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Ivermectin Should Not Be Recommended to Treat Severe Acute Respiratory Syndrome 2 Infection

To the Editor—Ivermectin is increasingly being used to treat coronavirus disease 2019 (COVID)-19 in South America and Africa, despite a lack of robust evidence that such treatment improves clinical outcome. Currently in South Africa, confronted with a third wave of COVID-19 infections, people are even turning to illicit sources to obtain ivermectin [1].

In their meta-analysis of the efficacy of ivermectin to treat COVID-19, published in this journal, Hill et al [2] found that ivermectin reduces clinical recovery time by 1.58 days and mortality from 9.5% to 2.1%. It is the fifth systematic review published on the topic, and 1 of 4 that concludes that there is currently insufficient evidence to recommend ivermectin for the treatment of COVID-19, and that this drug should only be used in clinical trials [3–5]. The only systematic review to conclude that there was strong evidence that ivermectin reduces hospitalization and mortality in COVID-19 patients was first retracted from publication in *Frontiers in Pharmacology* due to unsubstantiated claims, and later published in the *American Journal of Therapeutics* [6].

The problem with most ivermectin trials carried is their small sample size (less than 500 participants) and poor quality, which makes it difficult to interpret the results. This is illustrated by the fact that the risk for bias of the different studies is evaluated differently in the different reviews (see Table 1).

Since these 5 systematic reviews were published, the results of a new clinical trial have been published [7]. This trial was a well designed, double-blind, and placebo-controlled trial that enrolled 500 persons per arm. Currently, it is the second largest trial that assesses the effect of ivermectin on COVID-19 outcomes. Although it is still underpowered due to a lower percentage of events than expected, this trial did not detect a significant effect of ivermectin on preventing hospitalization nor the need for mechanical ventilatory support [7]. The only other randomized controlled trial considered to be at a low risk for bias in all the systematic reviews also found that ivermectin had no beneficial effect on time-to-recovery (Lopez-Medina et al) (Table 1). Both of these trials were peer-reviewed and published in reputable journals. All of the other trials were either much smaller, not placebo-controlled,

Table 1. Overview Risk of Bias of Primary Outcome, PCR Outcomes, and Survival Outcomes as Evaluated in Four Systematic Reviews Evaluating the Efficacy of Ivermectin in the Treatment of COVID-19 Infection

	Trial Characteristics										
Article	Outcome	Randomized	Placebo	Double-Blind	Sample Size	Peer Review	Underpower	Hill et al [2]	Zein et al [5]	Roman et al [3]	WHO
Elgazzar et al [8] *Res Square*	Recovery	Y	N	?	600	N	N	Low risk	High risk	X	X
Hashim et al [9] *medRxiv*	Mortality, recovery	Y	N	N	140	N	Y	High risk	High risk	X	X
Mahmud et al [10] *J Int Med Res*	Mortality, recovery	Y	N	Y	363	Y	Y	SC	High risk	X	X
Ahmed et al [11] *Int J Infect Dis*	Mortality, hospital, recovery	Y	N	?	72	Y	Y	Low risk	X	High risk	X
Lopez-Medina et al [12] *JAMA*	Recovery	Y	Y	Y[a]	398	Y	N	Low risk	Low risk	X	Low risk
Galan et al [13] *Pathog Glob Health*	Mortality, IC[b]	Y	N	Y	168	Y	N	Low risk	Low risk	X	X
Ravikirti et al [14] *medRxiv*	Mortality, IC, recovery	Y	Y	Y	112	N	Y	SC	X	X	SC
Mohan et al [15] *Res Square*	Hospital, IC, recovery	Y	Y	Y	125	N	Y	SC	X	X	Low risk
Okumus et al [16] *BMC Infect Dis*	Recovery, IC[b]	Y	N	N	66	Y	?	SC	High risk	X	X
Gonzalez et al [17] *medRxiv*	Mortality, hospital	Y	N	Y	106	N	Y	SC	X	X	Low risk
Podder et al [18] *IMC J Med Sci*	Recovery	Y	N	N	62	Y	Y	High risk	X	High risk	X

Abbreviations: COVID-19, coronavirus disease 2019; IC, intensive care; N, no; PCR, polymerase chain reaction; SC, some concerns; WHO, World Health Organization; Y, yes.

[a]The treatment and placebo tasted and smelled different for the first 65 patients.

[b]Only severe COVID-19 hospitalized patients included.

and/or not double-blinded. Furthermore, 5 of 11 studies included are unpublished and merely posted on preprint websites (Table 1).

The danger of including these studies is illustrated by the recent retraction of the Elgazzar et al study from the preprint site, which was hosting it after very serious allegations of scientific misconduct [19]. Of all the studies included in the Hill et al [2] review, this study had the biggest effect size. When this study, with a 90% reduction in mortality, is excluded from analysis, no beneficial effect of ivermectin is seen. Thus, we have 2 well conducted, randomized, controlled trials with a low risk of bias that show no effect of ivermectin and a number of other trials either unpublished or at a high risk of bias that show a beneficial effect of ivermectin. In this situation, we consider it inappropriate to use meta-analysis methodology to pool these results. We should limit our evaluation of ivermectin to the evidence derived from high-quality studies. Another high-quality, randomized, controlled trial, the United Kingdom's Principle outpatient trial, has already enrolled 5000 patients in its ivermectin arm and results are expected soon [20].

In conclusion, based on 4 well conducted systematic reviews and the results of the 2 best-designed clinical trials so far [7], we concur with most international COVID-19 guidelines that the current evidence does not support the use of ivermectin as treatment for COVID-19 infection.

Misinformation about the efficacy of ivermectin in COVID-19 infection should be countered. A paper such as the review by Kory et al [6] is used by influencers and the social media to create confusion and increase the distrust of people in international evidence-based COVID-19 recommendations. What low- and middle-income countries need is more access to oxygen and COVID-19 vaccines, and not ivermectin.

It is now time to conduct trials for a condition for which ivermectin is most useful: onchocerciasis. There is a critical need for clinical trials to evaluate the safety of ivermectin for the treatment of children below the age of 5 years and for pregnant women. Lowering the age to treat children and allowing pregnant women to be treated with ivermectin, together with increasing the frequency of ivermectin distribution, could not only reduce the time to eliminate onchocerciasis but also prevent onchocerciasis-associated morbidities such as onchocerciasis-associated epilepsy [21].

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A. G. Boven,[1] C. Kenyon,[2] and R. Colebunders[1]

[1]Global Health Institute, University of Antwerp, Antwerp, Belgium, [2]Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium

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Correspondence: Annelies G. Boven, BSc, University of Antwerp Drie Eiken Campus, Universiteit Antwerpen Campus Drie Eiken, Steenbergen, Noord-Brabant, Netherlands (annelies.boven@student.uantwerpen.be).

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