Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

From hydroxychloroquine to ivermectin: how unproven “cures” can go viral

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Since the onset of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, various therapeutic agents have been repurposed to treat patients with coronavirus disease 2019 (COVID-19) and used empirically before adequate clinical studies were performed. One of the most controversial drugs in the initial phase of the pandemic was hydroxychloroquine. This drug, which has been used to treat malaria, amebiasis, and autoimmune diseases (e.g. systemic lupus erythematosus and rheumatoid arthritis), had promising results in *in vitro* studies and observational studies [1], although cohorts were limited and there were significant methodological limitations. Over subsequent months, several randomized clinical trials reported that hydroxychloroquine, alone or in combination with azithromycin, was ineffective in preventing SARS-CoV-2 transmission, providing more rapid resolution of clinical symptoms, or reducing hospital admissions and mortality in patients with COVID-19 and was associated with no improved mortality compared with placebo [2–5].

Nevertheless, despite these consistent data and the publication of the living WHO guidelines recommending against the use of hydroxychloroquine for COVID-19 [6], the effectiveness of this drug is still asserted by some, who are using social networks and the media to spread their beliefs [1,7]. This (mis)information has created doubt, angry debate, and even threats to hydroxychloroquine detractors. Arguments such as “it was given too late,” “it was not administered at the right dose,” “it is cheap and safe,” or “it is unethical to perform a randomized trial and expose patients to placebo” have been used to explain the poor trial results during the fierce discussions on hydroxychloroquine use in COVID-19. The drug is still administered in several countries where national leaders have supported its use [8,9].

In a situation similar to that with hydroxychloroquine, ivermectin has been proposed as an interesting and potentially effective medication to treat patients with COVID-19. Ivermectin is an antiparasitic molecule that has shown potential antiviral and anti-inflammatory properties against SARS-CoV-2 in animal models [10]. However, the antiviral effects in *in vitro* and *in vivo* studies required serum and tissue drug concentrations that can only be obtained by administering daily doses significantly higher than for current antiparasitic regimens, with potentially toxic effects [11]. As with hydroxychloroquine, initial *in vitro* and observational studies suggested some outcome benefits with the use of ivermectin in patients with COVID-19.

Some randomized trials, limited by heterogeneity of populations receiving ivermectin, imbalanced allocation, selected doses, and uncontrolled cointerventions, also reported some benefits with ivermectin in different populations of patients with COVID-19 [12]. A systematic review that initially suggested an improved survival rate with ivermectin treatment compared with placebo in patients with COVID-19 [13] reanalyzed the available data by excluding studies at a high risk of bias (i.e. either retracted or considered potentially fraudulent) and reported no significant effect on survival or hospitalizations in favour of ivermectin. Other systematic reviews have also confirmed the low quality of published studies and the lack of any effectiveness of ivermectin on clinically relevant outcomes in patients with COVID-19 [14,15].

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Although a large retrospective cohort study of hospitalized patients with COVID-19 in Florida suggested that those treated with ivermectin ($n = 173$) had a significantly lower in-hospital mortality, even after adjustment for confounders and propensity matching analysis (13% vs. 25%) than untreated patients ($n = 107$) [16], those receiving the drug also more frequently received steroids (which can improve mortality in hospitalized patients with COVID-19 who require oxygen therapy) and were enrolled more recently (resulting in timing bias with possible improvement in medical knowledge and global patient care).

A good-quality, double-blind, randomized trial conducted in Colombia assigned 400 patients with mild COVID-19 within the first 7 days of symptoms to receive ivermectin (300 μg/kg of body weight per day for 5 days) or placebo and reported a nonsignificant reduction of 2 days for symptom resolution but no effects of the drug on escalation of therapies or mortality [17]. In another randomized study conducted in Argentina, ivermectin had no significant effect on preventing hospitalization in patients with COVID-19 [18]. Taking these data into consideration, the WHO guidelines recommended against the routine use of ivermectin in patients with COVID-19 [4].

However, adherence to these recommendations has again been hindered by social media's spread of incorrect information. Similar to the situation with hydroxychloroquine, the clinical efficacy of ivermectin in patients with COVID-19 has been strongly supported by some organizations, including the Front Line COVID-19 Critical Care Alliance and America's Frontline Doctors in the United States, Physicians for Life association in Brazil, and the BIRD group in the United Kingdom, and promoted on social media. In Brazil, unproven drugs against COVID-19, such as hydroxychloroquine and ivermectin, have been largely promoted in the so-called Covid Kit by national authorities, to the detriment of established interventions, such as social distancing, mask-wearing, and vaccination [9]. Another major source of misinformation has been c19early.com, a website containing several meta-analyses without credibility on the efficacy of many drugs against COVID-19, including ivermectin.

The resulting popular success of ivermectin has led to inappropriate therapeutic use. However, just recently, a manuscript promulgating ivermectin use by the Front Line COVID-19 Critical Care Alliance group was retracted by a main journal because of inappropriate report of mortality [19]. Importantly, no clinical study has adequately addressed the potentially toxic adverse effects of this drug, such as interactions with anticoagulants, gastrointestinal symptoms, hypotension, allergic reactions, dizziness, ataxia, and seizures, which might jeopardize the clinical condition of patients with COVID-19. Even the manufacturer, Merck, raised concerns about use of the drug after the first cases of people being hospitalized after ingestion of ivermectin bought at animal feed stores were reported.

In conclusion, therapy with ivermectin has several similarities to the use of hydroxychloroquine during COVID-19. After initial encouraging experimental and poor-quality clinical results, there has been no scientific evidence to support its routine use. Physicians should continue to enrol patients in properly designed randomized clinical trials (the TOGETHER study in Brazil has already been halted because of futility, but the PRINCIPLE and ACTIV-6 networks are actually evaluating ivermectin) to understand whether any useful effects of this drug, alone or in combination, can be identified in treating COVID-19. The development of Adaptive Platform Trials, which test multiple interventions, with some entering and leaving the platform on the basis of predefined decision algorithms, has significantly accelerated the evaluation process of therapeutic options for COVID-19. People have been eager for an easy solution to prevent infection and willing to latch on to any seemingly safe, reasonable therapy, especially when apparently supported by renowned professionals.

The vicious progression of anti-science, sowing doubts about vaccination and promoting treatments with unproven efficacy, such as hydroxychloroquine and ivermectin, has also shown that firm condemnation by the scientific community is not sufficient. As such, scientists should attempt to vulgarize medical information in newspapers and social media and even accept debates on television with fake news and disinformation providers, explaining to audiences without medical knowledge and using nonpolarized arguments about how complex the medical treatment of COVID-19 is.

Transparency declaration

FST is on the advisory board of Nihon Khoden, Eurosets, and Neuroptics and has received lecture fees from BD, Zoll, and Xenios. MH has been on advisory boards for the management of fungal diseases for Gilead. ND reports personal fees from Roche and Boehringer-Ingelheim, and non-financial support from Pfizer, and Merck Sharp & Dohme, outside the submitted work. No funding has been received for this manuscript.

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Conceptualization: FST. Literature research: FST, MH, and ND. Literature analysis: FST, MH, and ND. Original draft preparation: FST and ND. Review and editing: MH.

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