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Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines. *American Journal of Therapeutics*, 28, e434–e460, July 2021

To the Editor:

Our meta-analysis of trial data on ivermectin for prevention and treatment of COVID-19[1] is potentially affected by a recent newspaper article[2] making 2 significant claims. First, the preprint manuscript by Elgazzar et al[3] has been withdrawn; second, "if you get rid of just this research, most meta-analyses that have found positive results would have their conclusions entirely reversed." The first claim seems untrue at this writing and the second unsustainable.

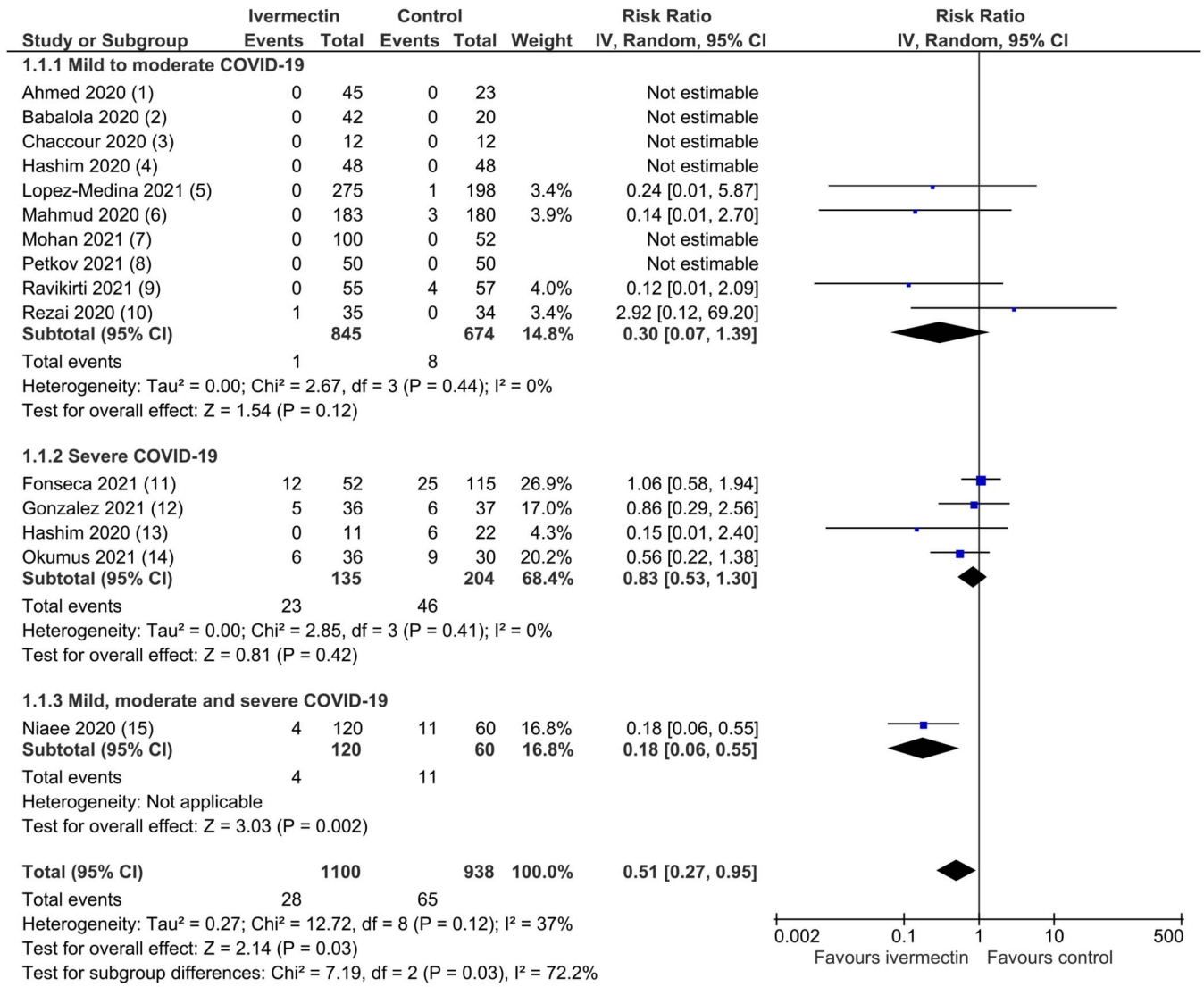
The preprint server *Research Square* makes explicit[3] that the preprint was not withdrawn by the authors but removed on receipt of a complaint, and Prof. Elgazzar has confirmed[4] that this was without any opportunity of reply. The complaints have been denied as defamatory, and his manuscript is said to remain under review for publication elsewhere. Currently, these claims and counterclaims have appeared only in news and social media and have had no independent adjudication.

