

FREQUENTLY ASKED QUESTIONS ON IVERMECTIN

answered by Dr. Pierre Kory and Dr. Paul Marik (FLCCC Alliance)
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There have been many questions about Ivermectin, and rightly so. Below we provide detailed and comprehensive answers to the most common questions we have received. First and foremost, many simply ask, “Can Ivermectin really do all you’ve said it can do—prevent and treat all phases of COVID-19 disease? It seems too good to be true – again.”

The answer to this question relies on the fact that ivermectin, since its development 40 years ago, has already demonstrated its ability to make historic impacts on global health, given it led to the eradication of a “pandemic” of parasitic diseases across multiple continents. These impacts are what awarded the discoverers of ivermectin the 2015 Nobel prize in Medicine.

More recently, profound anti-viral and anti-inflammatory properties of ivermectin have been identified. In COVID-19 specifically, studies show that one of its several anti-viral properties is that it strongly binds to the spike protein, keeping the virus from entering the cell. These effects, along with its multiple abilities to control inflammation, both explain the markedly positive trial results already reported, and poise ivermectin to again achieve similar historic impacts via the eradication of COVID-19.

Please read also our [One-page summary](#) of the “Review of the Emerging Evidence Supporting the Use of Ivermectin in the Prophylaxis and Treatment of COVID-19” (PDF; full review [here](#)).

“How could ivermectin be effective if the tissue concentrations needed to kill the virus would require a patient to take massive doses to achieve?”

The theory that ivermectin’s anti-viral activity is dependent on unachievable tissue concentrations is incorrect as follows:

- 1) In the cell culture study by Caly et al from Monash University in Australia, although very high concentrations of ivermectin were used, this was not a human model. Humans have immune and circulatory systems working in concert with ivermectin, thus concentration required in humans have little relation to concentrations used in a laboratory cell culture. Further, prolonged durations of exposure to a drug likely would require a fraction of the dosing in a short-term cell model exposure.
- 2) There are multiple mechanisms by which ivermectin is thought to exert its anti-viral effects, with the least likely mechanism that of the blocking of importins as theorized in the Monash study above. These other mechanisms are not thought to require either supraphysiologic doses or concentrations and include
 - a. competitive binding of ivermectin with the host receptor-binding region of SARS-CoV-2 spike protein, limiting binding to the ACE-2 receptor;

- b. binding to the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), thereby inhibiting viral replication (Swargiary, 2020);
 - c. binding/interference with multiple essential structural and non-structural proteins required by the virus in order to replicate.
- 3) The theory that ivermectin would need supraphysiologic tissue concentration to be effective is most strongly disproven by the now 24 controlled clinical trials which used standard doses of ivermectin yet reported large clinical impacts in reducing rates of transmission, deterioration, and mortality.

“My Primary care physician (PCP) will not prescribe ivermectin. Where can I get a script?”

We understand and empathize with the challenges faced in obtaining a prescription for ivermectin during this time period prior to its use being formally adopted in national or international COVID-19 treatment guidelines. However, we are anticipating these treatment guidelines to be updated in the near future. Alternately, please know our scientific review manuscript on ivermectin in COVID-19 is undergoing expedited peer-review at a prominent American medical journal, and if it passes peer review and becomes published, we anticipate that this will also make access to ivermectin more widespread. However, until such a time when its use as both a prophylactic and treatment agent is more widely accepted or recommended, many physicians will be reluctant to prescribe. We can only suggest the following approaches:

- 1) Discuss with your primary health care provider. If they are unconvinced of the data, share with them our manuscript which can be downloaded from the FLCCC Alliance Website (<https://covid19criticalcare.com/flccc-ivermectin-in-the-prophylaxis-and-treatment-of-covid-19/>) or from the OSF pre-print server (<https://osf.io/wx3zn/>). Please understand that many will prefer to avoid adoption of ivermectin treatment until such a time as the guidelines are updated or the manuscript gets published.
- 2) The second option is to try one of the doctors that can provide telemedicine consultation here: “Drs Prescribing Ivermectin.” <https://www.exstnc.com/> Confirm the price of any visit prior to the consultation. We have reports of some doctors charging exorbitant fees. We also provide a list of telemedicine contacts (US only) on our website: [Obtain a prescription for ivermectin](#)
- 3) If more pills are desired than can be provided locally, you can order in bulk from the Canadian King Pharmacy (www.canadianpharmacyking.com), however you will need a prescription.

“Can I request expert advice or consultation from the FLCCC Alliance?”

