Exhibit A

STATE OF NEBRASKA
Office of the Attorney General
2115 STATE CAPITOL BUILDING
LINCOLN, NE 68509-8920
(402) 471-2682
TDD (402) 471-2682
FAX (402) 471-3297 or (402) 471-4725

DOUGLAS J. PETERSON
ATTORNEY GENERAL

No. 21-017

SUBJECT: Prescription of Ivermectin or Hydroxychloroquine as Off-Label Medicines for the Prevention or Treatment of Covid-19

REQUESTED BY: Dannette R. Smith
Chief Executive Officer
Nebraska Department of Health and Human Services

WRITTEN BY: Douglas J. Peterson, Attorney General
James A. Campbell, Solicitor General
Mindy L. Lester, Assistant Attorney General

INTRODUCTION

On September 16, 2021, you requested our opinion on whether it would be "deemed unlawful or otherwise subject to discipline under [Neb. Rev. Stat. § 38-186] for an appropriately licensed health care provider, once informed patient consent has been appropriately obtained, to prescribe" ivermectin, hydroxychloroquine, or other "off label use" medications "for the treatment or prevention of COVID-19." You requested this opinion in your role as Chief Executive Officer of the Nebraska Department of Health and Human Services ("Department"). Neb. Rev. Stat. § 84-205(4) gives you, as the head of an executive department, the authority to ask our office's opinion on legal questions like this one.

The Department, acting through its Division of Public Health, enforces the Nebraska Uniform Credentialing Act ("UCA"). The purpose of the UCA is to protect public

health, safety, and welfare.[1] One way in which the Department protects the public is by investigating complaints alleging that licensed healthcare professionals have committed UCA violations.[2] After the Department completes an investigation, it refers the matter to the appropriate professional board to consider and make a recommendation to the Attorney General. Neb. Rev. Stat. § 38-186 then gives the Attorney General the authority to file a petition for discipline against the healthcare provider if such action is warranted.

You indicate in your request that "[c]onsumers and health care providers have been and continue to be inundated with information and opinions[] regarding COVID-19 treatment and prevention." You also note that due to the "sheer volume" of conflicting information, questions have been raised "regarding the permissibility of certain medications for the treatment or prevention of COVID-19." This observation is consistent with questions that our office has received from constituents and discussions that our office has witnessed at some of the professional boards' meetings.

After receiving your question and conducting our investigation, we have found significant controversy and suspect information about potential COVID-19 treatments. A striking example features one of the world's most prestigious medical journals—the Lancet. In the middle of the COVID-19 pandemic, the Lancet published a paper denouncing hydroxychloroquine as dangerous.[3] Yet the reported statistics were so flawed that journalists and outside researchers immediately began raising concerns.[4] Then after one of the authors refused to provide the analyzed data, the paper was retracted,[5] but not before many countries stopped using hydroxychloroquine and trials were cancelled or interrupted. The Lancet's own editor in chief admitted that the paper was a "fabrication," "a monumental fraud,"[6] and "a shocking example of research misconduct in the middle of

---

1 Neb. Rev. Stat. § 38-128(1).

2 Neb. Rev. Stat. § 38-1,124.

3 Mandeep R. Mehra et al., *Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis*, The Lancet (May 22, 2020), *available at* https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2931180-6 (last visited Oct. 14, 2021).

4 Melissa Davey, *Questions raised over hydroxychloroquine study which caused WHO to halt trials for Covid-19*, The Guardian (May 27, 2020), *available at* https://www.theguardian.com/science/2020/may/28/questions-raised-over-hydroxychloroquine-study-which-caused-who-to-halt-trials-for-covid-19 (last visited Oct. 14, 2021).

5 Sarah Boseley & Melissa Davey, *Covid-19: Lancet retracts paper that halted hydroxychloroquine trials*, The Guardian (Jun. 4, 2020), *available at* https://www.theguardian.com/world/2020/jun/04/covid-19-lancet-retracts-paper-that-halted-hydroxychloroquine-trials (last visited Oct. 14, 2021).

6 Roni Caryn Rabin, *The Pandemic Claims New Victims: Prestigious Medical Journals*, New York Times (Jun. 14, 2020), *available at* https://www.nytimes.com/2020/06/14/health/virus-journals.html (last visited Oct. 14, 2021).

a global health emergency."[7] When fraudulent information is published in a leading medical journal, it understandably leads to skepticism in some physicians and members of the public. Mindful of these concerns about misunderstandings and mistrust, we have drafted a rather lengthy opinion that aims to address the public confusion and outline the relevant scientific literature that supports our legal conclusions.

At the outset, we pause to delineate the parameters of this opinion. The question presented asked about ivermectin, hydroxychloroquine, and other drugs used "off label"—that is, for a purpose other than the specific use approved by the U.S. Food and Drug Administration ("FDA"). To enable us to respond in a timely manner, we have confined our discussion to ivermectin and hydroxychloroquine only. But in doing so, we do not mean to rule out the possibility that other off-label drugs might show promise—either now or in the future—as a prophylaxis or treatment against COVID-19. Also, because our investigation has revealed that physicians who currently use hydroxychloroquine for COVID-19 do so as either a prophylaxis or an early treatment for outpatients (as opposed to a late treatment in hospitalized patients), we will confine our consideration of hydroxychloroquine to those two uses. In addition, we note that there are treatment options the FDA has approved, either through an Emergency Use Authorization ("EUA") or through the regular FDA drug-approval process, for COVID-19 prophylaxis or treatment. These include monoclonal antibodies, vaccines, and remdesivir. We do not take any position on those options because they are outside the scope of the question asked.

In the end, as we explain below, we find that the available data does not justify filing disciplinary actions against physicians simply because they prescribe ivermectin or hydroxychloroquine to prevent or treat COVID-19. If, on the other hand, healthcare providers neglect to obtain informed consent, deceive their patients, prescribe excessively high doses, fail to check for contraindications, or engage in other misconduct, they might be subject to discipline. But based on the evidence that currently exists, the mere fact of prescribing ivermectin or hydroxychloroquine for COVID-19 will not result in our office filing disciplinary actions. While our terminology throughout this opinion focuses on physicians prescribing these medicines, what we conclude necessarily applies to other licensed healthcare professionals who prescribe, participate in, or otherwise assist with a treatment plan utilizing these medications.

ANALYSIS

1. The Nebraska Uniform Credentialing Act and Other Relevant Law

The UCA was enacted by the legislature to license and regulate persons and businesses that provide healthcare and health-related services.[8] The UCA was adopted

---

7 Boseley & Davey, *supra*.

8 Neb. Rev. Stat. §§ 38-102 & 38-104.

to protect public health, safety, and welfare, and to provide for the efficient, adequate, and safe practice of credentialed persons and businesses.[9] "It is the intent of the Legislature," the UCA explains, "that quality health care services and human services be provided to the public" and "that professionals be regulated by the state only when it is demonstrated that such regulation is in the best interest of the public."[10]

The UCA grants the Director of Public Health of the Department's Division of Public Health the authority to deny a credential, refuse a credential renewal, or discipline a credential holder, although the Chief Medical Officer (if one is appointed) shall perform the Director's duties for decisions in contested administrative cases.[11] The Department must provide "the Attorney General with a copy of all complaints it receives and advise the Attorney General of investigations it makes" regarding possible violations of the UCA.[12] Following review and recommendation from the appropriate professional health board, the Attorney General must then determine whether the credential holder has violated any statutes or regulations and decide whether to proceed with administrative action.[13]

If the Attorney General determines that a violation has occurred, he "shall" file a petition for disciplinary action with the Department.[14] The Attorney General cannot prevail in disciplinary proceedings against a licensed healthcare professional unless he proves the claim by clear and convincing evidence.[15]

The grounds for disciplinary action are set forth in Neb. Rev. Stat. § 38-178 and include, among other things, acting with "gross incompetence or gross negligence," practicing in "a pattern of incompetent or negligent conduct," or engaging in "unprofessional conduct" as set forth in Neb. Rev. Stat. § 38-179.[16] Gross incompetence is a very high standard; it occurs only when there is "such an extreme deficiency on the part of a physician in the basic knowledge and skill necessary for diagnosis and treatment that one may reasonably question his or her ability to practice medicine at the threshold level of

---

9 Neb. Rev. Stat. § 38-103.

10 Neb. Rev. Stat. § 38-128(1).

11 Neb. Rev. Stat. §§ 38-176(1) & 38-1,101.

12 Neb. Rev. Stat. § 38-1,107(1).

13 Neb. Rev. Stat. §§ 38-1,107 & 38-1,108.

14 Neb. Rev. Stat. § 38-186.

15 *Poor v. State*, 266 Neb. 183, 190, 663 N.W.2d 109, 115 (2003); *Davis v. Wright*, 243 Neb. 931, 936-37, 503 N.W.2d 814, 818 (1993).

16 Neb. Rev. Stat. § 38-178(6), (24).

professional competence."[17] Neb. Rev. Stat. § 38-179 generally defines unprofessional conduct as a "departure from or failure to conform to the standards of acceptable and prevailing practice of a profession or the ethics of the profession, regardless of whether a person, consumer, or entity is injured, or conduct that is likely to deceive or defraud the public or is detrimental to the public interest."[18] Along these same lines, the regulation governing physicians states that unprofessional conduct includes:

> [c]onduct or practice outside the normal standard of care in the State of Nebraska which is or might be harmful or dangerous to the health of the patient or the public, not to include a single act of ordinary negligence.[19]

Healthcare providers do not violate the standard of care when they "select between two reasonable approaches to . . . medicine."[20] Regulations also indicate that physicians may utilize reasonable "investigative or unproven therapies" that reflect a reasonable approach to medicine so long as physicians obtain "written informed patient consent."[21] "Informed consent concerns a doctor's duty to inform his or her patient," and it includes telling patients about "the nature of the pertinent ailment or condition, the risks of the proposed treatment or procedure, and the risks of any alternative methods of treatment, including the risks of failing to undergo any treatment at all."[22] Regulations require physicians "to keep and maintain" records that disclose the "advice and cautionary warnings provided to the patient."[23]

Prescribing medicines for off-label use—that is, for some purpose other than the use approved by the FDA—often falls within the standard of care. Indeed, "[o]ff-label use is legal, common, and necessary,"[24] and "[c]ourts have repeatedly recognized the propriety of off-label use."[25] This includes the U.S. Court of Appeals for the Eighth Circuit, which has acknowledged that "[d]octors may prescribe an FDA-approved drug for

---

17 *Langvardt v. Horton*, 254 Neb. 878, 895, 581 N.W.2d 60, 70-71 (1998).

18 Neb. Rev. Stat. § 38-179.

19 172 Neb. Admin. Code § 88-009(Q).

20 *Whittle v. Dep't of Health & Hum. Servs.*, 309 Neb. 695, 721-22, 962 N.W.2d 339, 356-57 (2021).

21 172 Neb. Admin. Code § 88-009(B).

22 *Curran v. Buser*, 271 Neb. 332, 337, 711 N.W.2d 562, 568 (2006) (citations omitted).

23 172 Neb. Admin. Code § 88-009(B).

24 James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 Food & Drug L.J. 71, 76 (1998) (capitalization omitted).

25 *Id.* (collecting cases).

nonapproved uses."[26] And the U.S. Supreme Court, in an analogous context, has affirmed that "'off-label' usage of medical devices" is an "accepted and necessary" practice.[27] Even the FDA recognizes that off-label use is legitimate: it has said for many decades that once it approves a drug, "a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling."[28] Expanding on that point, the FDA has explained that "healthcare providers generally may prescribe [a] drug for an unapproved use when they judge that it is medically appropriate for their patient."[29] Nothing in the federal Food, Drug, and Cosmetic Act ("FDCA") "limit[s] the manner in which a physician may use an approved drug."[30]

Based on these principles, we conclude that governing law allows physicians to use FDA-approved medicines that are unproven for a particular off-label use so long as (1) reasonable medical evidence supports that use and (2) a patient's written informed consent is obtained. In the context of this ever-changing global pandemic, we note that it is appropriate to consider medical evidence outside of Nebraska and to give physicians who obtain informed consent an added measure of deference on their assessment of the available medical evidence.

2. COVID-19 and SARS-CoV-2

The disease known as COVID-19 and the virus that causes it—SARS-CoV-2—took the world by storm in late 2019 and early 2020. While there is still so much that the medical community does not know about SARS-CoV-2 and COVID-19, it is widely recognized that COVID-19 is a multifaceted disease. "[A]dults with SARS-CoV-2 infection can be grouped" into at least three different categories depending on the progression of their disease.[31] The first group has an asymptomatic or presymptomatic infection, meaning that those individuals have "test[ed] positive for SARS-CoV-2" but "have no symptoms

---

[26] *Rhone-Poulenc Rorer Pharms., Inc. v. Marion Merrell Dow, Inc.*, 93 F.3d 511, 514 n.3 (8th Cir. 1996).

[27] *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001).

[28] FDA Drug Bulletin at 5 (Apr. 1982), *available at* https://play.google.com/books/reader?id=3f3YC3Gw6sEC&pg=GBS.PA6&hl=en (last visited Oct. 14, 2021).

[29] U.S. Food & Drug Administration, Understanding Unapproved Use of Approved Drugs "Off Label" (Feb. 5, 2018), https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label (last visited Oct. 14, 2021).

[30] FDA Drug Bulletin, *supra*, at 5. Because the question posed to us asks about prescribing drugs for off-label use, any view on the legality of efforts to market drugs for off-label use is outside the scope of this opinion.

[31] National Institutes of Health, Clinical Spectrum of SARS-CoV-2 Infection, COVID-19 Treatment Guidelines (Apr. 21, 2021), *available at* https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/ (last visited Oct. 14, 2021).

that are consistent with COVID-19."[32] A second group experiences a mild illness that manifests itself through "any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell)" but does not include "shortness of breath, dyspnea, or abnormal chest imaging."[33] And a third group suffers from a more severe illness marked by "evidence of lower respiratory disease" and deficient "oxygen saturation" levels.[34] When people in this third category reach a critical level, they often "have respiratory failure, septic shock, and/or multiple organ dysfunction."[35]

A recently published paper on COVID-19 recognized that "for reasons that are yet to be clarified, early treatment has not been emphasized" in Western countries like the United States.[36] Despite this, many healthcare providers in the United States advocate for early treatment, particularly for high-risk patients. In fact, scores of treating and academic physicians have published papers in well-respected journals like the American Journal of Medicine explaining that the "multifaceted pathophysiology of life-threatening COVID-19 illness . . . warrants early interventions"[37] and encouraging "outpatient treatment of the illness with the aim of preventing hospitalization or death."[38] Also, a declaration of the International Alliance of Physicians and Medical Scientists—which is apparently signed by over 10,000 physicians and scientists, more than 60 of whom are publicly identified online—supports a doctor's choice to provide early COVID-19 care rather than "advising their patients to simply go home . . . and return when their disease worsens."[39]

---

32 *Id.*

33 *Id.*

34 *Id.*

35 *Id.*

36 Matthieu Million et al., *Early combination therapy with hydroxychloroquine and azithromycin reduces mortality in 10,429 COVID-19 outpatients*, 22 Reviews in Cardiovascular Medicine 1063, 1063 (Sept. 2021), https://rcm.imrpress.com/article/2021/2153-8174/2153-8174-22-3-1063.shtml (last visited Oct. 14, 2021).

37 Peter A. McCullough et al., *Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19)*, 21 Reviews in Cardiovascular Medicine 517, 518 (Dec. 2020), *available at* https://rcm.imrpress.com/article/2020/2153-8174/RCM2020264.shtml (last visited Oct. 14, 2021) (including 57 co-authors) (hereinafter, "McCullough, *Multifaceted*").

38 Peter A. McCullough et al., *Pathophysiological Basis and Rationale for Early Outpatient Treatment of SARS-CoV-2 (COVID-19) Infection*, 134 American Journal of Medicine 16, 16 (Jan. 2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7410805/pdf/main.pdf (last visited Oct. 14, 2021) (including 23 co-authors) (hereinafter, "McCullough, *Pathophysiological*").

39 Physicians Declaration, Global COVID Summit, International Alliance of Physicians and Medical Scientists (Sept. 2021), https://doctorsandscientistsdeclaration.org/ (last visited Oct. 14, 2021).

