Rapid Response to Editor of *BMJ Evidence Based Medicine*

Re: Popp M, Kranke P, Meybohm P*, et al*. Evidence on the efficacy of ivermectin for COVID-19: another story of apples and oranges. *BMJ Evidence-Based Medicine* Published Online First: 20 August 2021. doi: 10.1136/bmjebm-2021-111791

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To the Editor

The integrity of our meta-analyses of trial data on Ivermectin for prevention and treatment of Covid-19[1] is questioned[2] by authors of a recent Cochrane review[3]. We agree that misleading information on Covid-19 treatment abounds in social and mainstream media[3] as well as in journal opinion pieces[4,5]. However, Bryant et al[1] is a non-commissioned research paper that strictly followed PRISMA[6] systematic review guidelines.

Popp et al.[3] itself contains several misleading items. The authors rehearse the outdated objection that whilst Ivermectin slows the reproduction[7] of SARS-CoV-2, "such effects would need major doses [e.g.[8]] in humans". This conjecture has long been falsified by the results of formal trials and clinical experience worldwide, at 1 – 3 times the anti-parasitic dose[9]. Professor Chris Whitty (CMO England), has stated: "The drug [Ivermectin] has proven to be safe. Doses up to 10 times[10] the approved limit [200 mcg/kg] are well tolerated by healthy volunteers. Adverse reactions are few and usually mild"[11].

Popp *et al.*[2] state "careful grading of the certainty of evidence", implying that Bryant *et al.*[1] did not. The review team for Bryant *et al.*[1] included three highly experienced systematic reviewers two of whom are guideline methodologists. In addition to applying GRADE criteria[12], we used WHO guidance[13] to rate the certainty of the evidence and conducted a series of sensitivity analyses to test the robustness of the findings.

Death being a wholly objective outcome, Risk of Bias (RoB) domains such as blinding are, for mortality, far less important. Popp *et al.*[3] fail to recognise this; their blanket approach inappropriately undermines their evidence certainty. In addition, they excluded trials reported on preprint and split up those remaining into artificial subgroups, so that the number of trials and participants was minimal for each "analysis". Actual meta-analyses are few, reducing their "systematic review" to an (incomplete) bibliography with synopsis of results.

Consequently, the authors failed to address a wider body of evidence. Preprints facilitate timely dissemination of results, e.g. during health emergencies. In 2015, the WHO stated[14] that "pre-publication information sharing should be the norm in future health emergencies", yet Popp *et al.*[3] chose to exclude them. Fragmentation of data was driven by analysing inpatient and outpatient data as separate comparisons. This left few data to pool.

Further misleading reporting by Popp *et al.*[3] includes the inappropriate use of 'death' (rather than 'infection') for the prophylaxis outcome, leading to a contrived conclusion of "insufficient evidence". Furthermore, they applied a pre-designed outcome measure 'PCR+ at 14 days' to define Covid-19 infection. By specifying the time point, they "found no data". Prophylaxis trials did not report Covid-19 tests at day 14. However, other measures of Covid-19 infection (PCR+ or symptomatic Covid at any point) were reported, but ignored.

Popp *et al.*[2] describe our review as a "bowl of colourful fruit salad"[2] because of our pre-specified comparison of "ivermectin" *vs* "no ivermectin". We did include trials with (potentially) active comparators. A moment's reflection should show that any bias is conservatively *against* ivermectin. It strengthens, not weakens, positive findings. Helpful control interventions would dilute the apparent benefit of ivermectin, relative to placebo comparators exclusively. If the outcome were the cure of scurvy, stronger results would be expected in comparing a diet of oranges to peeled potatoes, than if the comparator were fruit-salads rich in other citrus fruits. Only if all comparators were equally active would meta-analyses fail to demonstrate the value of oranges for scurvy. And the bias would understate, not overstate, their value.

Popp *et al.*[3] are themselves inconsistent regarding (potentially) active comparators. They state that hydroxychloroquine "does not work" for covid-19, yet excluded trials comparing ivermectin to a drug they hold to be inactive. Contrariwise, remdesivir was an acceptable comparator, though in some jurisdictions held to be an effective standard of care.

The approach of Popp *et al.*[3] thus offers no insight into an important research question in a health emergency requiring rapid decision-making. We affirm our pragmatic approach in Bryant *et al.*[1], including all possible ivermectin trials, rather than attempting to cherry-pick trials based on pre-conceptions of the efficacy of comparators. The pooled trials in Bryant *et al.*[1] were assessed as sufficiently homogeneous for inclusion in our meta-analyses, according to recognised criteria[15].

The effects found in Bryant *et al*.[1] involved point estimates across trials that were almost universally in the same direction and consistently favoured Ivermectin[1]. Our sensitivity analyses[1] show that, contrary to some claims, the headline mortality advantage is robust to removal of individual trials. In particular, it is robust to the removal of a recently disputed trial[16], as we show explicitly elsewhere[17]. Moreover a recent Bayesian analysis[18, 19] systematically shows that the hypothesis of a therapeutic effect remains sustained even after removal of *two* contested trials.

It is inappropriate for Popp *et al.* to claim[2] that we "misuse established evidence assessment tools as a guise for quality of evidence synthesis"[2], in reference to work by researchers with extensive experience in evidence synthesis. They further claim that Bryant *et al*.[1] tried "to create pseudo-trustworthiness" insinuating that we have deliberately tried to create, not solve, public health problems. Open scientific debate is essential, but should focus on material facts and logical reasoning. The basis of the critique[2] of Popp *et al.* remains unclear.

Instead of using all available evidence and presenting appropriate caveats, their own contribution[3] disregards sources selectively and presents threadbare analyses.

