# Ivermectin—

## Silver Bullet for COVID-19 or Hydroxychloroquine Sequel?

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Writing 101: *COVID-19: Facts or Fake News?*
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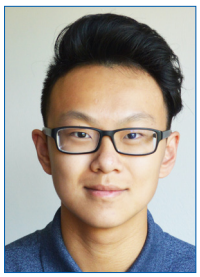
In March 2020, the World Health Organization declared the COVID-19 outbreak a pandemic, spurring researchers and physicians alike into an international initiative to discover and test potential treatments. Similar to previous infectious disease outbreaks, the development of new experimental therapies encountered a significant barrier: the rigorous pipeline from "bench to bedside", which can take upwards of ten years, must be required for proper evaluation of new medicines (DocWire News Featured Reading, 2019). As COVID-19 cases continued to increase around the world, many efforts turned instead to the repurposing of drugs previously approved by the FDA in an urgent rush to develop new therapies during this emergency phase.

Ivermectin is one such FDA-approved drug that has made global headlines as a repurposed medicine for COVID-19 treatment. The premise for exploring ivermectin as a COVID-19 therapy was motivated by its ability to block molecules from entering the cell nucleus, an essential step for the replication of viruses such as SARS-CoV-2 (Wagstaff et al., 2012). After Australian researchers demonstrated the drug to be a potent inhibitor of SARS-CoV-2 viral replication *in vitro* in April 2020 (Caly et al., 2020), ivermectin was touted as a "miracle drug" by some in the medical community (TrialSite Staff, 2020), and physicians began compassionate prescription of the drug as part of their COVID-19 treatment regimens (Mega, 2020). The wave of enthusiasm for ivermectin quickly disseminated through the public via global media outlets and perhaps gained the greatest traction in Latin America, where the Peru and Bolivia ministries of health authorized its use for treating COVID-19 patients (Hlavinka, 2020).

A significant majority in the medical community have remained skeptical, however, of the silver bullet promises of ivermectin. Citing faulty scientific data and a lack of concrete evidence, pharmaceutical researchers and FDA health officials alike have been extremely cautious in accepting the hype behind ivermectin, likely with the hydroxychloroquine fiasco still fresh in recent memory ("Merck Statement," 2021; "Why You Should Not Use," 2021). The NIH only recently upgraded their



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When the COVID-19 pandemic reached the United States a year and a half ago, I, like many others, suddenly found a surplus of spare time as shutdowns took place across the nation. I took this opportunity to spend more time on activities I enjoyed doing—hiking, making music, and taking long drives in the mountains, to name a few. But for the most part, my family and I spent our newfound time keeping up with global news. Whether we were playing card games or cooking dinner, we always kept the news on as a remaining connection to the outside world. Having been involved in translational medical research throughout high school, I particularly gravitated towards the developing research on COVID-19 therapies and vaccines. I would wind up spending many of those quarantine hours perusing the new journal articles being published each day, watching developments such as hydroxychloroquine come and go from the digital headlines.

So, when searching for a Writing 101 course, Dr. Cary Moskovitz's *COVID-19: Facts or Fake News?* immediately caught my eye. The class became an invaluable experience in exploring the diverse spectrum of online COVID-19 health claims from multiple unique modes of thought. From politics-infused opinions to conflicting scientific data, I learned strategies to harness these contradictory claims into my own arguments and conclusions. Our final project was a commentary—an evidence-based perspective on how the public should interpret an emerging COVID-19 health claim. Tapping again into my research experience, I chose to explore the opposing opinions on a controversial new drug for COVID-19 patients through an extensive review of current literature. I wanted to highlight the limitations in peer-reviewed scientific studies and emphasize the frequent disconnect between these limitations and how science news is presented to the public.

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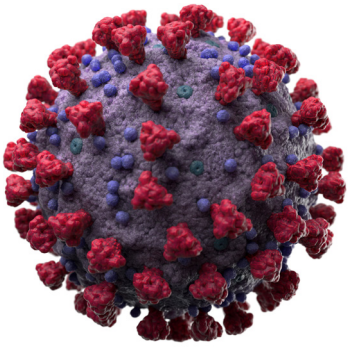


recommendation on ivermectin use for COVID-19 treatment from "against" to "neither for nor against" in January 2021 following a presentation to the NIH Treatment Guidelines Panel by Dr. Pierre Kory, the president of the Front-Line COVID-19 Critical Care (FLCCC) Alliance (FLCCC Alliance, 2021). Recently, the skepticism over ivermectin has increased after *Frontiers in Pharmacology,* a peer-reviewed pharmacology journal, removed a provisionally accepted review paper arguing for wider implementation of ivermectin in COVID-19 treatment regimens (Fenter, 2021). The review paper, incidentally written by Dr. Kory of the FLCCC Alliance, was removed due to its inclusion of "unbalanced or unsupported scientific claims" (Fenter, 2021). FLCCC Alliance members have remained insistent, however, on the scientific rigor of their report and believe they have been victims of a "censorship" (Offord, 2021). These recent events have left a pressing concern unresolved; namely, should ivermectin still attract public attention as a viable therapeutic option for COVID-19 patients?