These groups of physicians have established protocols for early treatment, and ivermectin and hydroxychloroquine are staples of those treatments.[40] As discussed in greater detail below, while the scientific literature is continuing to grow, some data suggest that ivermectin- or hydroxychloroquine-based early treatments of COVID-19 can be effective in thwarting hospitalization and death.[41]

3. Ivermectin

A. History of Ivermectin

Researchers discovered ivermectin in the 1970s, and while its first use was to treat parasites in animals, ivermectin has been used in humans since the 1980s.[42] In the early years, ivermectin effectively stymied the scourge of two devastating parasitic diseases—onchocerciasis (also known as river blindness) and lymphatic filariasis—"among poverty-stricken populations throughout the tropics."[43] These are two of the most "disfiguring diseases" that "have plagued the world's poor . . . for centuries."[44] Later, the use of ivermectin was expanded to include "the treatment of scabies and lice."[45]

---

40 *E.g.*, McCullough, *Multifaceted*, *supra*, at 519 Table 1 (listing early treatment kits that include both ivermectin and hydroxychloroquine); McCullough, *Pathophysiological*, *supra*, at 18–19 (discussing hydroxychloroquine).

41 *E.g.*, Flavio A. Cadegiani et al., *Early COVID-19 therapy with azithromycin plus nitazoxanide, ivermectin or hydroxychloroquine in outpatient settings significantly improved COVID-19 outcomes compared to known outcomes in untreated patients*, New Microbes and New Infections (Sept. 2021), *available at* https://www.sciencedirect.com/science/article/pii/S2052297521000792 (last visited Oct. 14, 2021) (finding that "the use of nitazoxanide, ivermectin[,] and hydroxychloroquine demonstrated unexpected improvements in COVID-19 outcomes when compared to untreated patients").

42 Andy Crump, *Ivermectin: enigmatic multifaceted 'wonder' drug continues to surprise and exceed expectations*, 70 The Journal of Antibiotics 495, 495 (2017), *available at* https://www.nature.com/articles/ja201711.pdf (last visited Oct. 14, 2021) (hereinafter, "Crump, *Ivermectin*").

43 *Id.*

44 Andy Crump & Satoshi Ōmura, *Ivermectin, 'wonder drug' from Japan: the human use perspective*, 87 Proceedings of the Japan Academy, Series B, Physical and biological sciences 13, 13 (2011), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3043740/pdf/pjab-87-013.pdf (last visited Oct. 14, 2021).

45 Andrew Bryant et al., *Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines*, 28 American Journal of Therapeutics 434, 435 (Jul./Aug. 2021), *available at* https://journals.lww.com/americantherapeutics/fulltext/2021/08000/ivermectin_for_prevention_and_treatment_of.7.aspx (last visited Oct. 14, 2021) (hereinafter, "Bryant, *Ivermectin*").

Given its track record as a medicine for humans, ivermectin has long since been "approved as an antiparasitic" by the World Health Organization (WHO) and the FDA.[46] The WHO has also recognized ivermectin as one of its "Essential Medicines."[47] Further recognizing the importance of this drug, in 2015 its discoverers won the Nobel Prize in Medicine for their work in uncovering it and bringing it to market.[48]

In the decade leading up to the COVID-19 pandemic, studies began to show ivermectin's surprising versatility. By 2017, ivermectin had "demonstrate[d] antiviral activity against several RNA viruses by blocking the nuclear trafficking of viral proteins."[49] One recent systematic review cited more than a handful of studies to "demonstrate that ivermectin has antiviral properties against an increasing number of RNA viruses, including influenza, *Zika*, HIV, [and] *Dengue*."[50] And another review summarized the "antiviral effects of ivermectin" demonstrated through "studies over the past 50 years."[51]

Before the pandemic, scholarly literature had also recognized ivermectin's "anti-inflammatory capacity."[52] Doctors thus have been using ivermectin to treat "rosacea, a chronic inflammatory disease," that manifests itself as a reddening of the face, and the FDA has approved ivermectin for that purpose.[53] Ivermectin's ability to "curb inflammation," one reviewer wrote, may also "be useful in treating . . . inflammatory airway diseases."[54] Summing it up, that same reviewer recognized that "ivermectin is continuing

---

46 *Id.*

47 *Id.*

48 The Nobel Prize, Press Release for The Nobel Prize in Physiology or Medicine 2015 (Oct. 5, 2015), https://www.nobelprize.org/prizes/medicine/2015/press-release/ (last visited Oct. 14, 2021).

49 Crump, *Ivermectin*, *supra*, at 500.

50 Pierre Kory et al., *Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19*, 28 American Journal of Therapeutics 299, 301 (2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8088823/ (last visited Oct. 14, 2021).

51 Fatemeh Heidary & Reza Gharebaghi, *Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen*, 73 The Journal of Antibiotics 593, 593 (2020), *available at* https://www.nature.com/articles/s41429-020-0336-z.pdf (last visited Oct. 14, 2021) ("Several studies reported antiviral effects of ivermectin on RNA viruses . . . . Furthermore, there are some studies showing antiviral effects of ivermectin against DNA viruses . . . .").

52 Crump, *Ivermectin, supra*, at 499.

53 Leon H. Kircik et al., *Over 25 Years of Clinical Experience With Ivermectin: An Overview of Safety for an Increasing Number of Indications*, 15 Journal of Drugs in Dermatology 325, 325 (Mar. 2016), *available at* https://jddonline.com/articles/dermatology/S1545961616P0325X (last visited Oct. 14, 2021).

54 Crump, *Ivermectin*, *supra*, at 499; *see also* Arianna Portmann-Baracco et al., *Antiviral and anti-inflammatory properties of ivermectin and its potential use in Covid-19*, 56 Archivos De Bronconeumologia

to surprise and excite scientists, offering more and more promise to help improve global public health by treating a diverse range of diseases."[55]

For more than three decades, ivermectin has also shown itself to be very safe. Indeed, the National Institutes of Health ("NIH") recognize that "ivermectin has been widely used and is generally well tolerated."[56] One recent systematic review similarly states that "ivermectin at the usual doses . . . is considered extremely safe for use in humans."[57] Other studies have noted that the medicine "has an established safety profile for human use,"[58] and it "provide[s] a high margin of safety for a growing number of indications."[59] Notably, a December 2018 WHO-supported application to add ivermectin as an essential medicine for scabies reviewed the data and concluded that the adverse events associated with ivermectin are "primarily minor and transient."[60]

The available data support this conclusion. The WHO's VigiAccess database, which compiles adverse drug reactions from throughout the world, breaks down the reported side effects for drugs into different categories.[61] The largest reported categories for ivermectin include skin issues, headaches, dizziness, and gastrointestinal disturbances such as diarrhea and nausea.[62] The NIH confirms that ivermectin's primary adverse side effects "include dizziness, pruritis [itchy skin], nausea, or diarrhea."[63] And

---

831, 831 (2020), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7578741/pdf/main.pdf (last visited Oct. 14, 2021) ("Ivermectin has a demonstrated anti-inflammatory effect *in vivo* and *in vitro*").

55 Crump, *Ivermectin*, *supra*, at 495.

56 National Institutes of Health, COVID-19 Treatment Guidelines: Ivermectin, https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ivermectin/ (last visited Oct. 14, 2021) (hereinafter, "NIH, COVID-19 and Ivermectin").

57 Bryant, *Ivermectin*, *supra*, at 435.

58 Leon Caly et al., *The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro*, Antiviral Research 178 at 3 (June 2020), *available at* https://www.sciencedirect.com/science/article/pii/S0166354220302011 (last visited Oct. 14, 2021).

59 Kircik, *Ivermectin*, *supra*, at 325.

60 WHO Expert Committee on the Selection and Use of Essential Medicines: Application for inclusion of ivermectin on the WHO Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc) for the indication of Scabies at 19 (Dec. 2018), *available at* https://www.who.int/selection_medicines/committees/expert/22/applications/s6.6_ivermectin.pdf (last visited Oct. 14, 2021).

61 VigiAccess, Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, http://www.vigiaccess.org/ (last visited Oct. 14, 2021).

62 *Id.*

63 NIH, COVID-19 and Ivermectin, *supra*.

a recent review of ivermectin similarly describes the common side effects as "itching, rash, swollen lymph nodes, joint pain[], fever, and headache."[64]

The data show not only that the adverse side effects are minor, but also that the percentage of people who report experiencing any adverse events is vanishingly small. The latest statistics available through VigiAccess report only 5,674 adverse drug reactions from ivermectin between 1992 and October 13, 2021.[65] This number is incredibly low considering that "more than 3.7 billion doses" of ivermectin have been administered to humans worldwide since the 1980s.[66]

To illustrate the safety of ivermectin, compare its VigiAccess report to that of remdesivir, an FDA-approved treatment for COVID-19.[67] Remdesivir was not released for widespread use until 2020. Yet in the short period of time that it has been on the market, people have reported at least 7,491 adverse drug reactions on VigiAccess, more than ivermectin has registered over the last 30 years.[68] What's more, serious adverse reactions from remdesivir are reported in high numbers. For example, in less than two years, those who have used remdesivir have reported over 560 deaths, 550 serious cardiac disorders (such as bradycardia and cardiac arrest), and 475 acute kidney injuries.[69] Since that safety profile is sufficient to retain FDA approval, ivermectin's safety record cannot reasonably be questioned.

B. Ivermectin and COVID-19

As discussed above, ivermectin had shown its antiviral and anti-inflammatory properties long before the pandemic began. So when COVID-19 began to spread across the globe, some in the medical community quickly identified ivermectin as a potential drug for the prevention and treatment of COVID-19. Initially, a group of researchers found that ivermectin significantly inhibited replication of SARS-CoV-2 in cell cultures.[70] Dismissing

---

64 Kory, *supra*, at 314.

65 VigiAccess, Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, http://www.vigiaccess.org/ (last visited Oct. 14, 2021).

66 Morimasa Yagisawa et al., *Global trends in clinical studies of ivermectin in COVID-19*, 74 The Japanese Journal of Antibiotics 44, 46 (Mar. 2021), *available at* http://jja-contents.wdc-jp.com/pdf/JJA74/74-1-open/74-1_44-95.pdf (last visited Oct. 14, 2021).

67 U.S. Food and Drug Administration, *FDA Approves First Treatment for COVID-19* (Oct. 22, 2020), https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19 (last visited Oct. 14, 2021).

68 VigiAccess, Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, http://www.vigiaccess.org/ (last visited Oct. 14, 2021).

69 *Id.*

70 Caly, *supra*, at 1.

that finding, ivermectin doubters argued that too much of the drug would be needed to achieve this antiviral activity in humans.[71] But peer-reviewed models undermined those concerns by showing that the predicted accumulation of ivermectin in the lungs—the site in the body where the medicine is most needed—would be over 10 times higher than necessary for antiviral activity.[72] In layman's terms, these models indicated that an effective level of the medicine can be reached in lung tissue without creating toxicity in the blood. Plus, other pro-ivermectin doctors have explained that the amount of the drug "required for an effect in cell culture models bear[s] little resemblance to human physiology" because cell cultures lack "an active immune system working synergistically with" the medicine.[73]

The doctors who believed that ivermectin could be effective against COVID-19 also identified its anti-inflammatory properties as an important countermeasure to the disease. One reason why COVID-19 progresses to its severe phase, many believe, is "the provocation of an overwhelming and injurious inflammatory response."[74] Thus, ivermectin's anti-inflammatory effects suggest that it can help COVID-19 patients as the disease worsens.

i. Ivermectin Studies and Meta-analyses

Since the COVID-19 pandemic began, researchers have conducted over 20 randomized controlled trials (RCTs) and more observational trials to evaluate ivermectin's effectiveness in the prevention and treatment of COVID-19.[75] Many of those trials showed promise. On the question of COVID-19 prevention, the Shouman study out of Egypt—a RCT—evaluated ivermectin as a potential prophylaxis for close family members of COVID-19 patients.[76] The test group included 203 family members who took

---

71 Virginia D. Schmith et al., *The Approved Dose of Ivermectin Alone is not the Ideal Dose for the Treatment of COVID-19*, 108 Clinical Pharmacology & Therapeutics 762, 762 (Oct. 2020), *available at* https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.1889 (last visited Oct. 14, 2021).

72 Usman Arshad et al., *Prioritization of Anti-SARS-Cov-2 Drug Repurposing Opportunities Based on Plasma and Target Site Concentrations Derived from their Established Human Pharmacokinetics*, 108 Clinical Pharmacology and Therapeutics 775, 785 (Oct. 2020), *available at* https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.1909 (last visited Oct. 14, 2021).

73 Kory, *supra*, at 301.

74 *Id.*

75 Bryant, *Ivermectin*, *supra*, at 435.

76 Waheed M. Shouman et al., *Use of Ivermectin as a Potential Chemoprophylaxis for COVID-19 in Egypt: A Randomised Clinical Trial*, 15 Journal of Clinical and Diagnostic Research 27, 27 (Feb. 2021), *available at* https://www.jcdr.net/articles/PDF/14529/46795_CE[Ra]_F(Sh)_PF1(SY_OM)_PFA_(OM)_PN(KM).pdf (last visited Oct. 14, 2021).

ivermectin, and only 15 of them (7.4%) developed COVID-19.[77] Compare that to the 101 family members in the control group, 59 of whom (58.4%) tested positive during the study.[78] These outcomes prompted the research team to conclude that ivermectin is "a promising, effective[,] and safe chemoprophylactic drug in management of COVID-19."[79] Also, the Behera study in India tested ivermectin as a prophylaxis in a group of 3,532 healthcare workers.[80] Of the 2,199 workers who took two doses of ivermectin prophylaxis three days apart, only 45 (2%) tested positive for COVID-19.[81] But of the 1,147 workers who did not take ivermectin, 133 (11.6%) contracted the disease.[82] Behera's team thus announced that two doses of ivermectin "as chemoprophylaxis among [healthcare workers] reduced the risk of COVID-19 infection by 83% in the following month."[83]

Moving beyond ivermectin's role as a prophylaxis, other studies have demonstrated its potential as a COVID-19 treatment. The Mahmud study—a RCT that explored ivermectin as an early treatment for 363 individuals—concluded that "[p]atients with mild-to-moderate COVID-19 infection treated with ivermectin plus doxycycline recovered earlier, were less likely to progress to more serious disease, and were more likely to be COVID-19 negative . . . on day 14."[84] And Niaee's research team found that ivermectin can help even hospitalized patients.[85] That group conducted a "randomized, double-blind, placebo-controlled, multicenter clinical trial" with 180 hospitalized patients diagnosed with COVID-19.[86] They concluded that ivermectin "reduces the rate of

---

77 *Id.*

78 *Id.*

79 *Id.*

80 Priyamadhaba Behera et al., *Prophylactic Role of Ivermectin in Severe Acute Respiratory Syndrome Coronavirus 2 Infection Among Healthcare Workers*, Cureus, at 1 (Aug. 2021), *available at* https://assets.cureus.com/uploads/original_article/pdf/64807/20210904-4912-omcmtf.pdf (last visited Oct. 14, 2021).

81 *Id.* at 5.

82 *Id.*

83 *Id.* at 1.

84 Reaz Mahmud et al., *Ivermectin in combination with doxycycline for treating COVID-19 symptoms: a randomized trial,* Journal of International Medical Research 49(5) (Apr. 2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8127799/pdf/10.1177_03000605211013550.pdf (last visited Oct. 14, 2021).

85 Morteza Shakhsi Niaee et al., *Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial*, 14 Asian Pacific Journal of Tropical Medicine 266, 266 (2021), *available at* https://www.apjtm.org/temp/AsianPacJTropMed146266-5371482_145514.pdf (last visited Oct. 14, 2021).

86 *Id.*

mortality . . . and duration of hospitalization in adult COVID-19 patients," and "[t]he improvement of other clinical parameters showed that the ivermectin, with a wide margin of safety, had a high therapeutic effect on COVID-19."[87]

As the data accumulated, scholars began conducting and publishing meta-analyses of the available studies. One such analysis—the Bryant review—focused on 24 total RCTs involving 3,406 participants and found "with moderate certainty that ivermectin treatment in COVID-19 provides a significant survival benefit."[88] It also concluded that "[u]sing ivermectin early in the clinical course may reduce numbers progressing to severe disease" and that "[t]he apparent safety and low cost suggest that ivermectin is likely to have a significant impact on the SARS-CoV-2 pandemic globally."[89] Following Bryant's publication of his team's review, the Elgazzar study—one of the RCTs included in the meta-analysis—was questioned and is now under review. This prompted Bryant's team to reanalyze the data without the Elgazzar study, and that review still found "a clear result, showing a 49% reduction in mortality in favor of ivermectin."[90]

Another meta-analysis known as the Popp review has reached more skeptical conclusions. That analysis, which excluded some of the RCTs that Bryant considered, evaluated only 14 studies with 1,678 participants and determined that the "completed studies are small and few are considered high quality."[91] Thus, the authors expressed "uncertain[ty] about the efficacy and safety of ivermectin used to treat or prevent COVID-19."[92] Recently, however, the Bryant team critiqued the Popp review, highlighting, among other things, that although "Popp claims to provide a 'complete evidence profile,'" it actually "excludes most of the available evidence."[93]

In further contrast, a third meta-analysis expressed doubt about ivermectin. That one—the Roman review—restricted the pool of RCTs even further, considering only 10

---

87 *Id.*

88 Bryant, *Ivermectin, supra*, at 451.

89 *Id.* at 435.