Our inclusion of Elgazzar[3] was in full conformity with the PRISMA guidelines[5] which encourage the use of unpublished data, supported where necessary by direct author inquiries, to ameliorate tendencies to publication bias. Such inquiries were indeed made during the review process. Where satisfactory clarification was received, the data were included. We had no basis for excluding a trial that met the inclusion criteria of our review protocol. This applied equally to the study by Lopez-Medina et al[6] that has also received postpublication criticism[7] for its trial protocol violations (with different consequences to the analysis) but likewise met our review protocol inclusion criteria. The mechanism in systematic reviews for noting doubts over reliability lies in the risk of bias assessments, made appropriately in both cases.

Pending clarification of data reliability in the study by Elgazzar et al,[3] we turn to the second claim made in the press[2] that conclusions are reversed if this study is removed. If Figure 3 in the study by Bryant et al[1] is reanalyzed to exclude the study by Elgazzar,[3] there is still a clear result, showing a 49% reduction in mortality in favor of ivermectin (aRR = 0.51, 95% confidence interval 0.27–0.95) (Figure 1). Similarly, if we conduct the same sensitivity analysis in Figure 15 (prophylaxis outcome), there was an 87% reduction in COVID-19 infection in favor of ivermectin (aRR = 0.13, 95% confidence interval 0.08–0.21) (Figure 2), virtually unchanged from the previous analysis. Revised Figures are shown below. Hence, the leading outcome conclusions (ie, for mortality and prophylaxis) are robust to the removal of the study by Elgazzar,[3] contrary to the press claims.[2]

Removal of a single study is part of the exercise of a "leave one out" sensitivity analysis. This has already been performed by others,[8] finding similarly that the evidence for ivermectin efficacy is robust. Other meta-analyses on selected subsets of the known randomized trials are already available. The WHO "Living Guideline"[9] noted in our Discussion[1] already excluded the study by Elgazzar[3] in March yet reported a mortality odds ratio reduction of 81%, with narrow 95% confidence intervals. Roman et al[10] have recently offered a reduced data set, including the study by Elgazzar.[3] Their conclusion that ivermectin shows no mortality advantage has been elegantly refuted by Neil and Fenton[11] in a Bayesian analysis of the same trial subset. This approach is likewise amenable to a sensitivity analysis removing the study by Elgazzar.[3] Preliminary findings[12] still show positive benefit in mortality. The Bayesian approach is of course applicable to other trial data selections, including our own. These will be reported in due course.

In conclusion, accusations of fraud are of course very serious. Prof. Elgazzar and colleagues must however be given appropriate opportunity to respond. A comprehensive correction to our meta-analyses will be issued if the data are found to be unreliable, but this would be premature while accusations remain disputed.



Footnotes

(1) IVM 12mg x 5 days (24 pts) or IVM 12 mg + doxy x 5 days (24 pts)
(2) IVM 6mg-12mg every 84 hrs for 2 wks; vs lopinavir/ritonavir
(3) IVM 0.4mg/kg single dose
(4) IVM 0.2mg/kg x 2-3 days + Doxy 100 mg BID x 10 days
(5) IVM 0.3mg/kg solution for 5 days vs placebo solution
(6) IVM 6mg once + Doxy 100 mg x 5 days
(7) IVM 12mg or 24 mg single dose
(8) IVM 0.4mg/kg x 3 days
(9) IVM 12 mg x 2 days
(10) IVM 0.2mg/kg single dose
(11) IVM 14 mg x 3 days vs HCQ x 5 days or CQ x 5 days
(12) IVM single dose 12mg or 18mg depending on weight
(13) IVM 0.2mg/kg x 2-3 days + Doxy 100 mg BID x 10 days
(14) IVM 0.2mg/kg x 5 days (both arms received HCQ, favipiravir, azithromycin)
(15) IVM 0.2mg/kg to 400 µgm/kg (1 to 3 doses) vs HCQ

FIGURE 1. Mortality outcome analysis as in Figure 3 of the study by Bryant et al[1] but with the study by Elgazzar[3] removed.

