kidneys, brain and pulmonary emboli in the lungs. By reducing hyper-inflammation, the risk of clots may be reduced. One histopathology study in dogs with *Dirofilaria immitis* (heartworm) showed that ivermectin plus doxycycline reduced lung tissue perivascular inflammation and endothelial proliferation leading to fewer arterial lesions and virtually removed the risk of thrombi [37]. However, the relevance of these findings to SARS-CoV-2 infection are unclear.

Ivermectin may also have a role in short-term prevention of SARS-CoV-2 infection, suggested by pilot studies [38, 39]. This potential benefit also needs to be validated in larger randomized trials.

At the time of writing, knowledge gaps prevent a robust conclusion about the mechanism of action, but current *in vitro* data do not support a direct antiviral activity of the drug. Interestingly, ivermectin has been demonstrated to induce autophagy as part of a proposed mechanism of action in cancer [40, 41] with autophagy providing an innate defense against virus infection [42]. Furthermore, other viruses such as cytomegalovirus have mechanisms to activate cyclooxygenase 2 and prostaglandin E2 promoting the inflammatory response, which supports their replication [43] and it is also possible that a pro-inflammatory phenotype may aid SARS-CoV-2 replication [44]. However, immunological mechanisms of action are usually highly complex and require careful empirical evaluation to understand the plausibility, which is currently absent for ivermectin use in COVID-19.

Conclusion

This meta-analysis of 18 RCTs in 2282 patients showed a 75% 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.

Despite the encouraging trend this existing data base demonstrates, it is not yet a sufficiently robust evidence base to justify the use or regulatory approval of ivermectin. However, the current paucity of high-quality evidence only highlights the clear need for additional, higher-quality and larger-scale clinical trials, warranted to investigate the use of ivermectin further.

The maximum effective dose of ivermectin needs to be clarified and new clinical trials should use a consistent multi-day dosing regime, with at least 0.4mg/kg/day. The appropriate dose and schedule of ivermectin still requires evaluation and the current randomized clinical trials of ivermectin need to be continued until ready for rigorous review by regulatory agencies.

Acknowledgements

We would like to thank all the clinical staff, the research teams and the patients who participated in these studies.

References

1. WHO. WHO Coronavirus Disease (COVID-19) Dashboard [Internet]. 2020 [cited 2021 Jan 8]. Available from: https://covid19.who.int/

2. Stolberg SG, LaFraniere S. Warning of Shortages, Researchers Look to Stretch Vaccine Supply. New York Times [Internet]. 2020; Available from: https://www.nytimes.com/2021/01/05/us/politics/coronavirus-vaccine-supply.html

3. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19—preliminary report. New England Journal of Medicine. 2020. DOI: 10.1056/NEJMoa2021436

4. The REMAP-CAP Investigators. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 - Preliminary report. medrXiv [preprint] 2020; Available at: https://doi.org/10.1101/2021.01.07.21249390

5. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results. medRxiv [Internet]. 2020; Available from: https://doi.org/10.1101/2020.10.15.20209817

6. 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. doi: 10.1016/j.antiviral.2020.104787.

7. Arshad U, Pertinez H, Box H, Tatham L, Rajoli RKR, Curley P et al. Prioritization of Anti-SARS-Cov-2 Drug Repurposing Opportunities Based on Plasma and Target Site Concentrations Derived from their Established Human Pharmacokinetics. Clin Pharmacol Ther. 2020 Oct;108(4):775-790. doi: 10.1002/cpt.1909.

8. Schmith, V., Zhou, J. and Lohmer, L., 2020. The Approved Dose of Ivermectin Alone is not the Ideal Dose for the Treatment of COVID‐19. *Clinical Pharmacology & Therapeutics*, 108(4), pp.762-765.