90 Andrew Bryant et al., *Letter to the Editor: Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines*, 28 American Journal of Therapeutics 573, 573 (Sept./Oct. 2021), *available at* https://covid19criticalcare.com/wp-content/uploads/2021/09/Response-to-Elgazzar.pdf (last visited Oct. 14, 2021).

91 Maria Popp et al., *Ivermectin for preventing and treating COVID-19*, Cochrane Database of Systematic Reviews, at 2 (July 28, 2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8406455/pdf/CD015017.pdf (last visited Oct. 14, 2021).

92 *Id.*

93 Edmund J. Fordham et al., *The uses and abuses of systematic reviews: the case of ivermectin in Covid-19*, OSF Preprints, at 7 (Sept. 3, 2021), *available at* https://osf.io/peqcj/ (last visited Oct. 14, 2021).

of them.[94] After doing this, the authors concluded that ivermectin does "not reduce all-cause mortality, [length of hospital stay], or viral clearance . . . in patients with mostly mild COVID-19."[95] As a result, the researchers announced that ivermectin "is not a viable option to treat patients with COVID-19."[96]

In the days since its publication, the Roman review has drawn some harsh criticism. In particular, the authors of the Bryant review have highlighted four categories of flaws with Roman's work: (1) "mis-reporting of source data," (2) "highly selective study inclusion," (3) "'cherry picking' of data within included studies," and (4) "conclusions that do not follow from the evidence."[97] To illustrate these flaws, consider that Roman's paper initially inverted the treatment and control arms for the Niaee study and thus indicated less mortality in the control group when in fact the opposite was true.[98] Once that error was fixed, the numbers no longer supported the conclusion that ivermectin does "not reduce all-cause mortality."[99] Yet the Roman team did not adjust that statement, and thus its "conclusions are no longer based on the data."[100]

Furthermore, in a letter to the editor of the *American Journal of Therapeutics*, two researchers recently explained that Roman's conclusion of no mortality reduction "is not based on the results of the statistical analysis of the data . . . ; instead, it was based on a somewhat vague and possibly biased subjective assessment of the quality of the trials

---

94 Yuani M. Roman et al., *Ivermectin for the treatment of Coronavirus Disease 2019: A systematic review and meta-analysis of randomized controlled trials*, Clinical Infectious Diseases, at 1 (June 28, 2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8394824/pdf/ciab591.pdf (last visited Oct. 14, 2021).

95 *Id.*

96 *Id.*

97 Letter from Andrew Bryant et al. to Robert T. Schooley, MD, Editor in Chief, Clinical Infectious Diseases, at 3, *available at* https://covid19criticalcare.com/wp-content/uploads/2021/07/RomanRebuttal_v7_EF_letterhead_ML-1.pdf (last visited Oct. 14, 2021) (hereinafter, "Bryant Letter to Schooley").

98 *Compare* Yuani M. Roman et al., *Ivermectin for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials*, Preprint Version 1, at 27 Figure 2 (May 25, 2021), *available at* https://www.medrxiv.org/content/10.1101/2021.05.21.21257595v1.full.pdf (last visited Oct. 14, 2021) (listing the Niaee study as having four deaths in the control arm and 11 in the ivermectin arm), *with* Yuani M. Roman et al., *Ivermectin for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials*, Preprint Version 2, at 27 Figure 2 (May 26, 2021), *available at* https://www.medrxiv.org/content/10.1101/2021.05.21.21257595v2.full.pdf (last visited Oct. 14, 2021) (correcting the Niaee study to list 11 deaths in the control arm and four in the ivermectin arm).

99 Bryant Letter to Schooley, *supra*, at 2.

100 *Id.*

themselves."[101] Those researchers conducted their own Bayesian analysis, a method of statistical inference, and found that the "probability for the hypothesis of a causal link between COVID-19 severity, ivermectin, and mortality is over 99%."[102] As they concluded, "[i]n our view, this Bayesian analysis, based on the statistical study data, provides sufficient confidence that ivermectin is an effective treatment for COVID-19 and this belief supports the conclusions of Bryant over those of Roman."[103] Those scholars have since published their full analysis in a paper available online.[104]

Additional supportive evidence for Bryant's conclusions is a non-peer-reviewed website that currently maintains a running list of 64 COVID-19-related ivermectin studies—RCTs and others—which include all the relevant ivermectin studies except the few (such as Elgazzar) whose data have been called into question.[105] Of those 64 studies, 31 are RCTs and 44 have been peer-reviewed.[106] That site posts multiple meta-analyses of different groupings of the data and concludes that "[m]eta analysis using the most serious outcome reported shows" that ivermectin leads to 66% "improvement for early treatment" and an 86% "improvement for . . . prophylaxis."[107] These "[r]esults are very robust," the site reports, because "in worst case exclusion sensitivity analysis 53 of 64 studies must be excluded to avoid finding statistically significant efficacy."[108]

Finally, a recent mini-review of ivermectin and COVID-19 considered the studies analyzing ivermectin's safety specifically in the context of COVID-19 treatments.[109] That mini-review—which was authored by Yale Professor Alessandro D. Santin—observed

---

101 Martin Neil & Norman Fenton, *Bayesian Hypothesis Testing and Hierarchical Modeling of Ivermectin Effectiveness*, 28 American Journal of Therapeutics 576, 576 (Sept./Oct. 2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8415515/pdf/ajt-28-e576.pdf (last visited Oct. 14, 2021).

102 *Id.*

103 *Id.* at 578.

104 Martin Neil & Norman Fenton, Bayesian hypothesis testing and hierarchical modelling of ivermectin effectiveness in treating Covid-19 (Oct. 1, 2021), *available at* https://arxiv.org/ftp/arxiv/papers/2109/2109.13739.pdf (last visited Oct. 14, 2021).

105 Ivermectin for COVID-19: Real-time meta analysis of 64 studies (Oct. 8, 2021), https://ivmmeta.com/ (last visited Oct. 14, 2021).

106 *Id.*

107 *Id.*

108 *Id.*

109 Alessandro D. Santin et al., *Ivermectin: a multifaceted drug of Nobel prize-honoured distinction with indicated efficacy against a new global scourge, COVID-19*, New Microbes New Infections (Aug. 2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8383101/pdf/main.pdf (last visited Oct. 14, 2021).

that ivermectin "has been safely used in 3.7 billion doses since 1987" and that the medicine has been "used without serious [adverse effects]" in multiple "COVID-19 treatment studies."[110]

The existing ivermectin studies and meta-analyses are subject to vigorous ongoing disputes, and there are large ongoing studies, at least one of which includes the NIH as a collaborator, that will hopefully provide additional clarity.[111] But based on the existing medical literature, we do not find clear and convincing evidence that a physician who prescribes ivermectin for COVID-19 after obtaining informed consent engages in unprofessional conduct or otherwise violates the UCA.

While we find the studies and meta-analyses sufficient to resolve this question, we note that epidemiological evidence—derived by analyzing COVID-related data from various states, countries, or regions—is also instructive in the context of a global pandemic. We highlight just a few examples.

One set of scholars analyzed data comparing the COVID-19 rates of countries that routinely administer ivermectin as a prophylaxis and countries that do not.[112] The research revealed that "countries with routine mass drug administration of prophylactic . . . ivermectin have a significantly lower incidence of COVID-19."[113] This "highly significant" correlation manifests itself not only "in a worldwide context" but also when comparing African countries that regularly administer prophylactic "ivermectin against parasitic infections" and African countries that do not.[114] Based on these results, the researchers surmised that these results "may be connected to ivermectin's ability to inhibit SARS-CoV-2 replication, which likely leads to lower infection rates."[115]

---

110 *Id.* at 4.

111 *E.g.*, U.S. National Library of Medicine, ACTIV-6: COVID-19 Study of Repurposed Medications, https://clinicaltrials.gov/ct2/show/NCT04885530?term=activ-6&draw=2&rank=1 (last visited Oct. 14, 2021) (purpose of this trial involving an estimated 15,000 participants is "to evaluate the effectiveness of repurposed medications" that include ivermectin "in reducing symptoms of non-hospitalized participants with mild to moderate COVID-19"); U.S. National Library of Medicine, COVID-OUT: Early Outpatient Treatment for SARS-CoV-2 Infection (COVID-19), https://clinicaltrials.gov/ct2/show/NCT04510194?_term=ivermectin+boulware&draw=2&rank=1 (last visited Oct. 14, 2021) (purpose of this trial involving 1,160 participants is to understand whether ivermectin is superior to other options, including placebo, in "non-hospitalized adults with SARS-CoV-2 disease for preventing Covid-19 disease progression").

112 Martin D. Hellwig & Anabela Maia, *A COVID-19 prophylaxis? Lower incidence associated with prophylactic administration of ivermectin*, International Journal of Antimicrobial Agents (2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7698683/pdf/main.pdf (last visited Oct. 14, 2021).

113 *Id.* at 1.

114 *Id.*

115 *Id.*

More specifically, Peru's COVID-19 statistics, which have been analyzed in pre-print studies and discussed in published ivermectin reviews, are also informative.[116] Peru deployed mass ivermectin-based COVID-19 treatments from April 2020 through November 2020 throughout its 25 states.[117] In ten of those states, a maximal amount of "mass [ivermectin] treatments of COVID-19 were conducted through a broadside, army-led effort, *Mega-Operación Tayta (MOT)*."[118] Fourteen other states had a medium distribution of ivermectin administered at the local level.[119] And one state, Lima, distributed a minimal amount of ivermectin due to restrictive government policies.[120] "The mean reduction in excess deaths 30 days after peak deaths was 74% for the maximal [ivermectin] distribution group, 53% for the medium group[,] and 25% for Lima."[121] Furthermore, throughout the country of Peru, "excess deaths decreased 14-fold over four months" leading up to December 1, 2020, "after which deaths then increased 13-fold when [ivermectin] use was restricted under a new president."[122]

---

116 Juan J. Chamie-Quintero et al., *Ivermectin for COVID-19 in Peru: 14-fold reduction in nationwide excess deaths, p < 0.002 for effect by state, then 13-fold increase after ivermectin use restricted* (Mar. 2021), *available at* https://osf.io/9egh4/ (last visited Oct. 14, 2021); *see also* Santin, *supra*, at 3–4 (discussing the Peruvian data); Kory, *supra*, at 311–13 (same).

117 Chamie-Quintero, *supra*, at 2.

118 Santin, *supra*, at 3.

119 Chamie-Quintero, *supra*, at 2.

120 *Id.*

121 *Id.*

122 *Id.*

Ivermectin for COVID-19 in Peru: 14-fold reduction in nationwide excess deaths, p=.002 for effect by state, then 13-fold increase after ivermectin use restricted

Juan J. Chamie-Quintero,[a] Jennifer A. Hibberd,[b] David E Scheim[c]

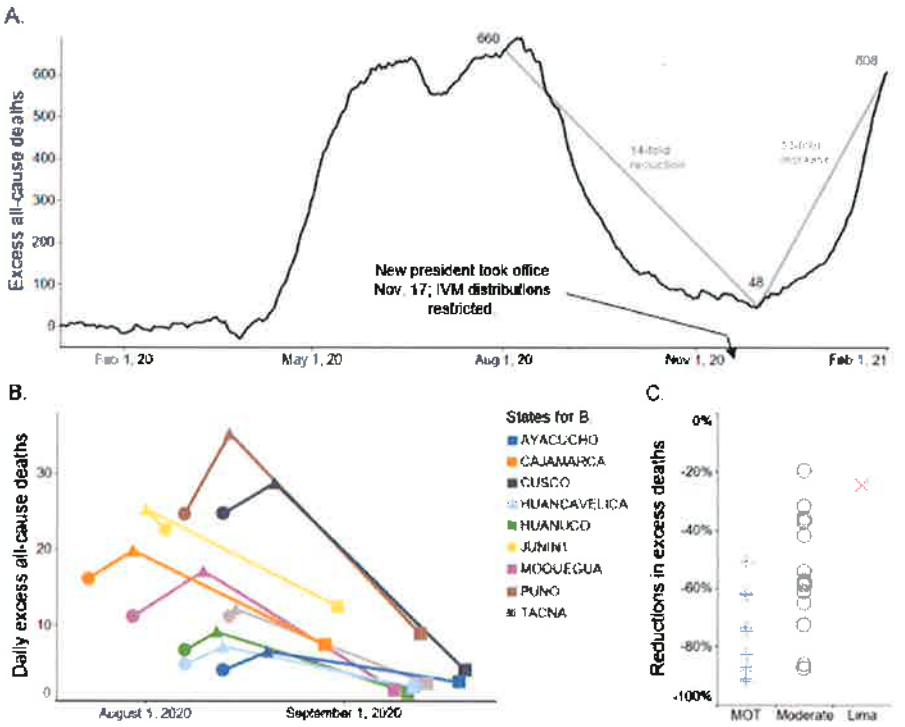


Figure 1. A) Excess all-cause deaths (all ages), national population of Peru. These decreased 14-fold August 1 through December 1, 2020; then, after IVM use was restricted, increased 13-fold through February 1. All y values are 7-day moving averages; for B,C, ages ≥ 60. Data are from Peru's National Death Information System (SINADEF).[12] B) Drops in excess deaths for all states of operation *MOT*, an army-led program of mass IVM distributions, but Pasco, which had them on 3 dates. ● *MOT* start date; ▲ peak deaths; ■ day of peak deaths + 30 days. Junin also distributed IVM 13 days before *MOT* start. C) Reductions in excess deaths at +30 days after peak deaths for the 25 states by extent of IVM distributions: maximal-*MOT* (+), mean -74%; moderate-local distributions (○), mean -53%; and minimal-Lima (x), -25%. These reductions for the 25 states correlated with extent of IVM distributions with Kendall τ_b p=0.002.

"Potential confounding factors, including lockdowns and herd immunity, were ruled out using Google community mobility data, seropositivity rates, population densities and geographic distributions of SARS-CoV-2 genetic variations."[123] While these figures do not prove causation, they demonstrate a strong correlation between ivermectin use and mortality reductions.

Moving from Peru to India, the government in the State of Uttar Pradesh—a jurisdiction with a population of more than 200 million—"introduced a large-scale 'prophylactic and therapeutic' use of [i]vermectin" that enabled it "to maintain a lower fatality and

123 Santin, *supra*, at 4.

positivity rate as compared to other states" in India.[124] As one state official explained, "Uttar Pradesh was the first state in [India] to introduce large-scale prophylactic and therapeutic use of Ivermectin."[125] The state's health department introduced ivermectin "as prophylaxis for close contacts of [COVID-19] patients" and "health workers," "as well as for the treatment of the patients themselves."[126] "Despite being [India's] state with the largest population base and a high population density," that state official added, Uttar Pradesh has "maintained a relatively low positivity rate and cases per million of population."[127] Although these statements from the Uttar Pradesh government do not prove ivermectin's effectiveness, they are informative and worthy of some consideration.

ii. U.S. Public Health Agencies on Ivermectin

Many public health agencies in the United States have now addressed the topic of ivermectin and COVID-19. The NIH has adopted a neutral position, saying that "[t]here is insufficient evidence . . . to recommend either for or against the use of ivermectin for the treatment of COVID-19."[128] This position, which the NIH adopted in January 2021, overrode its prior stance of "recommend[ing] against the use of ivermectin for the treatment" of COVID-19.[129] The reason for the change, the NIH recognized, was that "several randomized trials and retrospective cohort studies of ivermectin use in patients with COVID-19 have been published in peer-reviewed journals."[130] And some of those studies reported positive outcomes, including "shorter time to resolution of disease manifestations that were attributed to COVID-19, greater reduction in inflammatory marker levels, shorter time to viral clearance, [and] lower mortality rates in patients who received ivermectin than in patients who received comparator drugs or placebo."[131] The NIH nevertheless decided not to recommend the use of ivermectin for COVID-19 because other studies suggest "no benefits" and the NIH thought that the available studies

---

124 Maulshree Seth, *Uttar Pradesh government says early use of Ivermectin helped to keep positivity, deaths low*, The Indian Express (May 12, 2021), *available at* https://indianexpress.com/article/cities/lucknow/uttar-pradesh-government-says-ivermectin-helped-to-keep-deaths-low-7311786/ (last visited Oct. 14, 2021), and https://www.msn.com/en-in/news/other/uttar-pradesh-government-says-early-use-of-ivermectin-helped-to-keep-positivity-deaths-low/ar-BB1gDp5U (last visited Oct. 14, 2021).

