Future VIROLOGY

Editorial

A twisting tale of misinformation: should ivermectin be approved as a treatment for COVID-19 disease?

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"Numerous studies have reported various beneficial effects of ivermectin on the clinical outcomes of patients with COVID-19. However, the current body of evidence for ivermectin has been seriously undermined by a lack of good-quality evidence and the rapid dissemination of misleading information on social media."

Tweetable abstract: This editorial examines what has caused the evidence around ivermectin to be so controversial, provides a brief analysis of recently published evidence, and highlights why it is important to learn lessons from ivermectin for future re-purposed drugs.

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Ivermectin is a US FDA-approved anthelmintic medicine that has been successfully used to treat primarily veterinary, but also some human, parasitic infections.

The possible antiviral and immunomodulatory activities of ivermectin have been reported and have reinforced the hypothesis that ivermectin is a promising therapeutic option for treating COVID-19 disease [1–3]. Ivermectin in particular has sparked a great deal of public interest, as the high mortality and morbidity of COVID-19 in the early stages of the pandemic have driven a need for an inexpensive, widely available, easily administered drug that can be repurposed as a treatment of or prophylactic for COVID-19 [4]. Numerous studies have reported various beneficial effects of ivermectin on the clinical outcomes of patients with COVID-19. However, the current body of evidence for ivermectin has been seriously undermined by a lack of good-quality evidence and the rapid dissemination of misleading information on social media.

A heterogeneous body of evidence lacking a specific clinical application has been produced as a result of preprints, open-label trials, an uneven distribution of participants between intervention and control groups with significant baseline characteristic differences, small participant numbers, various interventions and inconsistent dosing across studies, unregistered trials and an inability to employ rigorous methodology [5]. Most of the evidence for the use of ivermectin is based on *in vitro* study findings. However, the high concentration of ivermectin used in these *in vitro* studies makes it impossible to pharmacologically achieve the dose required for the proposed antiviral activity, since the dose is significantly higher than the maximum plasma concentration of ivermectin achieved *in vivo* [6]. Numerous randomized controlled trials (RCTs) and observational studies have evaluated the evidence for the antiviral activity of ivermectin following initial *in vitro* investigations that demonstrated the drug's promise [7]. However, there have been some serious concerns regarding these studies. Many of these studies were rushed, driven by extremely high mortality rates, disease severity and transmissibility in the early stages of the pandemic and

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provided poor evidence with noticeable methodological pitfalls. It must be acknowledged that some of these studies were possibly intentionally designed to yield predetermined findings. The credibility of some of the studies that have suggested that ivermectin could be a game changer; therefore, have since been called into question. Several RCTs have recently been published that reinforce the ineffectiveness of ivermectin in treating COVID-19 patients (e.g., the results of COVID-OUT and ACTIV-6 groups).

Furthermore, Systematic Reviews and Meta-analyses of these investigations have therefore been based on inconsistent findings, with poor quality reporting caused by biases at different phases of the study process [8]. Attaining concrete results would have required meticulous clinical appraisal of the included studies, and since then, a number of Meta-analyses have been published considering the potential for such studies to be misleading [9,10]. Our own Meta-analysis on the effectiveness of ivermectin revealed that by removing trials with a high risk of bias, the findings tended to point to the medication's ineffectiveness [11]. Further studies have also shown the enormous positive effect of including high-risk and fraudulent studies on the pooled effect size for assessing the efficacy of ivermectin in both treatment and prevention of COVID-19 [12,13]. Such erroneous findings threaten the practice of evidence-based medicine, challenging physicians and preventing patients from receiving the most effective and appropriate treatments.

With such a threat to evidence-based medicine, it is important that authors, editors, reviewers, clinicians and readers adhere to the guidelines provided by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) group. This guideline has been developed to assess the certainty of evidence of reported outcomes in Meta-analyses by evaluating several different domains, including but not limited to: risk of bias, imprecision, inconsistency, indirectness and publication bias. There are four levels of evidence in the GRADE approach: very low, low, moderate and high. The leveling for Meta-analyses of RCTs starts from high certainty of evidence, and if there are concerns in any of the mentioned domains for each reported outcome, the level of evidence would be decreased. A search to identify how many available Systematic Reviews and Meta-analyses on the effect of ivermectin for the treatment of COVID-19 have assessed the certainty of evidence regarding their reported outcomes finds that some do not report the certainty of evidence [14–16]. Interestingly, these particular studies reported the beneficial effect of ivermectin in COVID-19 and were published in early 2021, when the pandemic was at its worst. Other Systematic Reviews are available reporting the certainty of their outcomes regarding the use of ivermectin to be low and very low. The misuse of ivermectin for treatment of COVID-19 can therefore be partially attributed to the lack of attention of some authors in using the available guidelines for reporting the certainty of their evidence (e.g., GRADE), and the lack of attention from readers and clinicians to the main results along with the certainty of the evidence reported. Putting additional emphasis on the certainty of evidence of Systematic Reviews and Meta-analyses could potentially be an important lesson to learn from ivermectin. Such controversial studies have sparked debate not only among the scientific community, but also among the public on the social media. The spread of misinformation through social media has been a major contributing factor influencing the general population's knowledge and opinion on the effectiveness of ivermectin. According to a study by Hua *et al.* [17] that examined social media activity trends and public opinion, there has been a considerable promotion in the off-label use of ivermectin as a result of misperceptions caused by 'fake news' and conspiracy theories lacking any supporting data. Ivermectin outpatient purchases increased in the USA and Canada after the spike in popularity [18] and, despite the lack of certainty regarding its efficacy, ivermectin has been prescribed and frequently used under the assumption that the worst case scenario would be that it is ineffective. However, prescription and usage of off-label medications poses consequences for the healthcare system and the practice of evidence-based medicine. Prescription of drugs without authorization takes away the opportunity for patients to benefit from medications that genuinely improve their clinical outcome early enough to prevent further complications associated with disease progression. From the perspective of healthcare management, prescription of a drug for an unauthorized use can result in medication supply shortages and reduces the availability for patients that specifically require that medication. Ivermectin, specifically, is an essential medicine for treatment of parasitic diseases worldwide, as stated by the WHO [19]. In addition, when ivermectin products intended for human use are unavailable, people will consume veterinary products that contain toxic doses of the drug [20]. Inappropriate prescriptions also interfere with ivermectin clinical studies, making it difficult for researchers to understand the advantages and disadvantages of the drug when patients who are being treated with ivermectin for COVID-19 do so outside of the clinical trial setting. These issues all serve to highlight the importance of evidence-based decision making, particularly in a worldwide public health crisis.

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