Given the sheer volume of requests and the limited number of expert clinicians that make up the FLCCC Alliance, the doctors are not able to respond to individual requests for expert consultation on patients ill with COVID-19. Furthermore, we cannot provide treatment recommendations for patients that are not under our direct care. However, we can offer interested patients, families, and health care providers our COVID-19 treatment expertise and guidance contained in our published and pre-published manuscripts. Given that the majority of requests for consultation have been on cases where patients are failing stan-

dard therapies, we suggest that those interested review the section on “salvage therapies” in An FLCCC Alliance guide to the management of COVID-19 (www.flccc.net/flccc-protocols-a-guide-to-the-management-of-covid-19/; #24, p. 19). We also emphasize the importance of recognizing that COVID-19 respiratory disease is not a viral pneumonia, but rather an “organizing pneumonia”, and as such, in fulminant cases, would typically require high doses of corticosteroids as in our protocol. For support of this, please refer to our paper on “SARS-CoV-2 Organizing Pneumonia” (bmjopenrespres.bmj.com/content/7/1/e000724.full). Lastly, we recommend that patients ill with COVID-19 at any stage of disease receive ivermectin, as per the accompanying manuscript which compiles and reviews the large evidence base supporting this therapy.

“Will ivermectin interfere with the vaccine and can I continue to take ivermectin once vaccinated?”

Our understanding of the importance of ivermectin in the context of the new vaccines, is that ivermectin prophylaxis should be thought of as complementary bridge to vaccination until the vaccines are made available to all those in need. At this time, and after speaking with the vaccine experts, we do not believe that ivermectin prophylaxis interferes with the efficacy/immune response to the vaccine, however it must also be recognized that no definitive data exists to more specifically answer this question. However, given that maximal immunity from the vaccines is only achieved 2 weeks after the second dose of vaccine, it is reasonable to take bi-weekly ivermectin until this time point.

“Is ivermectin safe and are there any contraindications for use?”

The discovery of ivermectin in 1975 was awarded the 2015 Nobel Prize in Medicine given its global impact in reducing onchocerciasis (river blindness), lymphatic filariasis, and scabies in endemic areas of central Africa, Latin America, India and Southeast Asia. It has since been included on the WHO’s “List of Essential Medicines with now over 4 billion doses administered. Numerous studies report low rates of adverse events, with the majority mild, transient, and largely attributed to the body’s inflammatory response to the death of parasites and include itching, rash, swollen lymph nodes, joint pains, fever and headache. In a study which combined results from trials including over 50,000 patients, serious events occurred in less than 1% and largely associated with administration in Loa Loa infected patients. Further, according to the pharmaceutical reference standard *Lexicomp*, the only medications contraindicated for use with ivermectin are the concurrent administration of anti-tuberculosis and cholera vaccines while the anticoagulant warfarin would require dose monitoring. Another special caution is that immunosuppressed or organ transplant patients who are on calcineurin inhibitors such as tacrolimus or cyclosporine or the immunosuppressant sirolimus should have close monitoring of drug levels when on ivermectin given that interactions exist which can affect these levels. A longer list of drug interactions can be found on the database of <https://www.drugs.com/ivermectin.html>, with nearly all interactions leading to a possibility of either increased or decreased blood levels of ivermectin. Given studies showing tolerance and lack of adverse effects in human subjects given even escalating, high doses of ivermectin, toxicity is unlikely although a reduced efficacy due to decreased levels may be a concern. Finally, ivermectin has been used safely in pregnant women, children, and infants.

“Can ivermectin be given to patients with acute or chronic liver disease?”

In regards to liver disease, ivermectin is well tolerated, given that there is only a single case of liver injury reported one month after use that rapidly recovered. ivermectin has not been associated with acute liver failure or chronic liver injury. Further, no dose adjustments are required in patients with liver disease.

“Shouldn’t we do a large, prospective, double-blind, placebo-controlled study to “prove” it works before adopting yet another treatment that will not work?”

There are several reasons why such a study would likely be unethical to conduct at the current time. We agree that further studies can and should be done but placebo controlled RCT’s should be avoided due to the following:

- Currently, a total of over 3,000 patients have been included within numerous randomized, controlled trials with the overall signal of benefit in important clinical outcomes strongly positive with tight confidence intervals. This would make the likelihood of causing significant harm to study subjects in a medical research trial using placebo to be unacceptably high given excessive morbidity and mortality associated with COVID-19.
- Further, the WHO ACT Accelerator Program (www.who.int/initiatives/act-accelerator/about) sub-section focused on treatments for COVID-19 and headed by UNITAID has hired research consultants to identify and perform a global systematic review and meta-analysis of all active ivermectin trials in COVID-19. The consultant anticipates having results available from several additional, large clinical trials within the next 4 weeks, and predicts the accumulation of sufficient patient data in these trials to reach a conclusion and recommendation for or against use of ivermectin in COVID-19 during the month of January 2021. Preliminary analyses by the consultants were recently presented at an international research conference and all the available trial results at the time strongly supported the efficacy of ivermectin in COVID-19. If, based on the projected amount of trial data in the coming month, a recommendation for use of ivermectin in COVID-19 is issued by the WHO, any planned subsequent placebo-controlled trials would have to be terminated.

