Rapid Response, *BMJ Evidence-Based Medicine*

<https://ebm.bmj.com/content/early/2021/08/19/bmjebm-2021-111791.responses#rapid-response-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

Ivermectin in Covid-19

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To the Editor

(361 words)

The sole substantive critique in this Letter¹ is the description of Bryant² *et al.* (hereafter “Bryant”) as a “bowl of colourful fruit salad”¹, because of the pre-specified comparison of “ivermectin” vs “no ivermectin”. Trials with (potentially) active comparators were indeed included. Reflection should show that any bias is conservatively *against* ivermectin. Helpful control interventions would dilute the apparent benefit of ivermectin, relative to inactive comparators exclusively. Efficacy will be understated, not overstated, with respect to controls.

Unsuspected active agents in ivermectin combination therapies might contribute bias the other way, but could only bias a meta-analysis toward an illusory conclusion of ivermectin efficacy if the same adjunct were dominant among studies or patients. An effective “Adjunct X” (ivermectin presumed ineffective) and synergy between the two would not be resolved, but either way an effective therapy would have been demonstrated.

Specifically, in Bryant², the only candidate (cited in Popp et al.³ – hereafter “Popp” – as grounds for exclusion) is doxycycline, which contributed just three included studies^{4,5,6} coming nowhere near dominance in Bryant².

The principal flaw in Popp³ is the exclusion of all prior data not conforming to their own *post hoc* specification, by which device most available evidence is simply disregarded. Tidy experimental design is no doubt to be welcomed, but wilful disregard of available but untidy evidence, merely because some thought may be required in interpretation, is intellectual laziness.

The insinuation¹ that Bryant did not perform “careful grading of the certainty of evidence” is baseless. The review team included three highly experienced systematic reviewers two of whom are guideline methodologists. GRADE criteria⁷, and WHO guidance⁸, were used to rate evidence certainty.

The further claims¹ that Bryant² “misuse[s] established evidence assessment tools as a guise for quality of evidence synthesis”¹ and tried “to create pseudo-trustworthiness” are unsupported by any evidence. Misleading information certainly abounds in social media¹ as well as journal opinion pieces^{9,10}. However, Bryant² is a non-commissioned research paper that followed PRISMA¹¹ systematic review guidelines and has no motives other than disinterested humanitarian ones, following other reviews of the large body of evidence of ivermectin’s utility in Covid-19¹². In a learned journal, unsupported assertions of insincere motives are best left to answer themselves.

Conflicts of interest: AB TAL EJF and SM are co-authors of Ref [2] attacked in the Letter [1]. They were members of the British Ivermectin Recommendation Development (BiRD) panel at the “Evidence to Decision” event convened on 20 February 2021. TAL and AB were members of the steering group and did not vote. EJF and SM were ordinary members of the panel. BiRD is a public information activity managed by EbMCsquared, a non-profit Community Interest Company funded by public donations. EJF and SM are unpaid volunteers entirely without financial interest. EJF is a member of the Health Advisory and Recovery Team (HART), an unincorporated membership association with no financial or material interests in ivermectin or any other medical product. This work, and Ref [2], are not projects of HART, and are not funded or influenced in any way by them.

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