An in-depth analysis of the current scientific data on ivermectin efficacy against COVID-19 indicate a narrative that more closely aligns with the emerging majority consensus among medical experts: Ivermectin does not have a strong enough scientific rationale to support the public attention and medical usage for COVID-19 that it has garnered in Latin America. While ivermectin should not be discarded from the list of potential treatments worthy of further scientific investigation, the current perspective on ivermectin should be an intriguing lead for the scientific community rather than a curative COVID-19 therapeutic option.

## Initial COVID-19 Study

In April 2020, a preprint of the first study on ivermectin efficacy against COVID-19 infection was published by Caly et al. at Monash University in Australia. The study, formally published in *Antiviral Research* in June 2020, demonstrated that ivermectin could effectively inhibit replication of the SARS-CoV-2 virus within 48 hours (Caly et al., 2020). Media outlets rushed to report these findings and gained particular traction in Latin America, where the study served as a rationale for many physicians to begin prescribing the drug for COVID-19 treatment (Mega, 2020; Hlavinka, 2020).

The worldwide dissemination of these findings through the general public, however, failed to report a major shortcoming in the dosages used in the study. Caly et al. evaluated ivermectin in cells cultured on Petri dishes, or *in vitro,* rather than in model organisms that can better represent human physiologies. Consequently, to achieve the impressive 99.9% reduction in viral infection after 48 hours of ivermectin treatment *in vitro,* Caly et al. used a dosage that was too high to be considered physiologically safe in humans. Researchers from Certara, a biotechnology company, predicted that the required dosage of ivermectin to replicate the *in vitro* results in the human body would result in a nine-fold higher concentration in the blood and 21-fold higher concentration in the lung compared to the highest tested dosage regimen of ivermectin in clinical trials (600 μg/kg per dose) (Bray et al., 2020). Comparatively, the highest single dose of ivermectin approved by the FDA is 200 μg/kg ("STROMECTOL," 2009), which presents an even greater disparity in physiological ivermectin concentration. Thus, immediate ivermectin implementation in COVID-19 treatment regimens is highly unfeasible, as severe side effects or toxicity can result from such extreme increases in dosage above clinically safe thresholds. Conversely, prescribing a physiologically safe ivermectin concentration may reduce its efficacy against COVID-19 infection to insignificant levels.

These stark realities set up a less-than-ideal outlook for ivermectin that was not

adequately conveyed to the general public upon the preprint of Caly et al. (2020). With media outlets such as 7NEWS, the largest news outlet in Australia, and News Medical, a medical news outlet with 13.6k Twitter followers, focused on reporting ivermectin as a promising new drug that could "kill COVID-19 within 48 hours" (McGinn, 2020; Laguipo, 2020), the significant dosage shortcoming became lost in the translation from scientific jargon to newsworthy stories. As COVID-19 cases and mortalities continued to rise, it became easy for these attention-grabbing headlines to instill a misleading optimism among a worldwide audience desperate for any signs of an end to the pandemic. Until well-designed clinical trials of ivermectin efficacy in COVID-19 patients were conducted and critically peer-reviewed, the Caly et al. findings should have been treated not as a headline-making story, but rather as a stepping-stone for continued scientific inquiry.

## Current Clinical Trials

Since the publication of Caly et al. (2020), over 50 clinical trials worldwide have reportedly been designed to assess ivermectin efficacy against COVID-19 infection and mortality in patients ("Search of," 2021). Most of these trials are still ongoing or in the recruitment phase; however, a handful of preprints and one published clinical trial are currently publicly available online. Collectively, these clinical trials have generally shown widely inconsistent evidence for ivermectin efficacy and require close evaluations of each individual study design to draw informed conclusions.

The published clinical trial was conducted by a team of medical researchers in Bangladesh and was reported in the *International Journal of Infectious Diseases* (Ahmed et al., 2021). The study was well designed; the researchers incorporated randomization, double-blinding, and placebo controls to limit unintentional biases. Overall, the researchers concluded that a five-day course of ivermectin treatment was effective in decreasing the time until an infected patient receives a negative PCR test by three days compared to the placebo control. These findings align with those from Caly et al., which suggests that ivermectin inhibits viral replication (Caly et al., 2020); however, the sample size used in this study (24 patients in both the ivermectin and placebo treatment groups) was too small to draw any significant conclusions. For instance, a randomized controlled trial conducted in Pakistan used a similar study design with comparable sample size (25 patients in each treatment group) and concluded no significant benefits for ivermectin treatment (Zeeshan Khan Chachar et al., 2020). The Bangladesh clinical trial also failed to adjust the observed efficacy of ivermectin for potential confounding variables such as age, ethnicity, or treatment history during data analysis. Since smaller sample sizes introduce greater risks for confounding variable effects, the absence of this adjustment greatly tempers the validity of these conclusions.