“Aren’t most of the trials poorly designed and executed, with high risks of bias?”

All clinical trials suffer from risks of bias in their design and conduct, as assessed by the Cochrane Risk of Bias 2.0 tool that assesses trial biases with the grades of “some concern, low, moderate, high, or serious”. Although one group of authors has assessed many of the trials as having moderate to severe risks of bias, performing meta-analyses of these trials can more accurately detect the true effects despite individual trial biases. Multiple groups, including ours, have performed meta-analyses of these trials, with all groups finding consistent benefits amongst the trials. In fact, the consistency of trial results from both sets of randomized and observational controlled trials from varied centers and countries and trial sizes and disease phases lend even more validity to the estimates of benefit. The references/links to two large meta-analyses can be found below, in addition to the meta-analyses of both prophylaxis and treatment trials performed in our review manuscript:

- 1) FLCCC Alliance review on ivermectin in COVID-19 – <https://covid19criticalcare.com/flccc-ivermectin-in-the-prophylaxis-and-treatment-of-covid-19/>;
- 2) <https://ivmmeta.com/> – this research group’s meta-analysis calculated that the odds of ivermectin not being effective in COVID-19 is one in 67 million;
- 3) Toxicology and Pharmacology Department from Lyon University, France:
<http://www.metaevidence.org/viewMApredictive2.aspx?exposition=684&pathology=87&selfocus=1&selSubgroup=0&domain=12>

“Given the large and rapidly rising numbers of U.S patients with COVID-19, couldn’t a large randomized controlled trial be performed quickly?”

“Peacetime” processes of waiting for “the perfect clinical trial” when we are “at war” with rising case counts, dwindling hospital beds, and increasing deaths is illogical and also unethical as above. All therapeutic decisions in medicine involve implicit risk/benefit calculations. When considering a safe, low-cost, widely available medicine that has been repeatedly shown to lead to consistent mortality and transmission decreases, deferring adoption of this therapy while waiting for “perfect” or “unassailable” data is far more likely to cause excessive harm compared to the lower risk of adopting a safe, low-cost therapy. Again, based on a minimum of the 24 controlled trials results available, the odds that ivermectin is ineffective is 1 in 67 million as per the Covid19 study research group above. ivermectin can and will be studied in well-designed observational trials which can provide equally accurate conclusions.

The odds that, in the US, we continue to descend further into a humanitarian disaster of historically adverse economic and public health impacts is simply the current reality. Humanist pragmatism, utilizing a therapeutic benefit/safety calculation must be emphasized in place of the now standard, overly strict evidence-based medicine paradigm given the state of the current public health crisis. Further, the numerous careful analyses reporting that, in regions with ivermectin distribution campaigns, precipitous decreases in both case counts and case fatality rates occurred immediately after these efforts began, this further supports the validity and soundness of the decision to immediately adopt ivermectin in the prophylaxis and treatment of COVID-19.

“Shouldn’t we wait for more data before widely adopting another medicine that may not work?”

Making a risk/benefit decision at this time, with the currently available data showing consistent high efficacy and safety with mortality benefits from 24 controlled trials, would far exceed the strength and validity of the rationales used to adopt the entirety of currently employed therapeutics in COVID-19 given all were adopted in the setting of either

- 1) weak clinical impacts measured (remdesivir, monoclonal antibodies, convalescent plasma);
- 2) high costs (remdesivir, monoclonal antibodies, convalescent plasma, vaccines);
- 3) significant adverse effects (remdesivir, vaccines);
- 4) weak, conflicting, or non-existing evidence bases to support use (remdesivir, monoclonal antibodies, convalescent plasma);

- 5) conflicting treatment guidelines (remdesivir – WHO and NIH recommendations conflict);
- 6) non-peer reviewed studies (remdesivir, monoclonal antibodies, convalescent plasma);
- 7) absence of even pre-print study data available for wider scientific review (vaccines).

“If ivermectin is so effective in COVID-19, how come no countries have adopted it into their national treatment guidelines?”