125 *Id.*

126 *Id.*

127 *Id.*

128 NIH, COVID-19 and Ivermectin, *supra*.

129 Yagisawa, *supra*, at 65.

130 NIH, COVID-19 and Ivermectin, *supra*.

131 *Id.*

generally suffered from "methodological limitations."[132] By making a neutral recommendation, the NIH—which is continuing to collaborate on at least one study investigating ivermectin as a treatment for "mild to moderate COVID-19"[133]—clearly signaled that physicians should use their discretion in deciding whether to treat COVID-19 patients with ivermectin.

Ignoring the NIH's official position, officials within its agencies have sent contradictory messages. On August 29, 2021, Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID) within the NIH, went on CNN and announced that "there is no clinical evidence" that ivermectin works for the prevention or treatment of COVID-19.[134] Expanding on that point, he reiterated that "there is no evidence whatsoever" that it works.[135] Yet this definitive claim directly contradicts the NIH's recognition that "several randomized trials . . . published in peer-reviewed journals" have reported data indicating that ivermectin is effective as a COVID-19 treatment.[136]

The FDA has similarly charted a course of confusion. In March 2021, the FDA posted a webpage entitled "Why You Should Not Use Ivermectin to Treat or Prevent COVID-19."[137] Although the FDA's concern was stories of some people using the animal form of ivermectin or excessive doses of the human form, the title broadly condemned any use of ivermectin in connection with COVID-19. Yet there was no basis for its sweeping condemnation. Indeed, the FDA itself acknowledged on that very webpage (and continued to do so until the page changed on September 3, 2021) that the agency had *not* even "reviewed data to support use of ivermectin in COVID-19 patients to treat or to prevent COVID-19."[138] But without reviewing the available data, which had long

---

132 *Id.*

133 U.S. National Library of Medicine, ACTIV-6: COVID-19 Study of Repurposed Medications, https://clinicaltrials.gov/ct2/show/NCT04885530?term=activ-6&draw=2&rank=1 (last visited Oct. 14, 2021).

134 CNN Health, *'Don't do it': Dr. Fauci warns against taking Ivermectin to fight Covid-19* (Aug. 29, 2021), https://edition.cnn.com/videos/health/2021/08/29/dr-anthony-fauci-ivermectin-covid-19-sotu-vpx.cnn (last visited Oct. 14, 2021).

135 *Id.*

136 NIH, COVID-19 and Ivermectin, *supra*.

137 U.S. Food and Drug Administration, Why You Should Not Use Ivermectin to Treat or Prevent COVID-19 (archived Mar. 5, 2021), https://web.archive.org/web/20210305163946/https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19 (last visited Oct. 14, 2021) (hereinafter, "FDA, Why You Should Not Use Ivermectin (Mar. 5, 2021)").

138 *Id.*; *see also* U.S. Food and Drug Administration, Why You Should Not Use Ivermectin to Treat or Prevent COVID-19 (archived Sept. 2, 2021), https://web.archive.org/web/20210902231921/https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19 (last visited Oct. 14, 2021) (hereinafter, "FDA, Why You Should Not Use Ivermectin (Sept. 2, 2021)").

since been available and accumulating, it is unclear what basis the FDA had for denouncing ivermectin as a treatment or prophylaxis for COVID-19.

On that same webpage, the FDA also declared that "[i]vermectin is not an anti-viral (a drug for treating viruses)."[139] It did so while another one of its webpages[140] simultaneously cited a study in *Antiviral Research* that identified ivermectin as a medicine "previously shown to have *broad-spectrum anti-viral activity*."[141] It is telling that the FDA deleted the line about ivermectin not being "anti-viral" when it amended the first webpage on September 3, 2021.[142]

The FDA has additionally assailed ivermectin's safety by suggesting, though not outright stating, that even a proper dose of human ivermectin might be dangerous when used to treat COVID-19. For example, the FDA announced that "[t]aking a drug for an unapproved use can be very dangerous" and "[t]his is true of ivermectin."[143] Yet this ignores the fact that, as discussed above, doctors routinely prescribe medicines for off-label use and that ivermectin is a particularly well-tolerated medicine with an established safety record. Moreover, it is inconsistent for the FDA to imply that ivermectin is dangerous when used to treat COVID-19 while the agency continues to approve remdesivir[144] despite its spottier safety record, as discussed above.

The FDA has also called into question ivermectin's potential effectiveness. When updating the "Why You Should Not Use Ivermectin" webpage on September 3, 2021, the FDA added this entry: "Currently available data do not show ivermectin is effective against COVID-19."[145] But this claim fails to recognize that several RCTs and at least one meta-analysis suggest that ivermectin is effective against COVID-19.

---

139 FDA, Why You Should Not Use Ivermectin (Mar. 5, 2021), *supra*.

140 U.S. Food and Drug Administration, FAQ: COVID-19 and Ivermectin Intended for Animals (Sept. 3, 2021), https://www.fda.gov/animal-veterinary/product-safety-information/faq-covid-19-and-ivermectin-intended-animals (last visited Oct. 14, 2021).

141 Caly, *supra*, at 1 (emphasis added).

142 U.S. Food and Drug Administration, Why You Should Not Use Ivermectin to Treat or Prevent COVID-19 (updated Sept. 3, 2021), https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19 (last visited Oct. 14, 2021) (hereinafter, "FDA, Why You Should Not Use Ivermectin (Sept. 3, 2021)").

143 FDA, Why You Should Not Use Ivermectin (Mar. 5, 2021), *supra*.

144 U.S. Food and Drug Administration, FDA Approves First Treatment for COVID-19 (Oct. 22, 2020), https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19 (last visited Oct. 14, 2021).

145 FDA, Why You Should Not Use Ivermectin (Sept. 3 2021), *supra*.

Moreover, a review of the studies on remdesivir makes it difficult to understand why the FDA would condemn the data supporting ivermectin. The NIH reports only five studies testing remdesivir's efficacy against COVID-19.[146] Three of those five studies show *no benefit* from remdesivir, with the largest of those concluding that remdesivir "did not decrease in-hospital mortality in hospitalized patients."[147] Even the two remaining studies are far from compelling. One found that "[h]ospitalized patients . . . who received 5 days of [remdesivir] had better outcomes," but the difference "was of uncertain clinical importance."[148] And while the other study indicated that remdesivir "reduced time to clinical recovery" for "patients with severe COVID-19," it also found "[n]o observed benefit . . . in patients with mild or moderate COVID-19" and "[n]o statistically significant difference in mortality."[149] Beyond that, in September 2021, the Lancet published the results of a large RCT (the DisCoVeRy trial) that found "[n]o clinical benefit . . . from the use of remdesivir in patients who were admitted to hospital for COVID-19, were symptomatic for more than 7 days, and required oxygen support."[150] The data on ivermectin thus appears at least as strong as the data on remdesivir.

The FDA's most controversial statement on ivermectin came on August 21, 2021, when it posted a link on Twitter to its "Why You Should Not Use Ivermectin" webpage with this message: "You are not a horse. You are not a cow. Seriously, y'all. Stop it."[151]

---

146 National Institutes of Health, Remdesivir: Selected Clinical Data, https://www.covid19treatmentguidelines.nih.gov/tables/table-2a/ (last visited Oct. 14, 2021).

147 *Id.*

148 *Id.*

149 *Id.*

150 Florence Ader et al., *Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial*, The Lancet, at 1 (Sept. 14, 2021), *available at* https://www.thelancet.com/action/showPdf?pii=S1473-3099%2821%2900485-0 (last visited Oct. 14, 2021).

151 U.S. FDA, Twitter, https://twitter.com/us_fda/status/1429050070243192839 (last visited Oct. 14, 2021).

This message is troubling not only because it makes light of a serious matter but also because it inaccurately implies that ivermectin is only for horses or cows.

Despite its attempts to impugn ivermectin, the FDA appears to recognize that doctors may prescribe it for COVID-19. On September 3, 2021, a change in its website makes this clear. The "Why You Should Not Use Ivermectin" webpage originally said that "[i]f you have a prescription for ivermectin for an FDA-approved use, get it from a legitimate source and take it exactly as prescribed."[152] That same sentence now omits the limitation on prescriptions to FDA-approved uses. It says that "[i]f your health care provider writes you an ivermectin prescription, fill it through a legitimate source such as a pharmacy, and take it *exactly* as prescribed."[153] This change implicitly acknowledges that ivermectin may be prescribed off-label for COVID-19.

The CDC has followed in the FDA's footsteps of implying that ivermectin is unsafe. On August 26, 2021, the CDC issued an official advisory entitled "Rapid Increase in Ivermectin Prescriptions and Reports of Severe Illness Associated with Use of Products Containing Ivermectin to Prevent or Treat COVID-19."[154] Like the FDA, the CDC's

---

152 FDA, Why You Should Not Use Ivermectin (Mar. 5, 2021), *supra*.

153 FDA, Why You Should Not Use Ivermectin (Sept. 3, 2021), *supra*.

154 Centers for Disease Control and Prevention, *Rapid Increase in Ivermectin Prescriptions and Reports of Severe Illness Associated with Use of Products Containing Ivermectin to Prevent or Treat*

sweeping title implies that severe illnesses are arising from the prescribed use of human ivermectin to combat COVID-19, but it supplies no data to indicate that human ivermectin in appropriate doses is harming anyone. On the contrary, the CDC's advisory acknowledges that the actual concerns arise from the "use of veterinary products not meant for human consumption" and that the reported "[a]dverse effects [are] associated with ivermectin misuse and overdose."[155] The CDC's instructions to the public confirm that its concerns arise from the improper use of ivermectin creams or animal formulas: "Do not swallow ivermectin products that should be used on skin (e.g., lotions and creams) or are not meant for human use, such as veterinary ivermectin products."[156]

None of this undermines the use of human ivermectin in proper doses for the treatment or prevention of COVID-19. If anything, the reported uptick in people resorting to animal ivermectin simply reinforces that COVID-19 patients should be encouraged to discuss human ivermectin with their healthcare providers and that those providers should be allowed to consider the available data with their patients. That would be more beneficial for public health than attempting to obscure the demonstrated safety profile of ivermectin.

The media has added to the confusion and misinformation. On August 30, 2021, the New York Times published an article about ivermectin stating that "Mississippi's health department said earlier this month that *70 percent* of recent calls to the state poison control center had come from people who ingested ivermectin from livestock supply stores."[157] Yet two weeks later, on September 13, 2021, the Times amended its story by deleting that sentence and adding this note after the article: "An earlier version of this article misstated the percentage of recent calls to the Mississippi poison control center related to ivermectin. It was 2 percent, not 70 percent."[158]

Similarly, on September 3, 2021, Rolling Stone published a story entitled "Gunshot Victims Left Waiting as Horse Dewormer Overdoses Overwhelm Oklahoma Hospitals,

---

COVID-19, Health Advisory, at 1 (Aug. 26, 2021), *available at* https://emergency.cdc.gov/han/2021/pdf/CDC_HAN_449.pdf (last visited Oct. 14, 2021).

155 *Id.*

156 *Id.* at 3.

157 Emma Goldberg, *Demand Surges for Deworming Drug for Covid, Despite No Evidence It Works*, New York Times (Aug. 30, 2021), *available at* https://web.archive.org/web/20210830091038/https://www.nytimes.com/2021/08/30/health/covid-ivermectin-prescriptions.html (last visited Oct. 14, 2021) (emphasis added).

158 Emma Goldberg, *Demand Surges for Deworming Drug for Covid, Despite No Evidence It Works*, New York Times (amended Sept. 28, 2021), *available at* https://www.nytimes.com/2021/08/30/health/covid-ivermectin-prescriptions.html (last visited Oct. 14, 2021).

Doctor Says."[159] Soon thereafter, one the hospitals where this doctor supposedly works denied that claim, and "the doctor [did] not respond[] to requests for further comment."[160] Rather than delete the article or substantially rewrite it, Rolling Stone left the article largely unchanged and amended the title to say: "One Hospital Denies Oklahoma Doctor's Story of Ivermectin Overdoses Causing ER Delays for Gunshot Victims."[161] In addition, the magazine added an "update" message stating, among other things, that "[o]ne hospital has denied [the doctor's] claim that ivermectin overdoses are causing emergency room backlogs and delays in medical care in rural Oklahoma, and Rolling Stone has been unable to independently verify any such cases as of the time of this update."[162] In other words, the publication allowed a story based on a discredited and nonresponsive source to remain available to the public. It is no wonder that some people are unsure what to believe about ivermectin.

iii. Foreign Public Health Agencies on Ivermectin

Looking abroad, in March 2021, the WHO "recommend[ed] not to use ivermectin in patients with COVID-19 except in the context of a clinical trial."[163] The basis for this recommendation rested not on proof that ivermectin is ineffective, but on the WHO's belief that the existing studies were of too low quality to support any conclusive determinations.[164] Notably, though, while the WHO questioned the quality of the evidence, its analysis determined, based on data from 1,419 patients in seven studies, that patients treated with ivermectin had a 14 per 1,000 chance of death while patients in the control groups had a 70 per 1,000 chance of death.[165] Also, the WHO considered only

---

159 Peter Wade, *Gunshot Victims Left Waiting as Horse Dewormer Overdoses Overwhelm Oklahoma Hospitals, Doctor Says*, Rolling Stone (Sept. 3, 2021), *available at* https://web.archive.org/web/20210903231939/https://www.rollingstone.com/politics/politics-news/gunshot-victims-horse-dewormer-ivermectin-oklahoma-hospitals-covid-1220608/ (last visited Oct. 14, 2021).

160 Peter Wade, *One Hospital Denies Oklahoma Doctor's Story of Ivermectin Overdoses Causing ER Delays for Gunshot Victims*, Rolling Stone (amended Sept. 5, 2021), *available at* https://www.rollingstone.com/politics/politics-news/gunshot-victims-horse-dewormer-ivermectin-oklahoma-hospitals-covid-1220608/ (last visited Oct. 14, 2021).

161 *Id.*

162 *Id.*

163 World Health Organization, Therapeutics and COVID-19: Living Guideline, at 20 (July 6, 2021), *available at* https://files.magicapp.org/guideline/a6e3f83e-bff5-481c-90ab-130aa86bbe83/published_guideline_5486-6_1.pdf (last visited Oct. 14, 2021) (hereinafter, "WHO COVID-19 Guidelines").

164 *Id.*

165 *Id.* at 23.

ivermectin's effectiveness as a COVID-19 treatment and did not assess its potential as a prophylaxis.[166]

Public health authorities in other countries have declined to follow the WHO's guidance. Most importantly, the NIH continues to embrace its neutral recommendation on ivermectin. Also, in May 2021, the State of Goa in India announced, through its health minister Vishwajit Rane, that "it would give [ivermectin] to all its adult residents" in its efforts to combat COVID-19.[167] Likewise, as discussed above, India's Uttar Pradesh continues to distribute ivermectin to people diagnosed with COVID-19. And El Salvador's Ministry of Public Health has included ivermectin as part of its recommendations for early COVID-19 treatment via home patient kit.[168] We did not conduct an exhaustive search on other countries' practices, so this list is simply intended to be illustrative.

iv. Professional Associations and Physicians on Ivermectin

Professional associations, both here in the United States and abroad, have adopted conflicting positions on ivermectin and COVID-19. The American Medical Association (AMA), American Pharmacists Association (APhA), and American Society of Health-System Pharmacists (ASHP) have issued a statement that "strongly oppose[s] the ordering, prescribing, or dispensing of ivermectin to prevent or treat COVID-19 outside of a clinical trial."[169] But this statement relies solely on the FDA's and CDC's statements. Consider the AMA, APhA, and ASHP's claim that "[u]se of ivermectin for the prevention and treatment of COVID-19 has been demonstrated to be harmful to patients."[170] Their only support for that alarming statement is the CDC Health Alert discussed above.[171] But as we explained, that CDC advisory gave no indication that any severe adverse effects are occurring from the use of human ivermectin in appropriate doses.

---

166 *Id.* at 18.

167 Siladitya Ray, *Indian State Will Offer Ivermectin To Entire Adult Population — Even As WHO Warns Against Its Use As Covid-19 Treatment*, Forbes (May 11, 2021), *available at* https://www.forbes.com/sites/siladityaray/2021/05/11/indian-state-will-offer-ivermectin-to-entire-adult-population---even-as-who-warns-against-its-use-as-covid-19-treatment/?sh=3d45adce6d9f (last visited Oct. 14, 2021).