In a pandemic context, the benefits of Ivermectin almost certainly outweigh any risks, given its outstanding safety profile, negligible base cost, and the existing large body of evidence showing that ivermectin provides benefit in a variety of important clinical outcomes[20, 1, 21].

Word Count: 925 words

References

[1] Bryant A, Lawrie TA, Dowswell T, et al. Ivermectin for prevention and treatment of covid-19 infection: a systematic review, meta-analysis, and trial sequential analysis to inform clinical guidelines. *Am J Therap* 2021;28:e434–460. doi:10.1097/MJT.0000000000001402

[2] Popp M, Kranke P, Meybohm P*, et al*. Evidence on the efficacy of ivermectin for covid-19: another story of apples and oranges. *BMJ Evidence-Based Medicine* Published Online First: 20 August 2021. doi: 10.1136/bmjebm-2021-111791

[3] Popp M, Stegemann M, Metzendorf M-I, et al. Ivermectin for preventing and treating covid-19. Cochrane Database Syst Rev 2021;7:CD015017. doi:10.1002/14651858.CD015017.pub2 pmid:http://www.ncbi.nlm.nih.gov/pubmed/34318930

[4] Parrish, A. G., Blockman, M., Cohen, K., Dawood, H., de Waal, R., Gray, A. L., Kredo, T., Leong, T. D., Nel, J., Rees, H. & Reubenson, G. (2021). Meta-analytic magic, ivermectin, and socially responsible reporting. *South Africa Medical Journal*, http://www.samj.org.za/index.php/samj/article/view/13373

[5] Garegnani, L. I., Madrid, E. & Meza, N. (2021). Misleading clinical evidence and systematic reviews on ivermectin for COVID-19. *BMJ Evidence-Based Medicine* , . doi: 10.1136/bmjebm-2021-111678

[6] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372. doi: 10.1136/bmj.n71. Accessed 22 July 2021.

[7] Caly, L., Druce, J. D., Catton, M. G., Jans, D. A. & Wagstaff, K. M. (2020). The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Research*, 178, 104787. doi: https://doi.org/10.1016/j.antiviral.2020.104787

[8] Schmith, V. D., Zhou, J. (J. & Lohmer, L. R. (2020). The Approved Dose of Ivermectin Alone is not the Ideal Dose for the Treatment of COVID-19. *Clinical Pharmacology and Therapeutics* , 108, 762-765. doi: https://doi.org/10.1002/cpt.1889

[9] Front-Line Covid-19 Critical Care Alliance (2021). The "I-MASK+" Prevention and Early Treatment protocol for Covid-19. https://covid19criticalcare.com/wp-content/uploads/2020/11/FLCCC-Alliance-I-MASKplus-Protocol-ENGLISH.pdf Accessed 3 September 2021

[10] Guzzo, C., Furtek, C., Porras, A., Chen, C., Tipping, R., Clineschmidt, C., Sciberras, D., Hsieh, J. & Lasseter, K. (2002). Safety, Tolerability, and Pharmacokinetics of Escalating High

Doses of Ivermectin in Healthy Adult Subjects. *Journal of Clinical Pharmacology*, 42, 1122-1133. doi: https://doi.org/10.1177/009127002237994

[11] Chaccour, C., Lines, J. & Whitty, C. J. M. (2010). Effect of Ivermectin on *Anopheles gambiae* Mosquitoes Fed on Humans: The Potential of Oral Insecticides in Malaria Control. *Journal of Infectious Diseases*, 202, 113-116. doi: 10.1086/653208

[12] GRADE Working Group 2020). GRADE 2020: Grading of Recommendations Assessment, Development and Evaluation (GRADE) https://www.gradeworkinggroup.org

[13] World Health Organization (2014). *WHO handbook for guideline development*. https://apps.who.int/iris/handle/10665/145714

[14] Modjarrad, K., Moorthy, V. S., Millett, P., Gsell, P.-S., Roth, C. & Kieny, M.-P. (2016). Developing Global Norms for Sharing Data and Results during Public Health Emergencies. *PLOS Medicine*, 13, 1-5. doi: 10.1371/journal.pmed.1001935. Previously published as a Statement from a WHO Consultation held on 1-2 September 2015.

[15] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

[16] Elgazzar, A., Hany, B., Youssef, S. A., Hafez, M., Moussa, H. & Eltaweel, A. (2020). Efficacy and Safety of Ivermectin for Treatment and prophylaxis of COVID-19 Pandemic. *Research Square* preprint (marked "withdrawn") doi: 10.21203/rs.3.rs-100956/v2

[17] Bryant, A., Lawrie, T. A. & Fordham, E. J. (2021). Letter to the Editor, *Am. J. Therapeutics,* to appear 7 September 2021.

[18] Neil, M. & Fenton, N. E. (2021). Bayesian Meta Analysis of Ivermectin Effectiveness in Treating Covid-19 Disease. *Research Gate* preprint doi: 10.13140/RG.2.2.31800.88323 12 July Accessed 3 September 2021

[19] Neil, M. & Fenton, N. E. (2021). Bayesian Meta Analysis of Ivermectin Effectiveness in Treating Covid-19 (with sensitivity analysis to account for possibly flawed studies). *Research Gate* preprint. doi: 10.13140/RG.2.2.19713.58723 Accessed 3 September 2021.

[20] Kory, P., Meduri, G. U., Varon, J., Iglesias, J. & Marik, P. E. (2021). Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19. *American Journal of Therapeutics*, 28, e299-e318. doi: 10.1097/MJT.0000000000001377

[21] Hill A, Garratt A, Levi J, et al. Meta-analysis of randomized trials of Ivermectin to treat SARS-CoV-2 infection. *Open Forum Infect Dis.* 2021. doi: 10.1093/ofid/ofab358. Accessed 22 July 2021.