Multiple countries and regions have formally adopted ivermectin into their treatment guidelines, with several having done so only recently, based on the emerging data compiled by the FLCCC Alliance.

Examples include:

- 1) Macedonia – December 23, 2020
- 2) Belize – December 22, 2020
- 3) Uttar Pradesh in Northern India – a state with 210 million people – adopted early home treatment kits which include ivermectin on October 10, 2020
- 4) State of Alto Parana in Paraguay – September 6, 2020
- 5) Capital City of Lucknow in Uttar Pradesh – August 22, 2020
- 6) State of Chiapas, Mexico – August 1, 2020
- 7) 8 state health ministries in Peru – Spring/summer 2020
- 8) Lima, Peru – Many clinics, districts use and distribute ivermectin, as of October the hospitals no longer use.

“Isn’t the existing set of clinical studies of ivermectin inconclusive since they are all small?”

While a minority have been “small” (generally defined as including less than 100 patients, particularly when looking at mortality as an endpoint), the majority have been large, with several including hundreds of patients. The smaller studies were, as expected, less likely to find statistically significant differences, while every randomized controlled trial (RCT) which included over 100 patients found highly statistically significant differences in important clinical outcomes, reporting decreases in rates of transmission, progression, or mortality as follows:

- 3 prophylaxis RCT’s with > 100 patients each – large benefits, all statistically significant;
- 3 outpatient RCT’s with > 100 patients each – large benefits, all statistically significant;
- 4 hospital patient RCT’s with > 100 patients each – large benefits, all statistically significant.

Further, the total number of patients within controlled trials now include over 6,500 patients with over 2,500 within randomized, controlled trials alone. This number of randomized patient data now approaches the number of treated patients with the RECOVERY randomized controlled trial, a study whose results immediately transformed the treatment of COVID-19 with widespread adoption of corticosteroids in patients with moderate to severe illness.

“Isn’t the promotion of ivermectin the same thing as hydroxychloroquine – everyone claims it works when all the randomized controlled trials showed it didn’t?”

The decision to adopt hydroxychloroquine was made early in the pandemic, when, despite the lack of clinical trials data to support use, there existed a scientific rationale given pre-clinical data suggesting anti-viral and anti-inflammatory properties. Thus, the decision at that time was likely a sound one based on a risk/benefit calculation given HCQ’s low cost, minimal adverse effect profile, wide availability/ease of compounding, and long history of use. Such a decision was also entirely in keeping with Principle 37 of the Helsinki Agreement on Medical Research, first formulated in 1964, which declares that *“physicians may use an unproven intervention if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research.”* In keeping with Declaration 37, immediately after the widespread adoption of HCQ, studies were immediately conducted by many centers. Unfortunately, all of the RCT’s reported negative results which led to rapid de-adoption with the exception of sporadic continued use in early phase disease. Note that the current widespread non-adoption of ivermectin in the face of hundreds of thousands of ill and dying, currently violates Declaration 37 in that adoption is being purposely and overtly avoided despite the efficacy/risk assessment of now numerous well controlled trials including over 3,000 total patients which report massive drops in transmission and large decreases in mortality when used in the treatment of COVID-19 patients. The data supporting adoption is now approaching that of corticosteroids, where widespread use began almost immediately upon the reporting of results of the 6,000 patient RECOVERY trial which demonstrated a mortality benefit (with only 2,000 patients treated with corticosteroids in that trial).

“How does the NIH arrive at their recommendations for current widely used therapies and why is the rationale for these recommendations so difficult to understand?”

We are unable to identify a consistent approach to the strength and timing of NIH recommendations and/or updates to the recommendations as illustrated in the following examples:

Convalescent plasma use was adopted early in the pandemic and fell into widespread use despite the absence of supportive clinical trials evidence at the time and the high cost/resource use associated. The current NIH recommendation, last updated July 17th, 2020 is that “there are insufficient data to recommend either for or against use.” As of December 26, 2020, 7 RCT’s and 6 OCT’s have been conducted without reporting a single statistically significant clinical outcome benefit. No updated recommendation has been issued despite these trial results. Widespread use continues.

Remdesivir – a purported anti-viral agent, currently has been given a “neutral” recommendation (i.e., neither for or against use) by the NIH in hospital patients who are not on oxygen, while it has a B-IIa in support of use in hospitalized patients on supplemental oxygen only (i.e., without need for either high flow or any form of mechanical ventilation). A B-IIa indicates that the recommendation is of moderate strength and is based on either an RCT with a major limitation or from a sub-group analysis of an RCT.