9. Jermain B, Hanafin PO, Cao Y, Lifschitz A, Lanusse C, Rao GG. Development of a Minimal Physiologically-Based Pharmacokinetic Model to Simulate Lung Exposure in Humans Following Oral Administration of Ivermectin for COVID-19 Drug Repurposing. J Pharm Sci. 2020;109(12):3574-3578. doi:10.1016/j.xphs.2020.08.024

10. González Canga A, Sahagún Prieto AM, Diez Liébana MJ, Fernández Martínez N, Sierra Vega M, García Vieitez JJ. The pharmacokinetics and interactions of ivermectin in humans--a mini-review. AAPS J. 2008;10(1):42-46. doi:10.1208/s12248-007-9000-9

11. Zhang X, Song Y, Xiong H, Ci X, Li H, Yu L et al. Inhibitory effects of ivermectin on nitric oxide and prostaglandin E2 production in LPS-stimulated RAW 264.7 macrophages. Int Immunopharmacol. 2009 Mar;9(3):354-9. doi: 10.1016/j.intimp.2008.12.016.

12. Ci X, Li H, Yu Q, Zhang X, Yu L, Chen N et al. Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway. Fundam Clin Pharmacol. 2009 Aug;23(4):449-55. doi: 10.1111/j.1472-8206.2009.00684.x.

13. Zhang X, Song Y, Ci X, An N, Ju Y, Li H et al. Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. Inflamm Res. 2008 Nov;57(11):524-9. doi: 10.1007/s00011-008-8007-8

14. Ventre E, Rozières A, Lenief V, Albert F, Rossio P, Laoubi L et al. Topical ivermectin improves allergic skin inflammation. Allergy. 2017 Aug;72(8):1212-1221. doi: 10.1111/all.13118.

15. Yan S, Ci X, Chen N, Chen C, Li X, Chu X et al. Anti-inflammatory effects of ivermectin in mouse model of allergic asthma. Inflamm Res. 2011 Jun;60(6):589-96. doi: 10.1007/s00011-011-0307-8.

16. de Melo GD, Lazarini F, Larrous F, Feige L, Kergoat L, Marchio A et al. Anti-COVID-19 efficacy of ivermectin in the golden hamster. bioRxiv 2020.11.21.392639; doi: https://doi.org/10.1101/2020.11.21.392639

17. Navarro, M., Camprubí, D., Requena-Méndez, A., Buonfrate, D., Giorli, G., Kamgno, J., Gardon, J., Boussinesq, M., Muñoz, J. and Krolewiecki, A., 2020. Safety of high-dose ivermectin: a systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy*, 75(4), pp.827-834.

18. NIH ClinicalTrials.gov. [Accessed 14th December]

19. Thu Van Nguyen, Gabriel Ferrand, Sarah Cohen-Boulakia, Ruben Martinez, Philipp Kapp, Emmanuel Coquery, for the COVID-NMA consortium. (2020). RCT studies on preventive measures and treatments for COVID-19 [Data set]. Zenodo. http://doi.org/10.5281/zenodo.4266528

20. Tzou PL, Tao K, Nouhin J, et al. Coronavirus Antiviral Research Database (CoV-RDB): An Online Database Designed to Facilitate Comparisons between Candidate Anti-Coronavirus Compounds. Viruses. 2020;12(9):1006. Published 2020 Sep 9. doi:10.3390/v12091006

21. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

22. 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. [Pre-print]. 28th December 2020. Research Square. https://www.researchsquare.com/article/rs-100956/v3

23. Okumus et al [unpublished] Ivermectin for Severe COVID-19 management. Available at: https://clinicaltrials.gov/ct2/show/NCT04646109. 12th January 2021, date last accessed

24. 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 mild COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial. [Preprint]. 7th December 2020. Research Square. Available at: https://doi.org/10.21203/rs.3.rs-116547/v1

25. Ahmed S, Karim M, Ross A, Hossain M, Clemens J, Sumiya M et al. A five day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis. 2020 Dec 2:S1201-9712(20)32506-6. doi: 10.1016/j.ijid.2020.11.191.