168 *El Salvador Minister of Public Health Includes Ivermectin as COVID-19 Pandemic Continues*, TrialSite News (Aug. 26, 2021), *available at* https://trialsitenews.com/el-salvador-minister-of-public-health-includes-ivermectin-as-covid-19-pandemic-continues/ (last visited Oct. 14, 2021).

169 American Medical Association, AMA, APhA, ASHP statement on ending use of ivermectin to treat COVID-19 (Sept. 1, 2021), *available at* https://www.ama-assn.org/press-center/press-releases/ama-apha-ashp-statement-ending-use-ivermectin-treat-covid-19 (last visited Oct. 14, 2021) (hereinafter, "AMA, APhA, and ASHP Statement on Ivermectin").

170 *Id.*

171 *Id.*

Those groups' opposition to ivermectin also conflicts with their otherwise steadfast support for healthcare providers' rights to prescribe medicines for off-label use. They call for ivermectin's ban because the FDA has not approved it "to prevent or treat COVID-19" and some public-health agencies have found "insufficient evidence" to support its use.[172] But just last year, these same professional associations, when discussing prescriptions for hydroxychloroquine to treat COVID-19, affirmed that "[n]ovel off-label use of FDA-approved medications is a matter for the physician's or other prescriber's professional judgment."[173] Moreover, the AMA elsewhere recognizes "its strong support for the autonomous clinical decision-making authority of . . . physician[s]" to "lawfully use an FDA approved drug product . . . for an off-label indication when such use is based upon sound scientific evidence."[174] In their recent ivermectin statement, however, the AMA, APhA, and ASHP ignore that some sound scientific evidence, including meta-analyses of RCTs, supports the use of ivermectin for COVID-19.

The AMA, APhA, and ASHP mentioned the statement of Merck—the original patentholder on ivermectin—as an additional basis for their position.[175] Yet that does not provide persuasive support for their opposition to ivermectin. Merck's February 2021 statement expressed its view that there is "[n]o meaningful evidence for . . . clinical efficacy in patients with COVID-19,"[176] but this simply ignores the RCTs demonstrating ivermectin's efficacy. Merck then claimed that there is "[a] concerning lack of safety data in the majority of studies."[177] While worded vaguely, this statement, when read carefully, says next to nothing. It simply acknowledges that many of the studies it references did not track safety data. It is not saying, though it might be implying, that the studies showed the medicine to be dangerous. But Merck, of all sources, knows that ivermectin is exceedingly safe, so the absence of safety data in recent studies should not be concerning to the company.

---

172 *Id.*

173 American Medical Association, Joint statement on ordering, prescribing or dispensing COVID-19 medications (Apr. 17, 2020), *available at* https://www.ama-assn.org/delivering-care/public-health/joint-statement-ordering-prescribing-or-dispensing-covid-19 (last visited Oct. 14, 2021).

174 American Medical Association, Patient Access to Treatments Prescribed by Their Physicians, https://policysearch.ama-assn.org/policyfinder/detail/Patient%20Access%20to%20Treatments%20Prescribed%20by%20Their%20Physicians%20H-120.988%20%20?uri=%2FAMADoc%2FHOD.xml-0-201.xml (last visited Oct. 14, 2021).

175 AMA, APhA, and ASHP Statement on Ivermectin, *supra*.

176 Merck, Merck Statement on Ivermectin use During the COVID-19 Pandemic (Feb. 4, 2021), https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/ (last visited Oct. 14, 2021).

177 *Id.*

Why would ivermectin's original patentholder go out of its way to question this medicine by creating the impression that it might not be safe? There are at least two plausible reasons. First, ivermectin is no longer under patent, so Merck does not profit from it anymore. That likely explains why Merck declined to "conduct[] clinical trials" on ivermectin and COVID-19 when given the chance.[178] Second, Merck has a significant financial interest in the medical profession rejecting ivermectin as an early treatment for COVID-19. "[T]he U.S. government has agreed to pay [Merck] about $1.2 billion for 1.7 million courses of its experimental COVID-19 treatment, if it is proven to work in an ongoing large trial and authorized by U.S. regulators."[179] That treatment, known as "molnupiravir, aims to stop COVID-19 from progressing and can be given early in the course of the disease."[180] On October 1, 2021, Merck announced that preliminary studies indicate that molnupiravir "reduced hospitalizations and deaths by half,"[181] and that same day its stock price "jumped as much as 12.3%."[182] Thus, if low-cost ivermectin works better than—or even the same as—molnupiravir, that could cost Merck billions of dollars.

While one side of the "professional associations" ledger includes the AMA, APhA, and ASHP (with Merck's backing), other associations disagree with their stance. In particular, the Association of American Physicians and Surgeons (AAPS)—a long-established group that has represented doctors in all specialties since 1943—has raised questions concerning those associations' "startling and unprecedented position that American physicians should immediately stop prescribing, and pharmacists should stop honoring their prescriptions for ivermectin for COVID-19 patients."[183] The AAPS pointed "out that many physicians disagree with the AMA, writing around 88,000 ivermectin

---

178 Yagisawa, *supra*, at 61.

179 *U.S. signs $1.2 bln deal for 1.7 mln courses of Merck's experimental COVID-19 drug*, Reuters (Jun. 9, 2021), *available at* https://www.reuters.com/business/healthcare-pharmaceuticals/merck-says-us-govt-buy-about-17-mln-courses-cos-covid-19-drug-2021-06-09/ (last visited Oct. 14, 2021).

180 *Id.*

181 Matthew Perrone, *Merck says COVID-19 pill cuts risk of death, hospitalization*, Associated Press (Oct. 1, 2021), *available at* https://apnews.com/article/merck-says-experimental-covid-pill-cuts-worst-effects-a9a2245fdcee324f6bbd776a0fffcc60 (last visited Oct. 14, 2021).

182 Lewis Krauskopf & Manojna Maddipatla, *Merck COVID-19 pill success slams Moderna shares, shakes up healthcare sector*, Reuters (Oct. 1, 2021), *available at* https://www.reuters.com/business/healthcare-pharmaceuticals/merck-covid-19-pill-success-slams-moderna-shares-shakes-up-healthcare-sector-2021-10-01/ (last visited Oct. 14, 2021).

183 Association of American Physicians and Surgeons, AAPS Challenges the AMA on Efforts to Suppress Ivermectin Use in COVID (Sept. 4, 2021), *available at* https://aapsonline.org/aaps-challenges-the-ama-on-efforts-to-suppress-ivermectin-use-in-covid/ (last visited Oct. 14, 2021).

prescriptions per week."[184] The AAPS has thus publicly resisted these groups' call to "stop[] the off-label use of long-approved drugs."[185]

In addition, the Tokyo Metropolitan Medical Association, as explained by its chairman Haruo Ozaki, recommended the use of ivermectin for COVID-19 patients in February 2021.[186] That organization emphasized that ivermectin should be administered to people diagnosed with COVID-19 because, among other reasons, it has been effective when used in other countries.[187] Other doctors' groups similarly advocate for ivermectin as a staple of early COVID-19 treatment. The Front Line COVID-19 Critical Care Alliance has been an outspoken supporter. Its organization "regard[s] ivermectin as a core medication in the prevention and treatment of COVID-19,"[188] and it includes a five-day course of ivermectin as part of its COVID-19 early treatment protocol.[189] Also, the British Ivermectin Recommendation Development Group (BIRD) is a UK-based association of "clinicians, health researchers[,] and patient representatives from all around the world" that collectively "advocate[s] for the use of ivermectin" against COVID-19.[190]

In summary, the evidence discussed above shows (1) that ivermectin has demonstrated some effectiveness in preventing and treating COVID-19 and (2) that its side effects are primarily minor and transient. Thus, the UCA does not preclude physicians from considering ivermectin for the prevention or treatment of COVID-19.

---

184 *Id.*

185 *Id.*

186 Tokyo Metropolitan Medical Association recommends ivermectin administration to prevent aggravation, Nikkei (Feb. 9, 2021), https://www.nikkei.com/article/DGXZQOFB25AAL0V20C21A1000000/ (last visited Oct. 14, 2021).

187 *Id.*

188 Front Line COVID-19 Critical Care Alliance, Ivermectin in COVID-19, https://covid19criticalcare.com/ivermectin-in-covid-19/ (last visited Oct. 14, 2021).

189 Front Line COVID-19 Critical Care Alliance, Prevention & Treatment Protocols for COVID-19, https://covid19criticalcare.com/wp-content/uploads/2020/11/FLCCC-Alliance-I-MASKplus-Protocol-ENGLISH.pdf (last visited Oct. 14, 2021).

190 British Ivermectin Recommendation Development Group, Who are the BIRD Group, https://bird-group.org/who-are-bird/ (last visited Oct. 14, 2021).

4. Hydroxychloroquine

A. History of Hydroxychloroquine

Hydroxychloroquine, a less toxic derivative of a medicine named chloroquine, was first developed in 1946[191] and approved by the FDA in 1955.[192] Since that time, hydroxychloroquine has been widely used as a prophylaxis and treatment for malaria.[193] It has also "prove[n] to be effective in a number of autoimmune diseases," including systemic lupus erythematosus,[194] primary Sjögren's syndrome, and rheumatoid arthritis, and for those uses, it is often taken daily for years at a time.[195] Hydroxychloroquine's success against these autoimmune diseases "is linked to its anti-inflammatory and immunomodulatory effects."[196] Because of its versatility and efficacy, "[m]illions of hydroxychloroquine doses are prescribed annually."[197] In just the year 2019, hydroxychloroquine was prescribed over 5.4 million times in the United States alone.[198]

In 2004, long before the COVID-19 pandemic began, a lab study revealed that chloroquine is "an effective inhibitor of the replication of the severe acute respiratory syndrome coronavirus (SARS-CoV) in vitro" and thus that it should "be considered for immediate use in the prevention and treatment of SARS-CoV infections."[199] The following

---

191 National Institutes of Health, COVID-19 Treatment Guidelines: Chloroquine or Hydroxychloroquine and/or Azithromycin, https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/chloroquine-or-hydroxychloroquine-and-or-azithromycin/ (last visited Oct. 14, 2021) (hereinafter, "NIH, COVID-19 and Hydroxychloroquine").

192 Georgi Fram et al., *Cardiac Complications Attributed to Hydroxychloroquine: A Systematic Review of the Literature Pre-COVID-19*, 17 Current Cardiology Reviews 389, 389 (2021), *available at* https://www.eurekaselect.com/186876/article (last visited Oct. 14, 2021).

193 *Id.*

194 Claudio Ponticelli & Gabriella Moroni, *Hydroxychloroquine in systemic lupus erythematosus (SLE)*, 16 Expert Opinion on Drug Safety 411, 411 (2017), *available at* https://www.tandfonline.com/doi/full/10.1080/14740338.2017.1269168?scroll=top&needAccess=true (last visited Oct. 14, 2021).

195 Eliise Laura Nirk et al., *Hydroxychloroquine in rheumatic autoimmune disorders and beyond*, EMBO Molecular Medicine, at 1 (Aug. 2020), *available at* https://www.embopress.org/doi/epdf/10.15252/emmm.202012476 (last visited Oct. 14, 2021).

196 *Id.*

197 Fram, *supra*, at 389.

198 ClinCalc, Hydroxychloroquine Drug Usage Statistics, United States, 2013–2019, https://clincalc.com/DrugStats/Drugs/Hydroxychloroquine (last visited Oct. 14, 2021).

199 Els Keyaerts et al., *In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine*, 323 Biochemical and Biophysical Research Communications 264, 264 (2004), *available at* https://www.sciencedirect.com/science/article/pii/S0006291X0401839X (last visited Oct. 14, 2021).

year, another paper explained that "chloroquine has strong antiviral effects on SARS-CoV infection" and "is effective in preventing the spread of SARS[-]CoV in cell culture."[200]

It is widely recognized in the medical community that hydroxychloroquine is generally safe, so safe in fact that it may be prescribed to pregnant women[201] and "children of all ages."[202] During the beginning of the pandemic, the FDA Commissioner stated that hydroxychloroquine has "a well-established safety profile" for malaria, lupus, and rheumatoid arthritis.[203] According to the CDC, hydroxychloroquine's "most common adverse reactions reported" are minor issues such as "stomach pain, nausea, vomiting, . . . headache," and "itching."[204] While the CDC recognizes that high doses, "such as those used to treat rheumatoid arthritis, have been associated with retinopathy," a serious eye condition, that side effect is "extremely unlikely" when hydroxychloroquine is used in short durations with moderate doses.[205] Notably, the CDC's guidance on hydroxychloroquine does not mention any concerns about cardiac disorders stemming from the drug.

B. Hydroxychloroquine and COVID-19

At the outset of the pandemic, researchers found—consistent with the prior studies demonstrating chloroquine's efficacy against SARS-CoV—that hydroxychloroquine "can efficiently inhibit SARS-CoV-2 infection in vitro."[206] These COVID-19 studies specifically

---

200 Martin J. Vincent et al., *Chloroquine is a potent inhibitor of SARS coronavirus infection and spread*, Virology Journal, at 1 (Aug. 2005), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1232869/pdf/1743-422X-2-69.pdf (last visited Oct. 14, 2021).

201 Ponticelli & Moroni, *supra*, at 411; *see also* Ewa Haładyj et al., *Antimalarials - are they effective and safe in rheumatic diseases?*. 56 Reumatologia 164, 171–72 (2018), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6052376/pdf/RU-56-33240.pdf (last visited Oct. 14, 2021) (noting that hydroxychloroquine "can be continued in the treatment of rheumatic diseases during pregnancy and lactation").

202 Centers for Disease Control and Prevention, Medicines for the Prevention of Malaria While Traveling Hydroxychloroquine (Plaquenil™), https://www.cdc.gov/malaria/resources/pdf/fsp/drugs/Hydroxychloroquine.pdf (last visited Oct. 14, 2021) (hereinafter, "CDC, Malaria Travel").

203 U.S. Food & Drug Administration, Bringing a Cancer Doctor's Perspective to FDA's Response to the COVID-19 Pandemic (Mar. 29, 2020), https://www.fda.gov/news-events/fda-voices/bringing-cancer-doctors-perspective-fdas-response-covid-19-pandemic (last visited Oct. 14, 2021) (hereinafter, "FDA, Bringing Perspective").

204 CDC, Malaria Travel, *supra*.

205 Centers for Disease Control and Prevention, Yellow Book, Chapter 4: Travel-Related Infectious Diseases – Malaria (2020), *available at* https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria#1939 (last visited Oct. 14, 2021).

206 Jia Liu et al., *Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro*, Cell Discovery, at 4 (2020), *available at* https://www.nature.com/articles/s41421-020-0156-0.pdf (last visited Oct. 14, 2021).

showed that hydroxychloroquine "can inhibit [SARS-CoV-2] virus entry, transmission[,] and replication."[207] In addition to this "antiviral activity," hydroxychloroquine also has "anti-inflammatory properties" that help regulate "pro inflammatory cytokines."[208] These characteristics—both the antiviral properties and the anti-inflammatory activity—are important countermeasures against COVID-19.

i. Hydroxychloroquine Studies and Meta-analyses

Many large observational studies suggest that hydroxychloroquine significantly reduces the risk of hospitalization and death when administered to outpatients—particularly high-risk outpatients—as part of early COVID-19 treatment. For example, the Mokhtari study "was a multicenter, population-based national retrospective-cohort investigation of 28,759 adults with mild COVID-19 seen . . . between March and September 2020 throughout Iran."[209] The data showed that "[t]he odds of hospitalization . . . reduced by 38%" and the chance of death decreased by 73% for those who took hydroxychloroquine.[210] Critically, those "effects were maintained after adjusting for age, comorbidities, and diagnostic modality," and "[n]o serious [hydroxychloroquine]-related adverse drug reactions were reported."[211]

In the same vein, the recently published Million study evaluated 10,429 "adult outpatients" in France infected with SARS-CoV-2 who were "treated early" with hydroxychloroquine plus azithromycin.[212] Only five deaths occurred among the 8,315 patients who received hydroxychloroquine plus azithromycin—a mere 0.6 per 1,000 patients—while 11 died among the 2,114 who received either no treatment or azithromycin alone—a much higher rate of 5.2 per 1,000 patients.[213] Based on these figures, the study's authors found that hydroxychloroquine "was associated with a lower risk of death, independently of age, sex[,] and epidemic period."[214] Million's team thus concluded that

---

207 Jyoti Bajpai et al., *Hydroxychloroquine and COVID-19 - A narrative review*, 67 Indian Journal of Tuberculosis 147, 148 (Dec. 2020), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7836863/pdf/main.pdf (last visited Oct. 14, 2021).