The RCT used in support of this recommendation found that in a subgroup of patients that received 5 days of remdesivir, their clinical condition on Day 11 was improved compared to standard care although the sub-group that received 10 days of therapy did not achieve an improved clinical condition on day 11. Note also that remdesivir is high cost (over \$3,000 per dose), requires IV administration, and resulted in a statistically significant increased number of adverse effects. Finally, no RCT has shown remdesivir to reduce the mortality rate of COVID-19 patients and the above NIH recommendation in support of use conflicts with the updated November 20, 2020 recommendation by the WHO against the use of remdesivir in COVID-19, regardless of disease severity, based on findings from their SOLIDARITY trial along with 3 other RCT's including a total of 7,000 patients. Despite this effort by an international guideline development group consisting of 28 clinical care experts, 4 patient-partners and an ethicist, the NIH COVID-19 treatment guideline, last updated December 3, continues to recommend the use of remdesivir in COVID-19.

Anti-IL-6 therapy (tocilizumab, siltuximab, sarilumab) – the NIH recommendation, last updated November 3, 2020 is a B-I against use (moderate strength, based on RCT data). Currently, only one RCT has been conducted and was negative, although it was performed prior to recommendations for corticosteroid use, indicating that as a stand-alone immunomodulatory therapy, it appears ineffective. However, a meta-analysis of findings from 16 observational trials including a total of 2,931 patients currently reports statistically significant decreases in mortality when used. Clearly the evidence for use conflicts, suggesting perhaps a “neutral” recommendation more appropriate, but the NIH rating scheme appears to weigh a single RCT over meta-analyses of observational trials in this instance.

Monoclonal Antibodies – guidance approach with these novel recombinant human monoclonal antibodies is even more complex/confusing. Currently, they (casirivimab, imdevimab, and bamlanivimab) all have an EUA (emergency authorization for use) by the FDA for patients with mild-to-moderate illness at high risk for progression. This EUA, although specifically stated that it does not constitute FDA approval of these products, appear to give the impression that they are either appropriate for use, or simply can be used as a treatment option. However, the NIH recommendation on these agents, of December 2nd, is a “neutral” one, i.e., “at this time, there are insufficient data to recommend either for or against the use of casirivimab plus imdevimab for the treatment of outpatients with mild to moderate COVID-19.” We interpret the totality of these actions to mean that these agents are permitted for use, but are not necessarily recommended for use and is thus left to clinician/patient judgement. It should be noted that these actions above were based on a single RCT whose primary endpoint, although a positive one, was the change in nasopharyngeal SARS-COV-2 levels over 7 days, a non-patient centered outcome. The secondary endpoint was a composite need for an ER visit or hospitalization, and although lower in the treated group, both were of low incidence and the data on hospitalization need compared to an ED visit was curiously not provided. Again, no mortality benefit was found with use of these, novel, high-cost agents, both requiring IV administration. However, it appears to have earned what we would interpret as a cautious, weak recommendation for use by our leading governmental health agencies. One clearly positive aspect of this action is the clear attempt to ensure an available option for early treatment with the hopes of preventing hospitalization. We encourage further such efforts, albeit with more effective and more widely available medications like ivermectin, given the numerous RCT's showing less transmission, need for hospitalization, and fatalities.

Ivermectin – the NIH recommendation, when updated August 27, 2020 was an A-III against use, indicating “strong level”, based on “expert opinion” only. This recommendation persisted until after our review manuscript, first available on a pre-print server on November 13, 2020, and Dr. Kory’s Senate Testimony on December 8, 2020 brought significant national and international attention to the topic. We were then invited to present our detailed compilation of the existing evidence base to the NIH Guidelines panel on January 6, 2021, in collaboration with the expert consultant to the WHO, Dr. Andrew Hill. Subsequently, on January 14, 2021 the NIH upgraded their recommendation and now considers ivermectin an option for use in COVID-19 — by no longer recommending “against” the use of ivermectin for the treatment of COVID-19. A similar neutral stance applies to monoclonal antibodies and convalescent plasma, both of which are widely used in COVID-19 treatment in the U.S.

However, the FLCCC considers the Panel’s unwillingness to provide more specific guidance in support of the use of ivermectin in COVID-19 to be severely out of alignment with the known clinical, epidemiological, and observational data. Our detailed response to the Panel’s criticism of the existing evidence base can be found [↗ here](#).

“Doesn’t most of the data on ivermectin come primarily from uncontrolled observational trials?”