Proponents of ivermectin may argue that another study by Khan et al. (2020) concluded results similar to the Bangladesh clinical trial by analyzing medical

records of 325 total patients, a much larger sample size that allows for greater statistical power. However, this study was conducted retrospectively and thus selected patients via convenience sampling rather than a random sample. Along with the absence of a proper placebo control and blinding, the retrospective nature of the study introduces several potential sources of bias and confounding factors that greatly decrease the interpretability and significance of these results in supporting the Bangladesh study.

The majority of other completed clinical trials reported in preprints follow these same shortcomings along with additional issues. For instance, a clinical trial conducted in Iran compared four different ivermectin treatment regimens to a single placebo control group and concluded that ivermectin had a "high therapeutic effect on COVID-19" (Niaee et al., 2020). Using the same placebo control as a general baseline for different treatment regimens is largely insufficient and renders their conclusion scientifically incorrect. Another clinical trial conducted in Egypt recruited a large cohort of 600 patients that would have been adequately powered for a robust analysis of ivermectin efficacy; however, the research group used hydroxychloroquine treatment as the control group instead of a standard placebo control (Elgazzar et al., 2020). Given that hydroxychloroquine is known to exhibit side effects that exacerbate COVID-19 comorbidities (Jakhmola et al., 2020), hydroxychloroquine-treated patients cannot be considered a valid control group, and the large effect sizes observed for ivermectin are not scientifically valid.


In contrast to the plethora of poorly-designed clinical trials currently in preprint, a study conducted in Peru stands out as a relatively well-designed and statistically powered inquiry on ivermectin efficacy for hospitalized COVID-19 patients. By analyzing the medical records of 203 patients receiving ivermectin compared to 2630 patients receiving standard of care, the researchers observed an increased risk of death in the ivermectin treatment group compared to the standard of care control group after adjusting for ten potential confounding variables, including age, gender, medical histories, and treatment histories (Soto-Becerra et al., 2020). While this study was conducted retrospectively, the researchers accounted for this shortcoming by emulating a randomized clinical trial to reduce potential bias in the results. Of course, factors such as the lack of a placebo control and blinding that cannot be accounted for with this approach still introduce possible sources of bias and should temper the conclusions; however, the robustness of the sample size and methodology suggests the results of this study to be the most compelling insight into ivermectin efficacy thus far.

**FLCCC Alliance Support for Ivermectin**

Proponents of ivermectin, led by Dr. Kory of the FLCCC Alliance, argue a completely alternative take on the results of the clinical trials reviewed above. In the review article that was removed from *Frontiers in Pharmacology,* Dr. Kory cites many of these clinical trials along with other unpublished data as concurrent evidence for ivermectin efficacy and bases an argument for ivermectin on the volume of conducted trials rather than the rigor of their design. As Dr. Kory stated in response to Frontiers' decision to remove their review article, he and the FLCCC Alliance believe that American health agencies should consider these "smaller, uncontrolled trials and observational studies" in formulating a decision

on ivermectin recommendation for COVID-19 treatment rather than solely "gold-standard trials" (Offord, 2021). Dr. Kory also argues that multiple larger multicenter clinical trials satisfying the gold-standard criterion are currently underway to provide the required rigor in supporting ivermectin use.

With only two NIH-recommended treatment options available as COVID-19 mortalities continue to rise worldwide, it would appear that Dr. Kory and the FLCCC Alliance make a compelling argument for using ivermectin in COVID-19 treatment. Indeed, the ministries of health in Peru and Bolivia have already authorized ivermectin use in COVID-19 treatment (Hlavinka, 2020). Even with the extremity of the COVID-19 pandemic, however, the established rigor within the scientific and medical communities cannot be traded in favor of advancing an unproven therapeutic. Especially with the heightened concern towards COVID-19 among the general public, it is particularly dangerous to promote treatments that cannot be supported by robustly collected scientific evidence. In the FLCCC Alliance review paper, Dr. Kory simply summarizes the results of studies reporting positive data for ivermectin efficacy without providing any discussion on their multiple shortcomings in design and execution.