208 *Id.*

209 Majid Mokhtari et al., *Clinical outcomes of patients with mild COVID-19 following treatment with hydroxychloroquine in an outpatient setting*, International Immunopharmacology, at 1 (Jul. 2021), *available at* https://www.sciencedirect.com/science/article/pii/S1567576921002721 (last visited Oct. 14, 2021).

210 *Id.*

211 *Id.*

212 Million, *supra*, at 1063.

213 *Id.* at 1066.

214 *Id.* at 1063.

"[e]arly ambulatory treatment of COVID-19" with hydroxychloroquine plus azithromycin "is associated with very low mortality" and it "improve[s] COVID-19 survival compared to other regimens."[215]

Another group of researchers assessed an elderly population living in a nursing home in the small European state of Andorra.[216] Their study included "100 COVID-19 confirmed cases" in the nursing home "from March 15 to June 5, 2020."[217] After evaluating the numbers, these researchers concluded that "[t]reatment with hydroxychloroquine and azithromycin was associated with lower mortality in these patients."[218] And "the multivariate logistic regression analysis identified hydroxychloroquine plus azithromycin treatment as an independent factor favoring survival compared with no treatment or other treatments."[219] The study also reinforced hydroxychloroquine's longstanding safety profile because "[c]ardiac monitoring was performed by electrocardiogram, and no rhythm changes were observed . . . in any patient."[220]

Added to all this, a preprint of another large observational study by Sulaiman supports the use of hydroxychloroquine as part of early COVID-19 treatment.[221] This "study took place in 238 ambulatory fever clinics in Saudi Arabia" during June 2020.[222] Of the 5,541 participating patients, 1,817 were given hydroxychloroquine, and 3,724 received only supportive care.[223] The researchers found that early hydroxychloroquine-based "therapy was associated with a lower hospital admission" of 9.4% compared to 16.6% for supportive care alone, which equated to a relative risk reduction of 43%. "Adjusting for age, gender, and major comorbid conditions, a multivariate logistic regression model" further confirmed the significant decrease in the hospitalization risk of

---

215 *Id.*

216 Eva Heras et al., *COVID-19 mortality risk factors in older people in a long-term care center*, 12 European Geriatric Medicine 601, 601 (2021), *available at* https://link.springer.com/content/pdf/10.1007/s41999-020-00432-w.pdf (last visited Oct. 14, 2021).

217 *Id.*

218 *Id.*

219 *Id.* at 606.

220 *Id.* at 603.

221 Tarek Sulaiman et al., *The Effect of Early Hydroxychloroquine-based Therapy in COVID-19 Patients in Ambulatory Care Settings: A Nationwide Prospective Cohort Study*, Preprint, at 1 (2020), *available at* https://www.medrxiv.org/content/10.1101/2020.09.09.20184143v1.full.pdf (last visited Oct. 14, 2021).

222 *Id.*

223 *Id.*

patients who received hydroxychloroquine.[224] Regression analysis also demonstrated that hydroxychloroquine reduced the mortality risk by an odds ratio of .36, which equates to a threefold drop in deaths.[225] Other observational studies further suggest that hydroxychloroquine has value as an early COVID-19 treatment.[226]

We acknowledge that other studies and meta-analyses have concluded that hydroxychloroquine has little to no effect on COVID-19.[227] Yet those materials generally blur the important distinction between hydroxychloroquine's efficacy as an early treatment for mild COVID-19 in nonhospitalized patients and its efficacy as a late treatment for severe COVID-19 in hospitalized patients.[228] As explained above, COVID-19 in its early stages, which consists primarily of cold- and flu-like symptoms, is very different from severe COVID-19, which is a lower respiratory disease often accompanied by respiratory failure and multiple organ dysfunction. Thus, evidence about hydroxychloroquine's use "in inpatients[] is irrelevant with regard to the efficacy of [the drug] in early high-risk outpatient disease."[229] So even if hydroxychloroquine is not effective against severe COVID-19, that does not disprove its value as an early treatment against the disease.

The key, then, is to focus on data that assess hydroxychloroquine's effectiveness in early treatment. A prime example of that is a recently published meta-analysis that combined the Million, Mokhtari, and Sulaiman studies discussed above with two other

---

224 *Id.*

225 *Id.* at 14.

226 *E.g.*, Andrew Ip et al., *Hydroxychloroquine in the treatment of outpatients with mildly symptomatic COVID-19: a multi-center observational study*, BMC Infectious Diseases (2021), *available at* https://bmcinfectdis.biomedcentral.com/track/pdf/10.1186/s12879-021-05773-w.pdf (concluding in a study of 1,274 outpatients with SARS-CoV-2 infection that "there was an association between exposure to hydroxychloroquine and a decreased rate of hospitalization from COVID-19"); Yi Su, *Efficacy of early hydroxychloroquine treatment in preventing COVID-19 pneumonia aggravation, the experience from Shanghai, China*, 14 BioScience Trends 408, 408 (2020), *available at* https://www.jstage.jst.go.jp/article/bst/14/6/14_2020.03340/_pdf/-char/en (last visited Oct. 14, 2021) (finding in a study of 616 individuals that "[t]he early use of hydroxychloroquine decreased the improvement time and the duration of COVID-19 detection in throat and stool swabs").

227 Tawanda Chivese et al., *Efficacy of chloroquine and hydroxychloroquine in treating COVID-19 infection: A meta-review of systematic reviews and an updated meta-analysis*, Travel Medicine and Infectious Disease, at 1 (Sept./Oct. 2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8273040/pdf/main.pdf (last visited Oct. 14, 2021) (concluding that hydroxychloroquine is "not effective in treating COVID-19").

228 *Id.* at 3 (noting that this meta-analysis considered studies of people with "confirmed COVID-19, regardless of . . . the severity of illness").

229 Harvey A. Risch, *Early Outpatient Treatment of Symptomatic, High-Risk COVID-19 Patients That Should Be Ramped Up Immediately as Key to the Pandemic Crisis*, 189 American Journal of Epidemiology 1218, 1218 (Nov. 2020), *available at* https://academic.oup.com/aje/article/189/11/1218/5847586 (last visited Oct. 14, 2021).

outpatient studies.[230] Those five studies together included 32,124 total outpatients, and the analysis revealed that hydroxychloroquine is associated with a 69% reduction in mortality when used as an early COVID-19 treatment.[231] In addition, a few months ago, another team of researchers reviewed "nine reports of early treatment outcomes in COVID-19 nursing home patients."[232] Data from those studies revealed that "hydroxychloroquine-based multidrug regimens were associated with a statistically significant > 60% reduction in mortality."[233] And another scholar, Dr. Harvey A. Risch, Professor of Epidemiology at Yale School of Public Health, has published online a non-peer-reviewed meta-analysis of ten studies exploring hydroxychloroquine as an early COVID-19 treatment.[234] He concluded that for people receiving that treatment the odds ratio of hospitalization was .56 and the odds ratio of death was .25. In other words, his meta-analysis demonstrated that when hydroxychloroquine is administered as an early COVID-19 treatment, it can reduce the risk of death by 75%.

To be sure, these data derive from large-scale observational studies rather than RCTs, and we understand that RCTs are considered the gold standard in medicine. But for at least two reasons, we find these observational studies sufficient for our purposes. First, our role is not to set a standard for the practice of medicine. Rather, we must simply confirm whether reasonable medical evidence supports the use of hydroxychloroquine as an early COVID-19 treatment, and we determine that a collection of large-scale observational studies suffices for that purpose. Second, a seminal review of the scientific literature has revealed that "on average, there is little evidence for significant effect estimate differences between observational studies and RCTs, regardless of specific observational study design, heterogeneity, or inclusion of studies of pharmacological interventions."[235] There is thus no basis to cast aside the observational studies demonstrating hydroxychloroquine's efficacy as an early COVID-19 treatment.

---

230 Million, *supra*, at 1070.

231 *Id.*

232 Paul E. Alexander et al., *Early multidrug treatment of SARS-CoV-2 infection (COVID-19) and reduced mortality among nursing home (or outpatient/ambulatory) residents*, Medical Hypotheses, at 1 (2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8178530/pdf/main.pdf (last visited Oct. 14, 2021).

233 *Id.*

234 Harvey A. Risch, *Hydroxychloroquine in Early Treatment of High-Risk COVID-19 Outpatients: Efficacy and Safety Evidence*, at 11 (Jun. 17, 2021), *available at* https://earlycovidcare.org/wp-content/uploads/2021/09/Evidence-Brief-Risch-v6.pdf (last visited Oct. 14, 2021).

235 Andrew Anglemyer et al., *Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials*, Cochrane Database of Systematic Reviews, at 1 (2014), *available at* https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.MR000034.pub2/epdf/full (last visited Oct. 14, 2021).

We turn now to discuss the use of hydroxychloroquine as a prophylaxis, and although the data on that point seem to be smaller, there is some evidence suggesting that it might work for that purpose too. One study was a RCT of migrant workers quarantined in a large dormitory in Singapore, and it compared a group who used hydroxychloroquine as a prophylaxis to a group that received only vitamin C.[236] The hydroxychloroquine group included 432 people, and only 31 of them (7.2%) contracted COVID-19 with acute respiratory symptoms.[237] In contrast, 619 individuals were in the vitamin C group, and 69 of them (11.1%) developed COVID-19 with acute respiratory symptoms.[238] Thus, the researchers concluded that prophylaxis with hydroxychloroquine is "superior to oral vitamin C in reducing SARS-CoV-2 infection."[239] Additionally, an observational study of healthcare workers in Bulgaria found that out of 156 workers who used hydroxychloroquine as a prophylaxis, none of them presented with COVID-19 symptoms.[240] By contrast, in the group of 48 workers who did not take hydroxychloroquine, three of them developed a symptomatic case of COVID-19.[241] These results prompted the administrators at the Bulgarian Cardiac Institute to start a prophylactic strategy for their workers that "includes alternative months of [hydroxychloroquine] intake (200 mg daily) and months without therapy."[242] In addition to these studies, there are a few others, some of which suggest marginal benefits, and some of which suggest that there might not be any. We are not aware of any of these studies showing serious adverse effects from use of low-dose hydroxychloroquine as a COVID-19 prophylaxis.

We pause here to reiterate that it is not our role to resolve the debate on hydroxychloroquine's effectiveness, either as an early COVID-19 treatment or as a preventative measure. These are matters for individual healthcare providers to assess based on the available data in consultation with their patients. Our only point is that reasonable data support the use of hydroxychloroquine as an early COVID-19 treatment and as a prophylaxis, and in light of that, we cannot find clear and convincing evidence

---

236 Raymond Chee Seong Seet et al., *Positive impact of oral hydroxychloroquine and povidone-iodine throat spray for COVID-19 prophylaxis: An open-label randomized trial*, 106 International Journal of Infectious Diseases 314, 314 (2021), *available at* https://www.ijidonline.com/action/showPdf?pii=S1201-9712%2821%2900345-3 (last visited Oct. 14, 2021).

237 *Id.* at 319.

238 *Id.*

239 *Id.* at 314.

240 Iana Simova et al., *Hydroxychloroquine for prophylaxis and treatment of COVID-19 in health-care workers*, New Microbes and New Infections, at 1 (Nov. 2020), *available at* https://www.sciencedirect.com/science/article/pii/S2052297520301657#! (last visited Oct. 14, 2021).

241 *Id.*

242 *Id.*

to file disciplinary actions against physicians who prescribe hydroxychloroquine for either of those purposes.

ii. Hydroxychloroquine, COVID-19, and Safety

During the pandemic, the FDA raised questions about hydroxychloroquine and adverse cardiac events.[243] These kinds of concerns prompted one group of scholars to conduct a systematic review of the hydroxychloroquine safety literature pre-COVID-19. Their review of the data indicated that people taking that medication in appropriate doses "are at very low risk of experiencing cardiac [adverse events], particularly with short term administration" of the drug.[244] The pre-COVID-19 data showed that heart issues occurred—albeit infrequently—only when patients took hydroxychloroquine in dangerously high doses or for many years on end.[245]

As to the increase of adverse cardiac events associated with COVID-19, the researchers questioned the prevalence of the problem by noting that several COVID-19 studies recorded "the use of [hydroxychloroquine] at variable doses without significant cardiac toxicity."[246] They also observed that COVID-19 itself often causes heart issues. As they explained, "[t]he underlying pathophysiology of SARS-CoV-2 contributes to cardiac complications in the population it infects, with estimates ranging from 20-40% incidence."[247] In particular, "[c]ardiac complications of cytokine storm have been well documented to involve fatal cardiac dysrhythmias and acute systolic heart failure."[248] These researchers thus concluded that "the reported increased arrhythmic events in the COVID-19 era appear to be more related with the direct inflammatory effect of the virus (myocarditis) or the concomitant administration of multiple drugs capable of prolonging QT intervals rather than to hydroxychloroquine itself."[249] They did not seem to think the medication itself had "change[d] after 70 years" of widespread use.[250]

---

243 U.S. Food and Drug Administration, FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems, https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or (last visited Oct. 14, 2021).

244 Fram, *supra*, at 391.

245 *Id.* at 390–92.

246 *Id.* at 393.

247 *Id.* at 392.

248 *Id.* at 393.

249 *Id.* at 394.

250 *Id.*

Others echoed these views. Another group reviewed the relevant studies and observed that "[m]ost of the available and credible data suggest that [hydroxychloroquine] is a safe drug."[251] That includes the pre-COVID-19 data—in "decades of . . . use by rheumatologists, . . . cardiac toxicity was rarely ever seen"—as well as the COVID-19-related studies—for example, the RECOVERY trial found "no cardiotoxicity" by hydroxychloroquine.[252] Indeed, the RECOVERY trial "prove[d] that [hydroxychloroquine] did not increase cardiac complications in COVID-19 cases despite using 4 times higher dosage than that used by rheumatologists."[253] These authors also emphasized that "[m]ultiple mechanisms cause cardiac complications in patients with COVID-19 infection";[254] thus, the infection's propensity to cause "intrinsic cardiac abnormalities . . . is probably acting as a confounder."[255]

Still another set of researchers reevaluated hydroxychloroquine's safety during the pandemic. They conducted a "meta-analysis to compare the safety of [hydroxychloroquine] versus placebo" for any indication.[256] Although their "meta-analysis of RCTs found a significantly higher risk of skin pigmentation [issues] in [hydroxychloroquine] users versus placebo," they did not find any statistically significant increases in other adverse events, including "cardiac toxicity."[257]

In addition to these data tending to confirm hydroxychloroquine's safety when used in appropriate doses, a few other factors further lessen the cardiac concerns. For starters, one piece of key evidence contributing to the safety concerns surrounding hydroxychloroquine rested on admittedly fraudulent data. As discussed above, it was a study published in the Lancet on May 22, 2020.[258] That study claimed that hydroxychloroquine was "associated with . . . an increased frequency of ventricular

---

251 Shivraj Padiyar & Debashish Danda, *Revisiting cardiac safety of hydroxychloroquine in rheumatological diseases during COVID-19 era: Facts and myths*, 8 European Journal of Rheumatology 100, 100 (2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8133889/pdf/ejr-8-2-100.pdf (last visited Oct. 14, 2021).

252 *Id.*

253 *Id.* at 102.

254 *Id.* at 102.

255 *Id.* at 100.

256 Khalid Eljaaly et al., *Hydroxychloroquine safety: A meta-analysis of randomized controlled trials*, Travel Medicine and Infectious Disease at 1 (Jul./Aug. 2020), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7342171/ (last visited Oct. 14, 2021).

257 *Id.*

258 Mehra, *supra.*

arrhythmias when used for treatment of COVID-19."[259] That supposed finding was so startling that "major drug trials" involving hydroxychloroquine "were immediately halted";[260] the WHO started pressuring countries like Indonesia that were widely using hydroxychloroquine to ban it;[261] and some countries—including France, Italy, and Belgium—decided to stop using it for COVID-19.[262]

The problem, however, is that the study was based on false data from a company named Surgisphere, whose founder and CEO Sapan Desai was a co-author on the published paper.[263] The data were so obviously flawed that journalists and outside researchers began raising concerns within days of the paper's publication.[264] Even the Lancet's editor in chief, Dr. Richard Horton, admitted that the paper was a "fabrication," "a monumental fraud,"[265] and "a shocking example of research misconduct in the middle of a global health emergency."[266] Approximately two weeks after its publication, the paper was retracted.[267] An article published in *The Guardian* declared that "[g]iven the seriousness of the topic and the consequences of the paper, this [was] one of the most consequential retractions in modern history."[268] Despite calls to "publish full explanations

---

259 *Id.* at 1.

260 James Heathers, *The Lancet has made one of the biggest retractions in modern history. How could this happen?*, The Guardian (Jun. 5, 2020), *available at* https://www.theguardian.com/commentisfree/2020/jun/05/lancet-had-to-do-one-of-the-biggest-retractions-in-modern-history-how-could-this-happen (last visited Oct. 14, 2021).