- 1) Every observational trial (ignoring the massive case series for a moment) that has studied ivermectin in COVID-19 have matched control groups for comparison, with some controlled using a technique called propensity-matching and with many others using contemporaneous, well-matched control groups of patients who did not receive ivermectin by their treating doctor (one would need a close reading of each study to see how well matched they are).
- 2) Observational controlled trials have historically been shown to reach identical conclusions to randomized controlled trials on average in almost all disease models and treatments studied. This fact has been reported in systematic reviews comparing findings from these trial designs and published in the Cochrane database multiple times. It is a fact and a truth about evidence-based medicine that is both neither taught nor emphasized by most of academia who have recently been described, for this reason, as “RCT fundamentalists.” We remind all that observational trials are scientifically valid and should be relied upon, even more so in a pandemic.
- 3) The consistency of findings among the observational and randomized trials of ivermectin is both profound and unique when large numbers of trials have accumulated in the study of a particular medicine. What is most often the case if not the rule, “conflicting results” between trials are typically found, particularly when the medicine is not potent and/or some of the trials are poorly designed. The remarkable consistency the trials studying ivermectin in COVID-19 cannot be over-emphasized. That consistency is unique and persuasive given the diverse set of centers and countries and sizes and designs and phases of illness studied in those trials. It was exactly this consistency that first alerted Professor Paul Marik and the FLCCC Alliance to ivermectin’s efficacy. That consistency has reliably continued in the face of rapidly increasing numbers of trial results becoming available.

“Aren’t the majority of the existing studies not yet peer-reviewed?”

- 1) 14 of the 24 controlled trial results have been peer reviewed, along with 2 of the 5 case series.
- 2) Applying findings from trial manuscripts posted on pre-print servers have been a standard in many of the sciences, including medicine, particularly during the pandemic. Every novel therapeutic that has been widely adopted in medical practice during COVID-19 happened before the peer-reviewed manuscript was available for analysis by the medical community, with the exception of hydroxy-chloroquine which was initially adopted without any posted or published clinical evidence base. Examples of pre-print adopted therapeutics are remdesivir, corticosteroids, monoclonal antibodies, convalescent plasma and the vaccines. Again, all were widely adopted before succeeding the peer-review process.
- 3) Note that the vaccines represent an even more unique case as inoculations of citizens began even before a pre-print manuscript was made available for wider review by the scientific community. Thus, to dismiss the value of ivermectin study results because only 50% have been published in peer-reviewed journals, would suddenly create a new evidentiary standard at a critical point in the pandemic that willfully ignores both the extreme importance that pre-prints play in the rapid dissemination of medical knowledge as well as the reason for their creation. Peer-review takes months. We do not have months. Thousands are dying every day.

“Isn’t it a problem that all the trials were done in foreign countries and may not be generalizable to our patients here?”

Such concerns reflect a surprising degree of ethnocentrism that we believe will lead to further harms against humanity. We cannot deny that these concerns currently present a significant barrier for the evidence compiled in our manuscript to influence practice. We recently learned that a COVID-19 therapeutics committee of a large hospital health care system in the Midwest recently reviewed the existing trials data for ivermectin in November and decided not to recommend ivermectin, with one of the stated reasons being that “many of the studies were performed abroad and are likely not generalizable to our patients”. The belief that a potent anti-viral medicine only works in foreigners and not in Americans is ludicrous and deserves no further comment or explanation except to note it as an example of the most extreme skepticism that can be displayed by providers who simply “do not believe” in the efficacy of ivermectin.

“Shouldn’t we wait until there are more randomized controlled trials?”

12 of the 24 controlled trials results are prospective and randomized and include over 2,000 patients. Again, note that the RECOVERY trial which made corticosteroids the standard of care in COVID-19 overnight was a randomized controlled trial which included 2,000 patients treated with dexamethasone. Further, the number of patients in the 9 observational controlled trials also total over 4,000 patients. Thus, we now have nearly 7,000 patients and 24 controlled trials of ivermectin in varying sizes and designs and countries, with nearly all resulting in consistent, reproducible, large magnitude, statistically significant findings of efficacy as a prophylactic and in early and late phase disease. Given these marked reductions in transmission, hospitalizations, and death, any further studies using a placebo would be

unethical. For any who require more clinical trials data, well-designed observational controlled trials are a perfectly valid alternative and will (and should) be conducted by many, even after adoption as a treatment agent.

“The NIH recommends against the use of ivermectin outside of clinical trials”

That recommendation is from August 27th, is graded IIIA, which means that it was expert opinion only and reflected a “strong” opinion against. Given the amount of data available as of today, December 26, 2020, we must ask the question, “What should the strength and level of recommendation for ivermectin be updated to by the NIH? First, all must understand how recommendations for medical therapies are created by the NIH. They essentially use the below grading scale which provides an assessment of both the strength of the recommendation and the quality of evidence to support that recommendation.