In providing a fair review of ivermectin, each of these aspects should have been considered. However, it appears that Dr. Kory and the FLCCC Alliance may be selectively reporting data to support their own conclusions, possibly to preserve their reputations following Dr. Kory's address to the US Senate in support of ivermectin (Offord, 2021). Members of the FLCCC Alliance have a history of making statements that were later debunked; Dr. Kory's Senate address was labeled "False" by fact-checkers at the Associated Press (Dupuy, 2020), and Dr. Paul Marik, the founder of the FLCCC Alliance, also wrote a review paper on ivermectin that referenced several retracted papers with discredited data (Offord, 2021).


Collectively, the current clinical data on ivermectin efficacy in alleviating COVID-19 infection appears to be a collection of hurriedly completed clinical trials with poor design and/or inadequate recruitment. The hastiness with which these trials were put together and carried out may be reflective of the public rush to utilize ivermectin as a COVID-19 therapeutic following the overstated positive press received by Caly et al. (2020). Pressured by an extremely short timeframe, all of these studies present multiple limitations that severely complicate their scientific and medical interpretation. This may lead (and have already led) to more harms than benefits in the long term, as doctors in Latin America continue to resort to ivermectin for treating COVID-19 patients (Mega, 2020; Hlavinka, 2020). Taken together, Frontiers made the prudent judgement in removing the FLCCC article on the grounds of "unbalanced or unsupported scientific claims" (Fenter, 2021).

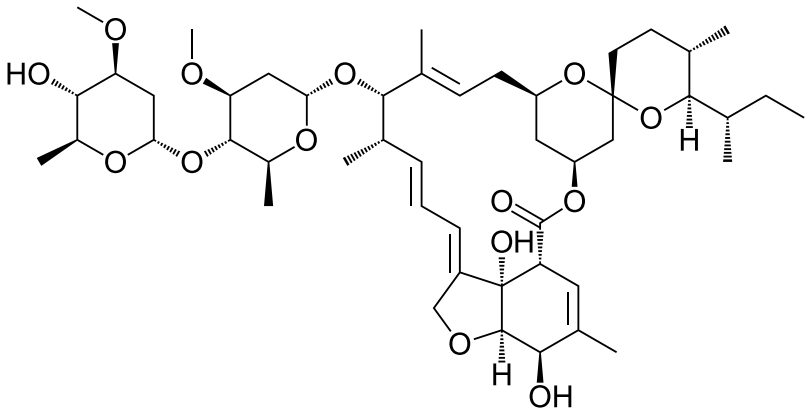
## Next Steps

At this stage, the current scientific data on ivermectin cannot be used to support its implementation as a therapeutic for COVID-19 patients. The use of ivermectin in treating COVID-19 patients, especially in the Latin American countries, was a product of media outlets rushing to report data yet to be peer-reviewed by the scientific community. As a consequence, the substantial limitation in ivermectin dosage was lost in translation to mainstream media. Recent clinical trials have failed to strengthen the argument for ivermectin use despite a continued push by

Dr. Kory and the FLCCC Alliance founded on flawed interpretations of scientific data.

Even with the pressure for better therapies instilled by the COVID-19 pandemic, patients and doctors alike should exercise considerable caution when evaluating a drug with incomplete evidence for its clinical efficacy. Multiple repurposed drugs have been used in clinical settings ahead of thorough research, only to be later withdrawn when no efficacies are observed and adverse side effects occur (Martinez, 2021). Hydroxychloroquine was a highly-publicized recent example, and ivermectin should be withheld from COVID-19 treatment regimens until robust clinical trials are completed to prevent a similar oversight. The extensive risks associated with using ivermectin over CDC-recommended therapies far outweigh the potential benefits—receiving an ineffective and potentially toxic drug in lieu of validated therapies can allow COVID-19 infections to progress beyond the optimal treatment window, where it becomes much harder to treat even with CDC-recommended regimens (Lipsitch et al., 2020).

What's next for ivermectin? For starters, a number of larger and better-designed clinical trials are on the horizon for elucidating the true efficacy of ivermectin. One such undertaking is the Together trial currently underway at McMaster University. An international effort across Canada, Brazil, and South Africa, the Together trial aims to recruit up to 3200 patients to assess the efficacy of ivermectin for COVID-19 treatment and may publish results within the next three to six months (McGuire, 2021). In addition, a recent surge in drug repurposing efforts across all diseases have seen multiple drugs with weak potency and poor clinical trial performance gain new hope in combinational therapy regimens (Sun et al., 2016). This trend supports ivermectin as of now—a drug with considerable efficacy at high concentrations *in vitro* but conflicting therapeutic benefit in clinical trials. Whether ivermectin merits consideration as a combinational therapy candidate remains to be seen and awaits the results of ongoing clinical trials that will ultimately determine its role as an individual treatment for COVID-19.




Ivermectin
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