261 Kate Lamb & Tom Allard, *Indonesia, major advocate of hydroxychloroquine, told by WHO to stop using it*, Reuters (May 26, 2020), *available at* https://www.reuters.com/article/us-health-coronavirus-indonesia-chloroqu/exclusive-indonesia-major-advocate-of-hydroxychloroquine-told-by-who-to-stop-using-it-idUSKBN23227L (last visited Oct. 14, 2021).

262 *France, Italy, Belgium act to stop use of hydroxychloroquine for COVID-19 on safety fears*, Reuters (May 27, 2020), *available at* https://www.reuters.com/article/health-coronavirus-hydroxychloroquine-fr/update-1-france-italy-belgium-act-to-stop-use-of-hydroxychloroquine-for-covid-19-on-safety-fears-idUKL1N2D911J (last visited Oct. 14, 2021).

263 Boseley & Davey, *supra*.

264 Davey, *supra*.

265 Rabin, *supra*.

266 Boseley & Davey, *supra*.

267 *Id.*

268 Heathers, *supra*.

of what happened," the Lancet has "declined to provide details regarding the retracted stud[y]."[269]

Further reducing the cardiac concerns is important information on the FDA's own website. The FDA "cautions against use of hydroxychloroquine . . . for COVID-19 *outside of the hospital setting* or a clinical trial due to risk of heart rhythm problems."[270] But the agency's referenced support for this cautionary statement concerning *nonhospitalized patients* is its "review of safety issues with the use of hydroxychloroquine . . . to treat *hospitalized patients* with COVID-19."[271] It is questionable, however, to theorize about risks to nonhospitalized patients with mild COVID-19 based on data about heart issues in hospitalized patients with severe COVID-19 because, as explained above, cardiac complications often accompany the late stages of COVID-19. The FDA's concerns thus derive from a context—using hydroxychloroquine to treat hospitalized patients—that we are not addressing in this opinion.

It is important to note that although the medical literature tends to confirm that hydroxychloroquine is a safe medication when used in appropriate doses, any concerns about heart issues, even if resting on limited evidence, are serious. Prevailing principles of informed consent likely require physicians who present patients with the option of using hydroxychloroquine for early treatment of COVID-19 to inform them about the cardiac concerns that the FDA has identified. Also, for patients who have underlying cardiac issues, physicians should carefully consider whether hydroxychloroquine is the right choice for them. Finally, physicians should pay attention to which drugs they combine with hydroxychloroquine and evaluate the potential cardiac risks of those combinations. Failure to take such precautions could result in disciplinary action.

iii. U.S. Public Health Agencies on Hydroxychloroquine

The public health agencies in the United States have addressed the topic of hydroxychloroquine and COVID-19. The NIH "recommends against" its use "for the treatment of COVID-19 in hospitalized patients . . . and in nonhospitalized patients."[272] To justify its position against hydroxychloroquine for nonhospitalized patients, the NIH relied heavily on a RCT conducted by Mitja.[273] While that study did not show great advantages in the hydroxychloroquine group, that group did have, as the NIH's own

---

269 Rabin, *supra*.

270 U.S. Food and Drug Administration, FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems, https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or (last visited Oct. 14, 2021) (emphasis added).

271 *Id.* (emphasis added).

272 NIH, COVID-19 and Hydroxychloroquine, *supra*.

273 *Id.*

website reports, a slight reduction in the risk of hospitalization (7.1% risk in the control arm versus 5.9% risk in the treatment arm) and in the time to resolution of symptoms (12 days in the control arm versus 10 days in the treatment arm).[274] As for serious adverse events, more (12) were reported in the control group than the hydroxychloroquine group (8), and the researchers determined that the serious adverse events in the hydroxychloroquine group were not related to the drug.[275] Thus, this study, particularly when considered in light of the large-scale observational studies discussed above, appears to be an insufficient basis to definitively recommend against using hydroxychloroquine as an early COVID-19 treatment.

The FDA, for its part, has questioned not only hydroxychloroquine's safety, as we discussed above, but also its efficacy. The agency's position grew out of its approval and subsequent disapproval of an Emergency Use Authorization (EUA) involving hydroxychloroquine. That EUA was issued on March 28, 2020, and it authorized licensed healthcare providers to use hydroxychloroquine donated to the Strategic National Stockpile to treat patients hospitalized with COVID-19.[276] Though this EUA was necessary to authorize the use of a specific source of hydroxychloroquine for a specific purpose, it was not required to allow healthcare providers to prescribe hydroxychloroquine off-label for COVID-19. That option was already available, as our prior discussion of off-label use makes clear. When the FDA revoked the EUA a few months later, on June 15, 2020, that is when it stated its current position on hydroxychloroquine and COVID-19.[277]

In that revocation, the FDA said that it no longer "believe[s] that oral formulations of [hydroxychloroquine] . . . may be effective in treating COVID-19" or that "that the known and potential benefits of these products outweigh their known and potential risks."[278]

---

274 National Institutes of Health, Table 2b. Chloroquine or Hydroxychloroquine and/or Azithromycin: Selected Clinical Data, https://www.covid19treatmentguidelines.nih.gov/tables/table-2b/ (last visited Oct. 14, 2021) (discussing Oriol Mitjà, *Hydroxychloroquine for Early Treatment of Adults With Mild Coronavirus Disease 2019: A Randomized, Controlled Trial*, Clinical Infectious Diseases (2020), *available at* https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1009/5872589 (last visited Oct. 14, 2021)).

275 *Id.* (discussing Mitjà, *supra*).

276 Letter from Denise M. Hinton, Chief Scientist, U.S. Food and Drug Administration, to Dr. Rick Bright, Director of Biomedical Advanced Research and Development Authority (BARDA), Office of Assistant Secretary for Preparedness and Response (ASPR), U.S. Department of Health and Human Services (HHS) (Mar. 28, 2020), *available at* https://www.fda.gov/media/136534/download (last visited Oct. 14, 2021).

277 Letter from Denise M. Hinton, Chief Scientist, U.S. Food and Drug Administration, to Gary L. Disbrow, Deputy Assistant Secretary, Director of Medical Countermeasure Programs, Biomedical Advanced Research and Development Authority (BARDA), Office of Assistant Secretary for Preparedness and Response (ASPR), U.S. Department of Health and Human Services (HHS) (Jun. 15, 2020), *available at* https://www.fda.gov/media/138945/download (last visited Oct. 14, 2021).

278 *Id.* at 2.

Because both the EUA and its revocation deal only with hydroxychloroquine's use in hospitalized patients, they do not address the treatment topic that we are considering in this opinion—hydroxychloroquine's use as an early COVID-19 treatment.

The FDA's EUA revocation included four justifications, none of which establishes—let alone by clear and convincing evidence—that hydroxychloroquine is ineffective as an early treatment of COVID-19. First, the FDA said that the "suggested dosing regimens . . . are unlikely to produce an antiviral effect" because they will not create sufficient "drug concentration" in the body.[279] But as the FDA's revocation itself acknowledged, hydroxychloroquine's "immunomodulatory effects," as opposed to its antiviral effects, are not "predicated on achieving [certain hydroxychloroquine] concentration[]" levels.[280] Moreover, the FDA based its views on the assumption that "free drug concentration in the plasma" are "likely to be equal to free extracellular tissue concentration."[281] But other researchers' simulations showed that hydroxychloroquine's "concentration in lung tissue was much higher than in plasma,"[282] leading them to conclude that moderate doses are "recommended to treat SARS-CoV-2 infection."[283] Thus, the FDA's pessimism about hydroxychloroquine's potential antiviral capacity is open to reasonable debate in the scientific community.

Second, the FDA wrote that "[e]arlier reports of decreased viral shedding" with hydroxychloroquine "treatment have not been consistently replicated."[284] Notice that the FDA did not say that the studies have *disproven* a reduction in viral shedding; rather, the agency recognized that the evidence was still evolving and that some studies did in fact observe a positive "impact on viral shedding."[285] This criticism, on its face, is thus insufficient to dismiss hydroxychloroquine's use as an early COVID-19 intervention. Additionally, doubts about hydroxychloroquine's effect on viral shedding question only one of the drug's many possible mechanisms of action against COVID-19. More salient

---

279 U.S. Food and Drug Administration, Memorandum Explaining Basis for Revocation of Emergency Use Authorization for Emergency Use of Chloroquine Phosphate and Hydroxychloroquine Sulfate, at 1, 4, *available at* https://www.fda.gov/media/138945/download (last visited Oct. 14, 2021) (hereinafter, "FDA EUA Revocation Memo").

280 *Id.* at 4.

281 *Id.*

282 Xueting Yao et al., *In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)*, Clinical Infectious Diseases, at 13 (2020), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7108130/pdf/ciaa237.pdf (last visited Oct. 14, 2021).

283 *Id.* at 2.

284 FDA EUA Revocation Memo, *supra*, at 1.

285 *Id.* at 6.

information is whether the drug is actually decreasing hospitalization and mortality rates when used as an outpatient treatment. As we discussed above, many large observational studies strongly suggest that hydroxychloroquine does in fact keep people diagnosed with COVID-19 out of the hospital and alive. That evidence is far more relevant of the drug's potential efficacy as an early COVID-19 treatment than debates about viral shedding.

Third, the FDA found it compelling that "NIH guidelines now recommend against" using hydroxychloroquine "outside of a clinical trial."[286] But as previously explained, the NIH's recommendation concerning COVID-19 outpatients does not rest on undisputed support. Thus, the NIH's guidelines should not be considered a basis upon which to ban healthcare providers from using hydroxychloroquine for COVID-19.

Fourth, the FDA stressed that "[r]ecent data from a large randomized controlled trial"—the RECOVERY trial mentioned above—"showed no evidence of benefit . . . of [hydroxychloroquine] treatment in hospitalized patients with COVID-19."[287] Yet as we have already discussed, a study about hospitalized patients does not address hydroxychloroquine's efficacy as an outpatient COVID-19 treatment. Indeed, the RECOVERY team itself reported that while its "findings indicate that hydroxychloroquine is not an effective treatment for hospitalized patients with Covid-19," it does "not address [the drug's] use as prophylaxis or in patients with less severe SARS-CoV-2 infection managed in the community."[288] In sum, none of the FDA's four reasons, in isolation or taken together, clearly establish that hydroxychloroquine is ineffective as an early treatment against COVID-19.

Despite raising doubts about hydroxychloroquine's use against COVID-19, the FDA has consistently affirmed that healthcare providers retain the right to use hydroxychloroquine as a part of early COVID-19 treatment. At least four statements demonstrate this.

First, the FDA's current website says (and has said since July 2020) that "[i]f a healthcare professional is considering use of hydroxychloroquine or chloroquine to treat or prevent COVID-19, FDA recommends checking www.clinicaltrials.gov for a suitable clinical trial and consider enrolling the patient." This plainly assumes that healthcare providers have the right to use hydroxychloroquine to treat COVID-19.

Second, on May 29, 2020, then-FDA Commissioner Stephen Hahn acknowledged that "[m]any physicians have . . . prescribed [hydroxychloroquine] for patients with COVID-19 based on an individual assessment of the potential benefits versus the risks

---

286 *Id.* at 1.

287 *Id.*

288 RECOVERY Collaborative Group, *Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19*, 383 The New England Journal of Medicine 2030, 2038 (Nov. 2020), *available at* https://www.nejm.org/doi/pdf/10.1056/NEJMoa2022926?articleTools=true (last visited Oct. 14, 2021).

for an individual patient."[289] He added that "[p]rescribing a product for uses not specifically included in the official labeling is common in the practice of medicine" and that the FDA does not "prohibit[] physicians from prescribing medications" because the agency does "not regulate the practice of medicine."[290] These statements are still posted on the FDA's website, and we are not aware of any subsequent FDA statements revoking them.

Third, in June 2020, after the FDA revoked the hydroxychloroquine EUA, Health and Human Services Secretary Alex Azar said: "At this point, hydroxychloroquine and chloroquine are just like any other approved drug in the United States. They may be used in hospital, they may be used in out-patient, they may be used at home—all subject to a doctor's prescription."[291] Leaving no doubt about this point, Secretary Azar added that "[i]f a doctor wishes to prescribe [hydroxychloroquine], working with a patient, they may prescribe it for any purpose that they wish."[292] We are not aware of any subsequent statement revoking this guidance.

Fourth, in late July 2020, then-FDA Commissioner Hahn reiterated that "whether people should take hydroxychloroquine as a treatment" for COVID-19 is a decision that "should be made between a doctor and a patient."[293] He specifically stated: "A doctor and a patient need to assess the data that's out there, FDA does not regulate the practice of medicine, and that in the privacy of the doctor-patient relationship is where that decision should be made."[294]

iv. Foreign Public Health Agencies, Professional Associations, and Physicians on Hydroxychloroquine

The WHO "recommend[s] against administering hydroxychloroquine . . . for treatment of COVID-19" for "patients with any disease severity and any duration of symptoms."[295] It reached this recommendation after concluding that hydroxychloroquine

---

289 FDA, Bringing Perspective, *supra*.

290 *Id.*

291 Trump White House Archives, Remarks by President Trump in Roundtable Discussion on Fighting for America's Seniors (Jun. 15, 2020), *available at* https://trumpwhitehouse.archives.gov/briefings-statements/remarks-president-trump-roundtable-discussion-fighting-americas-seniors/ (last visited Oct. 14, 2021).

292 *Id.*

293 Tal Axelrod, *FDA chief: Hydroxychloroquine use a decision between doctor and patient*, The Hill (Jul. 30, 2020), https://thehill.com/policy/healthcare/509733-fda-chief-hydroxychloroquine-use-a-decision-between-doctor-and-patient?rl=1 (last visited Oct. 14, 2021).

294 *Id.*

295 WHO COVID-19 Guidelines, *supra*, at 26.

"probably do[es] not reduce mortality" and that its "effect on . . . admission to hospital . . . remains uncertain."[296] To the extent that this recommendation purports to address hydroxychloroquine's effectiveness as an early treatment for COVID-19, it arguably rests on weak evidence. Although it is difficult to determine how many of the studied individuals were outpatients, it appears that most were hospitalized. For instance, the WHO says that it consulted 29 studies in concluding that "[h]ydroxychloroquine probably does not reduce mortality," but the only study specifically cited is the RECOVERY trial,[297] which, as we already indicated, included only patients hospitalized with COVID-19.[298] In addition, the WHO's statistics on hospitalization rates, which consisted of one RCT that included 465 outpatients, suggests hydroxychloroquine's efficacy.[299] That trial revealed a hospitalization rate of 47 per 1,000 people in the control group but only 19 of 1,000 people in the hydroxychloroquine arm.[300] It thus seems as if the WHO may have overreached in definitively declaring that hydroxychloroquine holds no promise as an early COVID-19 treatment.

The WHO also "recommend[s] against administering hydroxychloroquine prophylaxis to individuals who do not have COVID-19" because it believes that prophylaxis "hydroxychloroquine has a small or no effect on death and hospital admission" and that it "probably has a small or no effect on laboratory-confirmed COVID-19."[301] Disagreeing with this, the team of researchers conducting the COPCOV trial on prophylaxis hydroxychloroquine has announced that the WHO's conclusions are "scientifically unsound."[302] In their statement on this topic, the COPCOV team explained that the available RCTs "suggest substantial uncertainty as to the benefit of hydroxychloroquine in preventing COVID-19," but the "overall trend [is] towards benefit."[303]

---

296 *Id.* at 27.

297 *Id.* at 28.

298 RECOVERY Collaborative Group, *supra*, at 2030.

299 WHO COVID-19 Guidelines, *supra*, at 29.

300 *Id.*

301 World Health Organization, WHO Living guideline: Drugs to prevent COVID-19, at 12 (Mar. 2, 2021), *available at* https://apps.who.int/iris/bitstream/handle/10665/339877/WHO-2019-nCoV-prophylaxes-2021.1-eng.pdf?sequence=13&isAllowed=y (last visited Oct. 14, 2021).

302 The COPCOV Trial's position statement on "A living WHO guideline on drugs to prevent COVID-19," MORU Tropical Health Network (Mar. 5, 2021), https://www.tropmedres.ac/news/copcov-response-to-latest-who-guidelines-on-hydroxychloroquine-for-covid-19-trials-1 (last visited Oct. 14, 2021).