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	II: One or more well-designed, nonrandomized trials or observational cohort studies
C: Optional recommendation for the statement	III: Expert opinion

The last NIH recommendation on ivermectin from August 27th was graded AIII against use as per above table, indicating a strong recommendation based on expert opinion only, despite it being one of the world’s safest, cheapest and most widely available drugs. No rationale or supporting evidence. Further, the grade implies that there was no available clinical evidence at the time to make an “evidence-based” grading, yet we know of a number of trials results available at that time.

Currently, the strongest recommendation possible would be an A-I in support of ivermectin and thus would require “one or more randomized trials with clinical outcomes and/or laboratory endpoints.” Although not specifically stated, this grade typically requires a large, multi-center, randomized, double-blinded, placebo-controlled trial dependent on immense financial resources and infrastructure using the support of pharmaceutical companies or large government research grants. Neither has occurred with ivermectin nor do we think it reasonable or ethical to do so at this point. Despite this, we are fortunate that researchers from many single, academic and non-academic medical centers decided to conduct such trials. Although not a large multi-center trial, we have data from 15 randomized controlled trials (RCT’s) with nearly all reporting improvements in “clinical outcomes” and/or “laboratory endpoints.” Note that the 15 RCT’s consist of trials studying ivermectin as a prophylactic agent (4), early outpatient treatment (5), and in hospitalized patients (6). In each phase of illness, all the RCTs with over 100 patients found statistically significant reductions in rates of transmission, need for hospitalization/mechanical ventilation, or mortality. Thus, it would appear that ivermectin more than fulfills the criteria for a Level A-I recommendation in support of its use as a prophylactic and treatment agent for COVID-19 and thus health care providers would immediately adopt ivermectin.

However, if somehow the entirety of the above RCT results could be dismissed as constituting “insufficient” or “low quality” evidence, the question would then be whether the ivermectin trials data

meets Level A-II evidence. It should be noted that level A-II evidence, in the face of the pandemic and in the context of a cheap, safe and widely available drug, would effectively translate into the same level of action and adoption as level A-I evidence by the nation's health care providers given that remdesivir, a medication with only a B-IIa recommendation is widely used. For a level A-II recommendation, evidence, all that is required are supportive findings from "one or more well-designed non-randomized, or observational cohort studies". Again, fortunately, there are many such studies on ivermectin in COVID-19, with the largest and strongest being Dr. Rijter's study from Florida, published in the major medical journal *Chest* several weeks ago, where they used propensity matching, a technique accorded by many to be as valid a design as a well-conducted RCT's. His and many other well-designed OCT's exist, all reproducing the findings from the above mentioned RCT's. Thus, at a minimum, an A-II recommendation would be met, which would and should lead to immediate and widespread adoption. Further, given the amount of patient data and number of trials results available, it is not worth considering whether a recommendation would be issued as anything less, such as moderate strength (B), or weak strength (C) or a quality grade of III. So, it would appear that ivermectin clearly meets either an A-I or A-II level recommendation in favor of use in COVID-19. Note that this recommendation can be made without the epidemiologic data that has been amassed supporting the population-wide impacts of widespread ivermectin use.

“Why should we be convinced of findings from non-peer reviewed epidemiologic analyses that do not employ control groups?”

The epidemiologic data presented in our manuscript essentially provides the strongest level of medical evidence attainable as they consist of findings from what should be considered large, real-world “natural experiments” which spontaneously occurred within many cities and regions of the world when local and regional health ministries decided to initiate widespread ivermectin distribution to their citizen populations. The “control groups” in these natural experiments were the neighboring cities and regions that did not employ widespread ivermectin distribution. In the areas with ivermectin use compared to those without, large and temporally associated decreases in case counts and fatalities were found after the ivermectin distribution began. Again, the magnitude and reproducibility from city to city, region to region and country to country is unassailable. All data were sourced from universally used, publicly available COVID-19 epidemiologic databases. The manuscript by Chamie et al which focuses solely on these data, is currently near submission for publication, and has now been refined and reviewed by scientists and researchers under the direction of a dean at a major medical research university. A number of these scientist researchers have joined as co-authors of this historically important manuscript.

“Are veterinary ivermectin products considered to be pharmacologically equivalent to human formulations and are these products safe for use?”