26. Kirti R, Roy R, Pattadar C, Raj R, Agarwal N, Biswas B et al. Ivermectin as a potential treatment for mild to moderate COVID-19: A double blind randomized placebo-controlled trial. [Preprint]. 9th January 2021. Medrxiv. doi: https://doi.org/10.1101/2021.01.05.21249310

27. Podder S, Chowdhury N, Sina M, Ul Haque W. Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomized controlled study. IMC J Med Sci 2020; 14 (2): 002

28. Mohan et al. Randomised controlled trial of ivermectin in hospitalized patients with COVID-19. 2020. Available at: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=44196 [unpublished]

29. Chowdhury et al. A randomised trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients. 2020 [Internet] Available at: https://doi.org/10.21203/rs.3.rs-38896/v1

30. Babaloa et al. Ivermectin shows clinical benefits in mild to moderate COVID19: A randomised controlled double blind dose response study in Lagos. [Internet] available at https://doi.org/10.1186/ISRCTN40302986 [unpublished]
Babalola et al., medRxiv, doi:10.1101/2021.01.05.21249131

31. 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 Pilot Randomised, Controlled, Open Label, Multicentre Trial. [Preprint]. 11th November 2020. SSRN. Available at: http://dx.doi.org/10.2139/ssrn.3714649

32. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med*. 2020;**58**(7):1021-1028. https://doi.org/10.1515/cclm-2020-0369

33. Singh K, Mittal S, Gollapudi S, Butzmann A, Kumar J, Ohgami RS. A meta-analysis of SARS-CoV-2 patients identifies the combinatorial significance of D-dimer, C-reactive protein, lymphocyte, and neutrophil values as a predictor of disease severity. International journal of laboratory hematology. 2020 Oct 3.

34. Niaee M, Gheibi N, Namdar P, Allami A, Zolghadr L, Javadi A et al. Invermctin as an adjunct treatment for hospitalized adult COVID-19 patients: a randomized, multi-center clinical trial. [Preprint]. 24th November 2020. Research Square. Available at: https://doi.org/10.21203/rs.3.rs-109670/v1

35. Rezai et al. Effect of Ivermectin on COVID-19: A multicenter double-blind randomized clinical trial. 2020. Available at: https://en.irct.ir/trial/49174[unpublished]

36. Hashim H, Maulood M, Rasheed A, Fatak D, Kabah K, Abdulamir A. Controlled randomized clinical trial on using Ivermectin with doxycycline for treating COVID-19 patients in Baghdad, Iraq. [Preprint]. 27th October 2020. medRxiv. Available at: https://doi.org/10.1101/2020.10.26.20219345

37. Kramer L, Grandi G, Passeri B, Gianelli P, Genchi M, Dzimianski MT, Supakorndej P, Mansour AM, Supakorndej N, McCall SD, McCall JW. Evaluation of lung pathology in Dirofilaria immitis-experimentally infected dogs treated with doxycycline or a combination of doxycycline and ivermectin before administration of melarsomine dihydrochloride. Veterinary parasitology. 2011 Mar 22;176(4):357-60.

38. Clinicaltrials.gov. NCT04701710. Prophylaxis Covid-19 In Healthcare Agents By Intensive Treatment With Ivermectin And Iota-Carrageenan. Available at: https://clinicaltrials.gov/ct2/show/NCT0470171019 [Accessed 12/01/2021].

39. Clinicaltrials.gov. NCT04422561. Prophylactic Ivermectin In COVID-19 Contacts - Study Results. Available at: https://clinicaltrials.gov/ct2/show/results/NCT04422561. [Accessed 12/01/2021].

40. Wang K, Gao W, Dou Q, Chen H, Li Q, Nice EC et al. Ivermectin induces PAK1-mediated cytostatic autophagy in breast cancer. Autophagy. 2016 Dec;12(12):2498-2499. doi: 10.1080/15548627.2016.1231494.

41. Liu J, Liang H, Chen C, Wang X, Qu F, Wang H et al. Ivermectin induces autophagy-mediated cell death through the AKT/mTOR signaling pathway in glioma cells. Biosci Rep. 2019 Dec 20;39(12):BSR20192489. doi: 10.1042/BSR20192489.

42. Cottam EM, Maier HJ, Manifava M, Vaux LC, Chandra-Schoenfelder P, Gerner W et al. Coronavirus nsp6 proteins generate autophagosomes from the endoplasmic reticulum via an omegasome intermediate. Autophagy. 2011 Nov;7(11):1335-47. doi: 10.4161/auto.7.11.16642.

43. Zhu H, Cong JP, Yu D, Bresnahan WA, Shenk TE. Inhibition of cyclooxygenase 2 blocks human cytomegalovirus replication. Proc Natl Acad Sci U S A. 2002 Mar 19;99(6):3932-7. doi: 10.1073/pnas.052713799.

44. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020 Jun;20(6):363-374. doi: 10.1038/s41577-020-0311-8

45. ClinicalTrials.gov. National Library of Medicine. NCT04523831. Clinical trial of ivermectin plus doxycycline for the treatment of confirmed COVID-19 infection. Available at: https://clinicaltrials.gov/ct2/show/study/NCT04523831 [Accessed 15/12/2020]

46. Spoorthi et al. Utiilty of Ivermectin and Doxycycline combination for the treatment of SARS-CoV-2. IAIM, 2020; 7(10): 177-182.

47. Raad et al. 2020. In vivo use of ivermectin (IVR) for treatment for corona virus infected patients (COVID-19): a randomized controlled trial. 2020
Avaiable at: http://www.chictr.org.cn/showproj.aspx?proj=54707 [unpublished]

48. Asghar et al. Efficacy of Ivermectin in COVID-19. 2020. Available at: https://www.clinicaltrials.gov/ct2/show/NCT04392713?cond=covid-19&intr=ivermectin&draw=2&rank=20 [unpublished]

49. Chachar A, Khan K, Asif M, Khaqan A, Basri R. Effectiveness of ivermectin in SARS-CoV-2 / COVID-19 patients. International Journal of Sciences 09(2020):31-35 DOI: 10.18483/ijSci.2378

List of Tables and figures

Table 1: Trial Summaries

A: Ivermectin trials with Dosing on day 1 only

B: Ivermectin trials with multi-day dosing

Table 2: Changes in Inflammatory Markers

Table 3: Effects of ivermectin on viral clearance

A: Effects of ivermectin on viral clearance (binary)

B: Effects of ivermectin on time to viral clearance

C: Effects of ivermectin on other measures of viral clearance

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

A: Time to clinical recovery

B: Effects of ivermectin on duration of hospitalization

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

Table 5: Effects of ivermectin on survival

Figure 1: Time to viral clearance

Figure 2: Forest plot of survival

Table 1: Trial Summaries

Table 1: Trial Summaries

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

Study	Country	Sample Size	Daily dose	Duration	Patients	Intervention Arm	Comparator Arm
Mahmud et a l [45]	Bangladesh	363	12 mg	1 day (DB)	Mild/ moderate	Ivermectin + Doxycycline + SOC	SOC
Mohan et al [28]	India	157	0.2-0.4 mg/kg (elixir)	1 day (DB)	Mild / moderate	Ivermectin + SOC	Placebo + SOC
Chowdhury [29]	Bangladesh	116	0.2 mg/kg	1 day (DB)	PCR positive	Ivermectin + Doxycycline	HCQ + Azithromycin
Rezai et al [35]	Iran	103	0.2 mg/kg	1 day (DB)	Moderate / severe	Ivermectin + SOC	SOC
Spoorthi et al [46]	India	100	0.2 mg/kg	1 day (DB)	Mild to moderate	Ivermectin + Doxycycline	Placebo
Raad et al [47]	Lebanon	100	0.2 mg/kg	1 day (SB)	Mild	Ivermectin + SOC	SOC
Asghar et al [48]	Pakistan	100	0.2 mg/kg	1 day (OL)	Mild / moderate	Ivermectin + SOC	SOC
Podder et al [27]	Bangladesh	62	0.2 mg/kg	1 day (OL)	Mild	Ivermectin + SOC	SOC
SAINT [24]	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	Intervention Arm	Comparator Arm
Elgazzar et al [22]	Egypt	400	0.4 mg/kg	5 days (OL)	Mild to severe	Ivermectin + SOC	HCQ + SOC
Niaee et al [34]	Iran	180	0.2 - 0.4 mg/kg	1-3 days (DB)	Mild / moderate	Ivermectin + SOC	SOC + Placebo
Hashim et al [36]	Iraq	140	0.2 mg/kg	2-3 days (SB)	Symptomatic	Ivermectin + Doxycycline + SOC	SOC
Kirti et al [26]	India	112	12 mg	2 days (DB)	Mild / moderate	Ivermectin + SOC	SOC + Placebo
Ahmed et al [25]	Bangladesh	72	0.2 mg/kg	5 days (DB)	Mild	Ivermectin + SOC	SOC + Placebo
Okomus et al [23]	Turkey	60	0.2 mg/kg	5 days (DB)	Severe	Ivermectin + SOC	FAVI/HQ/AZI (SOC)
Babaloa et a [30]	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 [31]	Argentina	45	0.6 mg/kg	5 days (OL)	Mild to moderate	Ivermectin + SOC	SOC