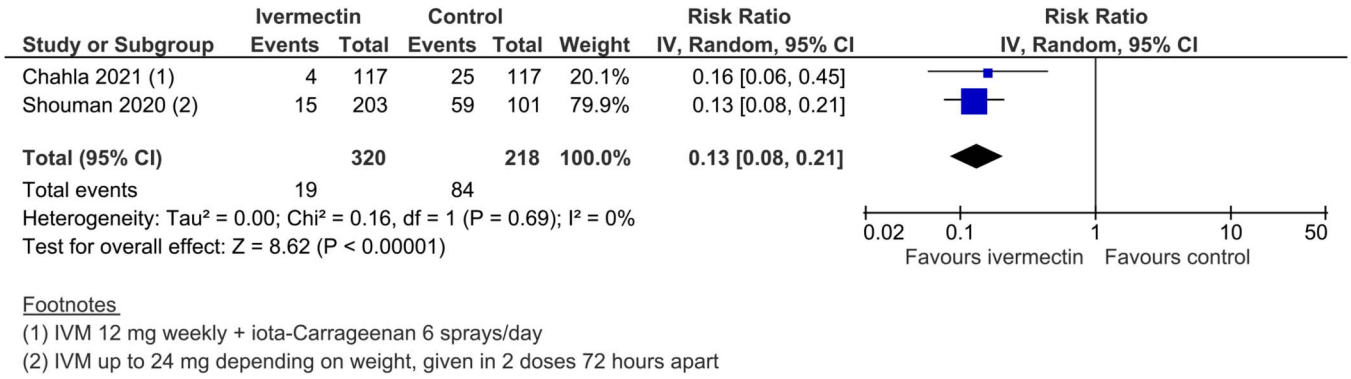


FIGURE 2. Prophylaxis outcome analysis as in Figure 15 of the study by Bryant et al[1] but with the study by Elgazzar[3] removed.

Pending resolution of the conflicting claims and counterclaims, we simply point out that while quantitative measures of effect do of course change on removal of any study, the overall findings of a significant mortality advantage in ivermectin treatment, and in prophylaxis, remain robust to removal of the disputed data. The claim that conclusions are "entirely reversed"[2] cannot be sustained on the evidence.

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The authors have no conflicts of interest to declare. With regard to the authorship of the original article (and the present Letter), all authors except Dr. Dowswell attended the BiRD (British Ivermectin Recommendation Development) meeting comprised of medical doctors, healthcare professionals and other stakeholders, with international representation, which was convened for an "Evidence to Decision" framework event on 20 February 2021. A. Bryant and T. A. Lawrie were members of the Steering Group and did not vote on the decisions. E. J. Fordham, Hill, Mitchell and Tham were ordinary members of the panel. The panel voted to recommend the deployment of ivermectin for the treatment and prevention of Covid-19, upon an evidence base comprising an earlier version of the meta-analysis as published in Am. J. Therap., plus additional supporting evidence. BiRD remains an unincorporated, not-for-profit, ad hoc association with no financial or material interests in ivermectin or any other medicine or any other product. Its continuing activities are transparently managed through EbMCsquared, a not-for-profit Community Interest Company.

E. J. Fordham is a member of HART (Health Advisory and Recovery Team) a British not-for-profit, unincorporated membership association, wherein all consulting members collaborate on an entirely voluntary (unpaid) basis for research on multiple aspects of public health policy relating to Covid-19. HART has no material or financial interests in ivermectin or any other medical product. E. J. Fordham is not a member of its Executive Committee. HART bulletins are circulated to UK Parliamentarians but it remains firmly non-party political.

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Bayesian Hypothesis Testing and Hierarchical Modeling of Ivermectin Effectiveness

To the Editor:

A recent meta-analysis of the trials evaluating ivermectin that was published in AJT[1] (referred to here as Bryant) was widely welcomed by those who argue that this antiparasitic drug is a cheap and effective treatment for COVID-19 infections. The study concluded:

> "Moderate-certainty evidence finds that large reductions in COVID-19 deaths are possible using ivermectin. Using ivermectin early in the clinical course may reduce numbers progressing to severe disease. The apparent safety and low cost suggest that ivermectin is likely to have a significant impact on the severe acute respiratory syndrome coronavirus 2 pandemic globally."

These conclusions stand in stark contrast to those of a later meta-analysis[2] (referred to here as Roman) that looked at a subset of the trials. Roman concluded:

> "In comparison to standard of care or placebo, ivermectin (IVM) did not reduce all-cause mortality, length of stay, or viral clearance in randomized controlled trials in COVID-19 patients with mostly mild disease. IVM did not have effect on adverse events or severe adverse events. IVM is not a viable option to treat COVID-19 patients."

Irrespective of the errors in the data and the analysis performed by Roman that were already highlighted by Crawford,[3] we believe that this conclusion is not based on the results of the statistical analysis of the data, which were very similar to those of Bryant; instead, it was based on a somewhat vague and possibly biased subjective assessment of the quality of the trials themselves and erroneously concluding "no effect" from what was merely weaker evidence of a positive effect.

In a recently completed analysis[4] we have applied a Bayesian approach, to what we believe are the relevant trials data used by Bryant and Roman (we made a number minor necessary changes to the trials, including removing the Niaee study[5]). Applying diverse alternative analysis methods, which reach the same conclusions, should increase overall confidence in the result.

The Bayesian approach brings with it several advantages over the classical statistical approaches applied to this trials' data thus far:

1. It allows the evaluation of competing causal hypotheses: we can test whether COVID-19 mortality is independent of COVID-19 severity, treatment, or both treatment and severity. The results show that the posterior probability for the hypothesis of a causal link between COVID-19 severity, ivermectin, and mortality is over 99%.