Yes, the ivermectin in both formulations is pharmacologically equivalent, however there is a difference in the amount of impurities contained within each. The human formulations have highly regulated and thus very low levels of impurities. We cannot recommend veterinary formulations given the lack of safety data around their use, however we are also not aware of any associated toxicity.

“Is it possible to get an off-label prescription for ivermectin?”

FDA-approved drugs, like ivermectin, may be prescribed for an unapproved use (“off-label”) when the physician believes it to be medically appropriate for their patients. The FDA affords clinicians the freedom to prescribe and treat using medications that they deem to be in the best interest of the patient.

The practice of prescribing drugs “off-label” is so common that 1 out of 5 prescriptions dispensed in the U.S. is for an off-label use. The reason why off-label prescriptions are issued so frequently is because there might not be an approved drug to treat a specific disease or medical condition. Also, patients may have tried all approved treatments without seeing any benefits.

- The [NIH COVID-19 Treatment Panel](#) states that, “Providers can access and prescribe investigational drugs or agents that are approved or licensed for other indications through various mechanisms, including Emergency Use Authorizations (EUAs), Emergency Investigational New Drug (EIND) applications, compassionate use or expanded access programs with drug manufacturers, and/or **off-label use.**”
- The panel also recommends that promising, unapproved, or unlicensed treatments for COVID-19 be studied in well-designed, controlled clinical trials. This includes drugs that have been approved or licensed for other indications. It is important to note that there have been multiple published, peer-reviewed controlled clinical trials throughout the world that point to the efficacy of ivermectin in the prevention and treatment of COVID-19.
- The panel also stipulates that the treatment recommendations in their guidelines are not mandates; but rather that “the choice of what to do or not to do for an individual patient is ultimately decided by the patient and their provider.”

Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgement. Doctors may prescribe what they wish as long as they believe themselves to be well-informed and basing their decision on sound medical evidence. It should be noted, however, that individual institutions may set their own standards for off-label prescriptions if they so choose.

To read more about off-label prescriptions, [click here](#).

“Can a pharmacist refuse to fill a valid prescription for ivermectin written by a licensed health care provider?”

No. Although it is true that in some states in the U.S., pharmacists have the right to refuse to fill a prescription, they can only do so if they are concerned about potential harm to the patient, a concern that is valid in few circumstances such as the following:

- 1) **A known allergy** – i.e. the pharmacist would need to cite a documented history of an allergic reaction during prior treatment with ivermectin that the provider has not indicated they were aware of.
- 2) **A known adverse interaction** with another medication the patient is taking. In this case, the pharmacist would need to cite an absolute contraindication to concurrent use with another

medication. Since there are no absolute contraindications to any medicine given with ivermectin (only dose adjustments or monitoring of levels are required with some) this reason is invalid.

- 3) **The prescribed dose is above the recommended dosage** – given that studies using ivermectin doses up to 10 times the FDA approved dose of 0.2mg/kg have not been associated with any increased adverse effects, this reason would be invalid. Further, doctors can and do prescribe medicines above normal doses for patients and this practice is perfectly legal. Finally, of the many treatment studies of ivermectin in COVID-19, multi-day dose regimens of up to 0.3mg/kg have been used with no reported increase in adverse effects.

Note that if a pharmacist refuses to fill the ivermectin prescription by claiming that “it is not recommended or approved for COVID-19” they should be made aware of the following:

- NIH treatment guidelines are not mandates and thus do not and cannot restrict any provider’s decision to prescribe a medication that the NIH Guidelines panel does not recommend. As stated in the introduction to the NIH guideline for COVID-19: <http://bit.ly/3cu2p33>:
 - “It is important to stress that the rated treatment recommendations in these Guidelines *should not be considered mandates*. The choice of what to do or not to do for an individual patient is ultimately decided by the patient and their provider.”
- “Off-label” prescribing of a medicine that has received FDA-approval for another indication is both legal and common. Further, it is estimated that one in five prescriptions written today are for such off-label use.

Thus, if a pharmacist refuses to fill a prescription without an accepted indication for refusal as above, this can be considered “practicing medicine.” Given that pharmacists have no legal right to practice medicine, in such a case, a complaint to the state medical licensing board may be appropriate. Further, the permit holder/store owner, the pharmacist in charge, the pharmacist who refuses to fill a prescription, and the wholesaler are all licensed by their state’s Board of Pharmacy. A complaint for unprofessional conduct can be filed against each with the appropriate Board of Pharmacy.

State Boards of Pharmacy: <https://nabp.pharmacy/about/boards-of-pharmacy/>

State Medical Licensing Boards: <https://www.fsmb.org/contact-a-state-medical-board/>