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	n.s	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
Okomus, 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	n.s	5.9	3.6	n.s
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	n.s+	-	-	
Ahmed, Bangladesh (n= 46, Ivermectin 1 day)									
Baseline	26.0	29.0		259	222		-	-	
Day 7	11.0	14.0	n.s+	213	218	n.s+	-	-	
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.

+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 IVA 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=103	0.2 mg/kg	1 day	Undetectable Day 7	90% vs 44%	p < 0.001
Mohan et al	India, n=157	0.2mg/kg Elixir	1 day	Undetectable Day 5	35% vs 31%	p = n.s.
Mohan et al	India, n=157	0.4mg/kg Elixir	1 day	Undetectable Day 5	48% vs 31%	p = n.s.
Kirti et al	India, n=112	12 mg	2 days	Undetectable Day 6	24% vs. 32%	p = n.s.
Podder et al	Bangladesh, n=62	0.2 mg/kg	1 day (OL)	Day 10 PCR neg	90% vs 95%	p = n.s.
Okomus et al	Turkey, n=60	0.2 mg/kg	5 days (DB)	Day 10 PCR Neg	88% vs 38%	p = 0.01

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

Study	Country (n)	Daily dose	Duration	Viral load endpoint	Result IVA 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 = n.s.
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 = n.s

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

Study	Country (n)	Daily dose	Duration	Viral load endpoint	Result IVA 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 IVS vs control	P value
Time to clinical recovery						
Mohan et al	India n=157	0.2 mg/kg Elixir	1 day (SB)	Time to clinical recovery	4.8 vs 4.6 days	p = n.s.
Mohan et al	India n=157	0.4 mg/kg Elixir	1 day (SB)	Time to clinical recovery	4.3 vs 4.6 days	p = n.s.
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 = n.s.
Rezai et al	Iran n=103	0.2 mg/kg	1 days (OL)	Time to clinical recovery	4.1 vs 5.2 days	p = 0.018
Spoorthi et al	India n=100	0.2 mg/kg	1 day (SB)	Time to clinical recovery	3.7 vs 4.7 days	p=0.03

Table 4B: Effect of Ivermectin on duration of hospitalization

Study	Country	Daily dose	Duration	Endpoint	Results IVS vs control	P value
Duration of hospitalization						
Rezai et al	Iran n=103	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
Spoorthi et al	India n=100	0.2 mg/kg	1 day (SB)	Time in hospital	6.7 vs 7.9 days	p=0.01
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 Severe	Egypt n=200	0.4 mg/kg	5 days (OL)	Days in hospital	6 vs 18 days	p < 0.001

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

Study	Country	Daily dose	Duration	Endpoint	Results IVS 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 = n.s.
Okomus 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=400	12 mg	1 day (DB)	Day 7 Clinical Recovery	61% vs 44%	p <0.03

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
Okomus 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
Total			**14/658 (2.1%)**	**57/597 (9.5%)**

