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Evidence on the efficacy of ivermectin for COVID-19: another story of apples and oranges

Maria Popp ,¹ Peter Kranke,¹ Patrick Meybohm,¹
 Maria-Inti Metzendorf ,² Nicole Skoetz ,³
 Miriam S Stegemann,⁴ Stephanie Weibel ¹

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¹Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, University Hospital Würzburg, Würzburg, Bayern, Germany

²Institute of General Practice, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany

³Evidence-Based Oncology, Department I of Internal Medicine, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

⁴Department of Infectious Diseases and Respiratory Medicine, Humboldt-Universität zu Berlin, Berlin, Germany

Correspondence to:
Dr Stephanie Weibel,
 Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, University Hospital Würzburg, 97080 Würzburg, Germany; weibel_s@ukw.de



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The antiparasitic ivermectin has received particular attention as a potential treatment option for COVID-19. Understandably, there is high interest in repurposing an approved inexpensive drug, readily available as an oral formulation. However, Garegnani *et al*¹ recently pointed out the proportion of misleading information on ivermectin for COVID-19 published in journals, on preprint servers and websites.

A relevant number of systematic reviews report the use of methodological tools such as assessing bias at study level with the Cochrane Risk of Bias tool or grading the certainty of the evidence following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, thus suggesting a putative high credibility. Indeed, some published findings seem impressive. A recent meta-analysis by Bryant *et al* found that ivermectin reduces the risk of death by an average of 62% (RR 0.38, 95%CI 0.19 to 0.73) compared with no ivermectin in hospitalised patients.²

In our Cochrane Review,³ we assessed the identical set of trials. However, only 4 of the 15 trials included in Bryant's meta-analysis on mortality met our predefined eligibility criteria, and our conclusion, incorporating careful grading of the certainty of evidence, reveals a less rosy picture. The bottom line demonstrates an important uncertainty whether ivermectin compared with placebo or standard of care reduces or increases mortality in moderately ill hospitalised patients (RR 0.60, 95%CI 0.14 to 2.51; two studies) and mildly ill outpatients (RR 0.33, 95%CI 0.01 to 8.05; two studies), due to serious risk of bias and imprecision. How do the different assessments come about? The answer lies partly in the baseline data of included studies. Bryant *et al* pooled heterogeneous patient populations, interventions, comparators and outcomes. In other words, they compare apples and oranges, serving a large bowl of a colourful fruit salad. Usually, pooling of heterogeneous studies increases imprecision of effects in meta-analyses. Why does this not apply to ivermectin? Its alleged effect is driven by studies where the effect size is extremely positive, which has influenced the conclusions in other reviews. One of these studies with a huge effect has now been retracted over ethical concern.⁴

Evidence syntheses must be pieces of the highest trustworthiness. However, reliability is at risk when researchers publish problematic trials or misuse established evidence assessment tools as a guise for quality of evidence synthesis in general, but

especially during a pandemic, by trying to create pseudotrustworthiness for substances that cannot be considered effective and safe treatment options nor game changers, at this stage.

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ORCID iDs

Maria Popp <http://orcid.org/0000-0002-1155-3060>

Maria-Inti Metzendorf <http://orcid.org/0000-0002-4154-5782>

Nicole Skoetz <http://orcid.org/0000-0003-4744-6192>

Stephanie Weibel <http://orcid.org/0000-0003-1900-2535>

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