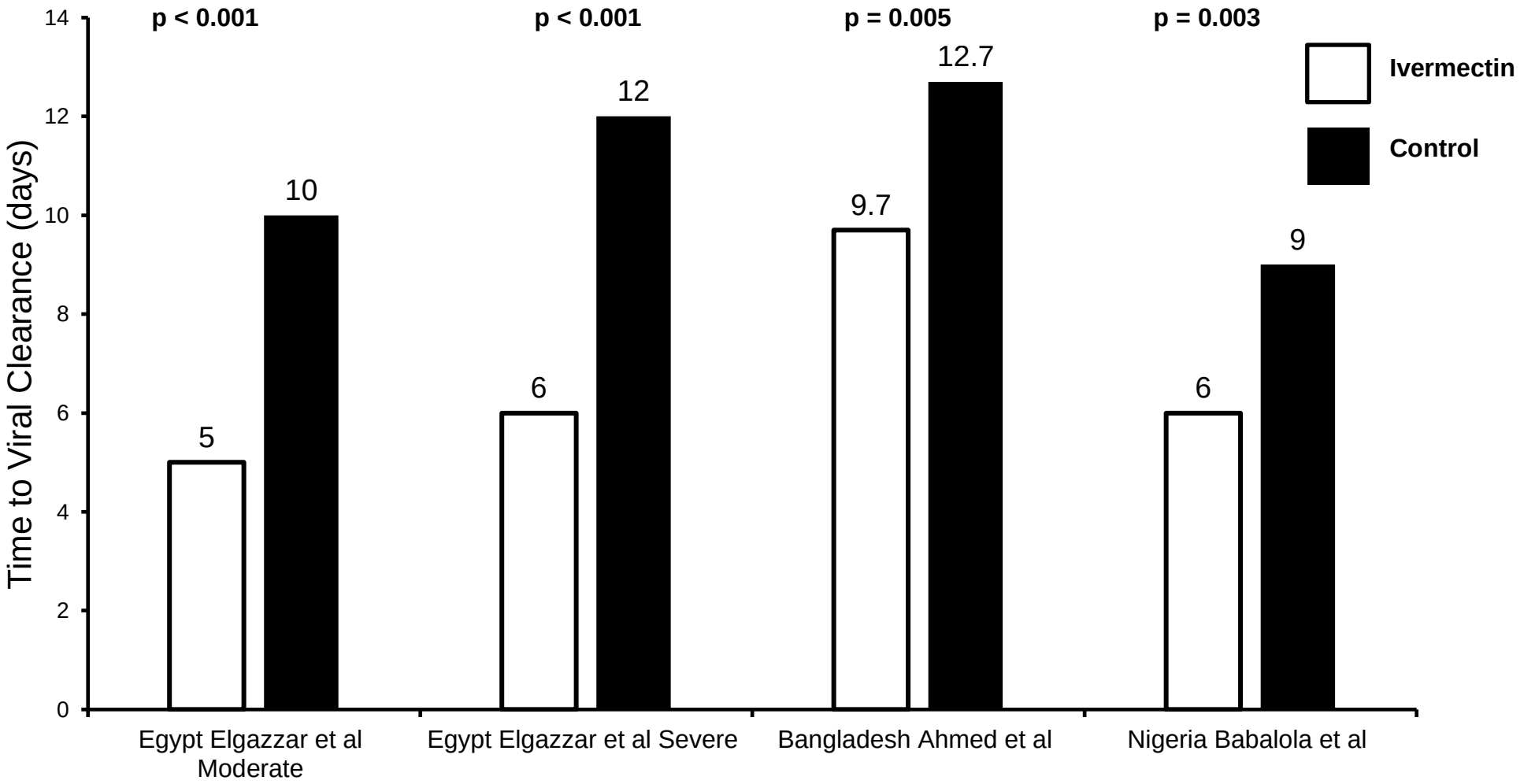

Figure 1: Effects of ivermectin on time to viral clearance

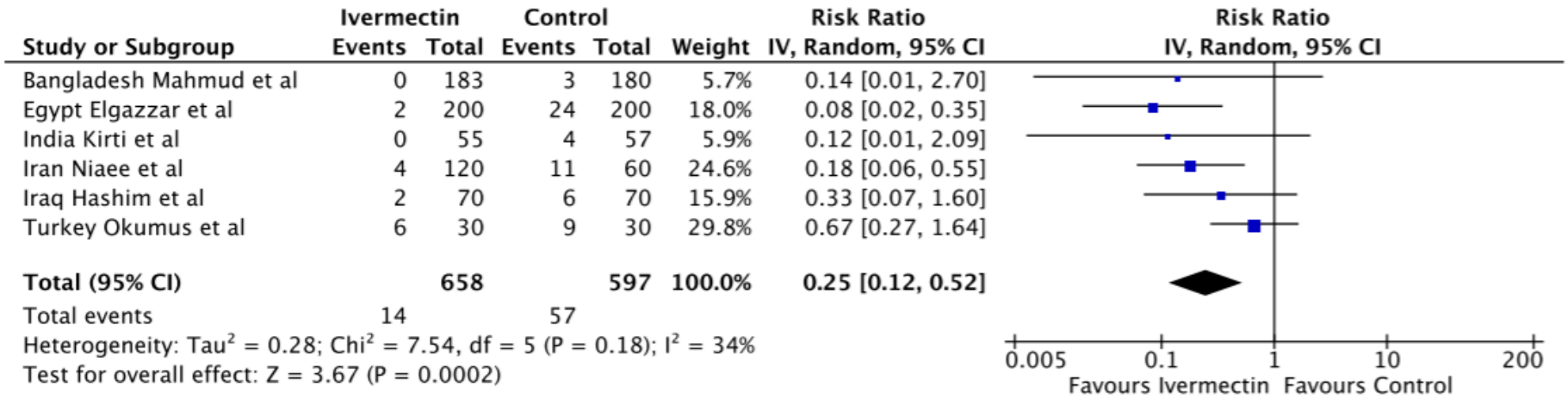

Figure 2: Forest plot of survival.

Supplementary table 1. Assessment of Risk of Bias

Graded low, high or unclear risk of bias on the bases of the prespecified criteria set out in the Cochrane Risk of Bias Tool

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Overall Quality of Evidence
Mahmud et a l [R2]	Low	Low	Low	Low	High (*21% of patients randomized not included in the analysis)*	Unclear	**Limited**
Mohan et al [R14]	Unclear	Unclear	Low *(Unblinded but objective outcome measure (PCR and viral load)*	Unclear	Unclear	Low	**Limited**
Chowdhury [R15]	High *(Odd/Even randomization based on registration numbers)*	Unclear	Unclear	Unclear	Low	Low	**Limited**
Rezai et al [R13]	Low	Low	Low	Low	Low	Unclear	**Fair**
Spoorthi et al [R10]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	**Limited**
Raad et al [R11]	Unclear	Unclear	Low	Low	Unclear	Unclear	**Limited**
Asghar et al	Unclear	Unclear	Unclear	Low	High *(5% (control) vs 18% (ivermectin) attrition rate between arms)*	Low	**Limited**
Podder et al [R6]	High *(Odd/Even randomization based on registration*	Unclear	High *(Open Label + primary endpoint symptoms resolution (subjective element))*	High *(Open Label + primary endpoint symptoms resolution*	Unclear	Unclear	**Limited**

	numbers)			*(subjective element))*			
SAINT [R9]	Low	Low	Low	Low	Low	Low	**Good**
Elgazzar et al [R1]	Unclear	Unclear	Low *(Unblinded but primary endpoint based on PCR and laboratory markers)*	High *(Investigators interpreting and collating results were unblinded)*	Unclear	Unclear	**Limited**
Niaee et al [R3]	Low	Low	Low *(Unblinded - but objective outcome measures used (lab markers)*	Unclear	Low	Low	**Fair**
Hashim et al [R4]	High *(Randomization based on date of enrollment)*	High *(Randomization based on date of enrollment)*	High *(Unblinded and outcome dependent on reporting of symptoms)*	High *(Unblinded - outcome dependent on subjective judgement of disease progression)*	Unclear	Low	**Limited**
Ahmed et al [R5]	Unclear	Unclear	Low	Low	Low	Low	**Fair**
Okomus et al [R16]	Unclear	Unclear	Low *Objective measures (Lab/PCR/FiO2/Mortality)*	Unclear	Unclear	Unclear	**Limited**
Babaloa et a [R17]	Unclear	Unclear	Low	Low	Low	Low	**Fair**
Chachar et al [R7]	Low	Low	High *Open Label + primary endpoint symptoms resolution (subjective element)*	High *Open Label + primary endpoint symptoms resolution (subjective element)*	Low	Unclear	**Limited**
Krolewiecki et al [R8]	Unclear	Unclear	Low (*Low Risk Bias - Objective measures*	Unclear	Unclear	Unclear	**Limited**

			(Lab/PCR/FiO2/Mortality))				
Kirti et al [R18]	Low	Low	Low	Low	Low	Low	**Good**