303 *Id.*

As for the professional associations' and physician groups' views on hydroxychloroquine, it appears that they generally adopt the same position they took on ivermectin. Those like the AAPS that support ivermectin as an option for early COVID-19 treatment generally support hydroxychloroquine too, while those like the AMA, APhA, and ASHP that oppose one typically resist the other. Additionally, many physician groups use early COVID-19 treatment protocols that include hydroxychloroquine. For example, an article co-authored by over 50 doctors in Reviews in Cardiovascular Medicine outlines an early treatment protocol that includes hydroxychloroquine as a key component.[304]

Considering the evidence discussed above, we do not find that clear and convincing evidence would warrant disciplining physicians who prescribe hydroxychloroquine for the prevention or early treatment of COVID-19 after first obtaining informed patient consent.

CONCLUSION

Based on the available data, we do not find clear and convincing evidence that a physician who first obtains informed consent and then utilizes ivermectin or hydroxychloroquine for COVID-19 violates the UCA. This conclusion is subject to the limits noted throughout this opinion. Foremost among them are that if physicians who prescribe ivermectin or hydroxychloroquine neglect to obtain informed consent, deceive their patients, prescribe excessively high doses, fail to check for contraindications, or engage in other misconduct, they might be subject to discipline, no less than they would be in any other context.

As we have stressed throughout, this opinion is based only on the data and information available at this time. If the relevant medical evidence materially changes, that could impact our conclusions. Also, though an opinion from our office about possible UCA violations would ordinarily focus on healthcare practices within Nebraska, the context of a global pandemic necessitates looking for evidence far beyond our State's borders, as we have done here. Thus, the analytical roadmap in this opinion likely has limited application outside the circumstance of a global pandemic.

We emphasize in closing that our office is not recommending any specific treatments for COVID-19. That is not our role. There are multiple treatment options outside the scope of this opinion—including treatments that have been officially approved by the FDA—that physicians and their patients should carefully consider. This opinion takes no position on them. Rather, we address only the off-label early treatment options discussed in this opinion and conclude that the available evidence suggests that they might work for some people. Allowing physicians to consider these early treatments will free them to evaluate additional tools that could save lives, keep patients out of the hospital, and provide relief for our already strained healthcare system.

---

304 McCullough, *Multifaceted*, *supra*, at 522-23.

Very truly yours,

DOUGLAS J. PETERSON
Attorney General

James A. Campbell
Solicitor General

Mindy L. Lester
Assistant Attorney General

Approved by:

Attorney General

Exhibit B

Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19

Pierre Kory, MD[1]*, G. Umberto Meduri, MD[2]†, Jose Iglesias, DO[3], Joseph Varon, MD[4], Keith Berkowitz, MD[5], Howard Kornfeld, MD[6], Eivind Vinjevoll, MD[7], Scott Mitchell, MBChB[8], Fred Wagshul, MD[9], Paul E. Marik, MD[10]

1 Front-Line Covid-19 Critical Care Alliance
2 Memphis VA Medical Center, Univ. of Tennessee Health Science Center, Memphis, TN
3 Hackensack School of Medicine, Seton Hall, NJ.
4 Chief of Critical Care at United Memorial Medical Center in Houston, TX
5 Center for Balanced Health, New York
6 Recovery Without Walls
7 Volda Hospital, Volda, Norway
8 Princess Elizabeth Hospital, Guernsey, UK
9 Lung Center of America, Dayton, Ohio
10 Eastern Virginia Medical School

* **Correspondence:**
Corresponding Author: Pierre Kory, MD, MPA
pkory@flccc.net
1 These authors have contributed equally to this work
† Dr. Meduri's contribution is the result of work supported with the resources and use of facilities at the Memphis VA Medical Center. The contents of this commentary do not represent the views of the U.S. Department of Veterans Affairs or the United States Government

Keywords

Ivermectin, COVID-19, infectious disease, pulmonary infection, respiratory failure

Abstract

In March 2020, the Front Line COVID-19 Critical Care Alliance (FLCCC) was created and led by Professor Paul E. Marik to continuously review the rapidly emerging basic science, translational, and clinical data to develop a treatment protocol for COVID-19. The FLCCC then recently discovered that ivermectin, an anti-parasitic medicine, has highly potent anti-viral and anti-inflammatory properties against COVID-19. They then identified repeated, consistent, large magnitude improvements in clinical outcomes in multiple, large, randomized and observational controlled trials in both prophylaxis and treatment of COVID-19. Further, data showing impacts on population wide health outcomes have

resulted from multiple, large "natural experiments" that occurred when various city mayors and regional health ministries within South American countries initiated "ivermectin distribution" campaigns to their citizen populations in the hopes the drug would prove effective. The tight, reproducible, temporally associated decreases in case counts and case fatality rates in each of those regions compared to nearby regions without such campaigns, suggest that ivermectin may prove to be a global solution to the pandemic. This was further evidenced by the recent incorporation of ivermectin as a prophylaxis and treatment agent for COVID-19 in the national treatment guidelines of Belize, Macedonia, and the state of Uttar Pradesh in Northern India, populated by 210 million people. To our knowledge, the current review is the earliest to compile sufficient clinical data to demonstrate the strong signal of therapeutic efficacy as it is based on numerous clinical trials in multiple disease phases. One limitation is that half the controlled trials have been published in peer-reviewed publications, with the remainder taken from manuscripts uploaded to medicine pre-print servers. Although it is now standard practice for trials data from pre-print servers to immediately influence therapeutic practices during the pandemic, given the controversial therapeutics adopted as a result of this practice, the FLCCC argues that it is imperative that our major national and international health care agencies devote the necessary resources to more quickly validate these studies and confirm the major, positive epidemiological impacts that have been recorded when ivermectin is widely distributed among populations with a high incidence of COVID-19 infections.

Introduction

In March 2020, an expert panel called the Front Line COVID-19 Critical Care Alliance (FLCCC) was created and led by Professor Paul E. Marik.[1] The group of expert critical care physicians and thought leaders immediately began continuously reviewing the rapidly emerging basic science, translational, and clinical data in COVID-19 which then led to the early creation of a treatment protocol for hospitalized patients based on the core therapeutic interventions of methylprednisolone, ascorbic acid, thiamine and heparin (MATH+), with the "+" referring to multiple, optional adjunctive treatments. The MATH+ protocol was based on the collective expertise of the group in both the research and treatment of multiple other severe infections causing lung injury.

Two manuscripts reviewing different aspects of both the scientific rationale and evolving published clinical evidence in support of the MATH+ protocol were published in major medical journals at two different time points in the pandemic (Kory et al., 2020;Marik et al., 2020). The most recent paper reported a 6.1% hospital mortality rate in COVID-19 patients measured in the two U.S hospitals that systematically adopted the MATH+ protocol (Kory et al., 2020). This was a markedly decreased mortality rate compared to the 23.0% hospital mortality rate calculated from a review of 45 studies including over 230,000 patients (unpublished data; available on request).

Although the adoption of MATH+ has been considerable, it largely occurred only after the treatment efficacy of the majority of the protocol components (corticosteroids, ascorbic acid, heparin, statins, Vitamin D, melatonin) were either validated in subsequent randomized controlled trials or more strongly supported with large observational data sets in COVID-19 (Entrenas Castillo et al., 2020;Horby et al., 2020;Jehi et al., 2020;Nadkarni et al., 2020;Rodriguez-Nava et al., 2020;Zhang et al., 2020a;Zhang et al., 2020b). Despite the plethora of supportive evidence, the MATH+ protocol for hospitalized patients has not yet become widespread. Further, the world is in a worsening crisis with

[1] https://www.flccc.net

the potential of again overwhelming hospitals and ICU's. As of December 31st, 2020, the number of deaths attributed to COVID-19 in the United States reached 351,695 with over 7.9 million active cases, the highest number to date.[2] Multiple European countries have now begun to impose new rounds of restrictions and lockdowns.[3]

Further compounding these alarming developments was a wave of recently published results from therapeutic trials done on medicines thought effective for COVID-19 which found a lack of impact on mortality with use of remdesivir, hydroxychloroquine, lopinavir/ritonavir, interferon, convalescent plasma, tocilizumab, and mono-clonal antibody therapy (Agarwal et al., 2020;Consortium, 2020;Hermine et al., 2020;Salvarani et al., 2020).[4] One year into the pandemic, the only therapy considered "proven" as a life-saving treatment in COVID-19 is the use of corticosteroids in patients with moderate to severe illness (Horby et al., 2020). Similarly, most concerning is the fact that little has proven effective to prevent disease progression to prevent hospitalization.

Fortunately, it now appears that ivermectin, a widely used anti-parasitic medicine with known anti-viral and anti-inflammatory properties is proving a highly potent and multi-phase effective treatment against COVID-19. Although growing numbers of the studies supporting this conclusion have passed through peer review, approximately half of the remaining trials data are from manuscripts uploaded to medical pre-print servers, a now standard practice for both rapid dissemination and adoption of new therapeutics throughout the pandemic. The FLCCC expert panel, in their prolonged and continued commitment to reviewing the emerging medical evidence base, and considering the impact of the recent surge, has now reached a consensus in recommending that ivermectin for both prophylaxis and treatment of COVID-19 should be systematically and globally adopted.

The FLCCC recommendation is based on the following set of conclusions derived from the existing data, which will be comprehensively reviewed below:

1) Since 2012, multiple *in vitro* studies have demonstrated that Ivermectin inhibits the replication of many viruses, including influenza, Zika, Dengue and others (Mastrangelo et al., 2012;Wagstaff et al., 2012;Tay et al., 2013;Götz et al., 2016;Varghese et al., 2016;Atkinson et al., 2018;Lv et al., 2018;King et al., 2020;Yang et al., 2020).
2) Ivermectin inhibits SARS-CoV-2 replication and binding to host tissue via several observed and proposed mechanisms (Caly et al., 2020a).
3) Ivermectin has potent anti-inflammatory properties with *in vitro* data demonstrating profound inhibition of both cytokine production and transcription of nuclear factor-κB (NF-κB), the most potent mediator of inflammation (Zhang et al., 2008;Ci et al., 2009;Zhang et al., 2009).
4) Ivermectin significantly diminishes viral load and protects against organ damage in multiple animal models when infected with SARS-CoV-2 or similar coronaviruses (Arevalo et al., 2020;de Melo et al., 2020).
5) Ivermectin prevents transmission and development of COVID-19 disease in those exposed to infected patients (Behera et al., 2020;Bernigaud et al., 2020;Carvallo et al., 2020b;Elgazzar et al., 2020;Hellwig and Maia, 2020;Shouman, 2020).

[2] https://www.worldometers.info/coronavirus/country/us/
[3] https://www.npr.org/sections/coronavirus-live-updates/2020/12/15/946644132/some-european-countries-batten-down-for-the-holidays-with-new-coronavirus-lockdo
[4] https://www.lilly.com/news/stories/statement-activ3-clinical-trial-nih-covid19

6) Ivermectin hastens recovery and prevents deterioration in patients with mild to moderate disease treated early after symptoms (Carvallo et al., 2020a;Elgazzar et al., 2020;Gorial et al., 2020;Khan et al., 2020;Mahmud, 2020;Morgenstern et al., 2020;Robin et al., 2020).
7) Ivermectin hastens recovery and avoidance of ICU admission and death in hospitalized patients (Elgazzar et al., 2020;Hashim et al., 2020;Khan et al., 2020;Niaee et al., 2020;Portmann-Baracco et al., 2020;Rajter et al., 2020;Spoorthi V, 2020).
8) Ivermectin reduces mortality in critically ill patients with COVID-19 (Elgazzar et al., 2020;Hashim et al., 2020;Rajter et al., 2020).
9) Ivermectin leads to striking reductions in case-fatality rates in regions with widespread use (Chamie, 2020).[5]
10) The safety, availability, and cost of ivermectin is nearly unparalleled given its near nil drug interactions along with only mild and rare side effects observed in almost 40 years of use and billions of doses administered (Kircik et al., 2016).
11) The World Health Organization has long included ivermectin on its "List of Essential Medicines".[6]

Following is a comprehensive review of the available efficacy data as of December 12, 2020, taken from *in vitro*, animal, clinical, and real-world studies all showing the above impacts of ivermectin in COVID-19.

History of ivermectin

In 1975, Professor Satoshi Omura at the Kitsato institute in Japan isolated an unusual *Streptomyces* bacteria from the soil near a golf course along the south east coast of Honshu, Japan. Omura, along with William Campbell, found that the bacterial culture could cure mice infected with the round-worm *Heligmosomoides polygyrus*. Campbell isolated the active compounds from the bacterial culture, naming them "avermectins" and the bacterium *Streptomyces avermitilis* for the compounds' ability to clear mice of worms (Crump and Omura, 2011). Despite decades of searching around the world, the Japanese microorganism remains the only source of avermectin ever found. Ivermectin, a derivative of avermectin, then proved revolutionary. Originally introduced as a veterinary drug, it soon after made historic impacts in human health, improving the nutrition, general health and well-being of billions of people worldwide ever since it was first used to treat Onchocerciasis (river blindness) in humans in 1988. It proved ideal in many ways, given that it was highly effective, broad-spectrum, safe, well tolerated and could be easily administered (Crump and Omura, 2011). Although it was used to treat a variety of internal nematode infections, it was most known as the essential mainstay of two global disease elimination campaigns that has nearly eliminated the world of two of its most disfiguring and devastating diseases. The unprecedented partnership between Merck & Co. Inc., and the Kitasato Institute combined with the aid of international health care organizations has been recognized by many experts as one of the greatest medical accomplishments of the 20th century. One example was the decision by Merck & Co to donate ivermectin doses to support the Meztican Donation Program which then provided over 570 million treatments in its first 20 years alone (Tambo et al.). Ivermectins' impacts in controlling Onchocerciasis and Lymphatic filariasis, diseases which

[5] https://trialsitenews.com/an-old-drug-tackles-new-tricks-ivermectin-treatment-in-three-brazilian-towns/
[6] https://www.who.int/publications/i/item/WHOMVPEMPIAU201907

blighted the lives of billions of the poor and disadvantaged throughout the tropics, is why its discoverers were awarded the Nobel Prize in Medicine in 2015 and the reason for its inclusion on the WHO's "List of Essential Medicines." Further, it has also been used to successfully overcome several other human diseases and new uses for it are continually being found (Crump and Omura, 2011).

Pre-Clinical Studies of Ivermectin's activity against SARS-CoV-2

Since 2012, a growing number of cellular studies have demonstrated that ivermectin has anti-viral properties against an increasing number of RNA viruses, including influenza, Zika, HIV, Dengue, and most importantly, SARS-CoV-2 (Mastrangelo et al., 2012;Wagstaff et al., 2012;Tay et al., 2013;Götz et al., 2016;Varghese et al., 2016;Atkinson et al., 2018;Lv et al., 2018;King et al., 2020;Yang et al., 2020). Insights into the mechanisms of action by which ivermectin both interferes with the entrance and replication of SARS-CoV-2 within human cells are mounting. Caly et al first reported that ivermectin significantly inhibits SARS-CoV-2 replication in a cell culture model, observing the near absence of all viral material 48h after exposure to ivermectin (Caly et al., 2020b). However, some questioned whether this observation is generalizable clinically given the inability to achieve similar tissue concentrations employed in their experimental model using standard or even massive doses of ivermectin (Bray et al., 2020;Schmith et al., 2020). It should be noted that the concentrations required for effect in cell culture models bear little resemblance to human physiology given the absence of an active immune system working synergistically with a therapeutic agent such as ivermectin. Further, prolonged durations of exposure to a drug likely would require a fraction of the dosing in short term cell model exposure. Further, multiple co-existing or alternate mechanisms of action likely explain the clinical effects observed, such as the competitive binding of ivermectin with the host receptor-binding region of SARS-CoV-2 spike protein, as proposed in six molecular modeling studies (Dayer, 2020; Hussien and Abdelaziz, 2020;Lehrer and Rheinstein, 2020;Maurya, 2020;Nallusamy et al., 2020; Suravajhala et al., 2020). In four of the studies, ivermectin was identified as having the highest or among the highest of binding affinities to spike protein S1 binding domains of SARS-CoV-2 among hundreds of molecules collectively examined, with ivermectin not being the particular focus of study in four of these studies (Scheim, 2020). This is the same mechanism by which viral antibodies, in particular, those generated by the Pfizer and Moderna vaccines, contain the SARS-CoV-2 virus. The high binding activity of ivermectin to the SARS-CoV-2 spike protein could limit binding to either the ACE-2 receptor or sialic acid receptors, respectively either preventing cellular entry of the virus or preventing hemagglutination, a recently proposed pathologic mechanism in COVID-19 (Dasgupta J, 2020;Dayer, 2020;Lehrer and Rheinstein, 2020;Maurya, 2020;Scheim, 2020). Ivermectin has also been shown to bind to or interfere with multiple essential structural and non-structural proteins required by the virus in order to replicate (Lehrer and Rheinstein, 2020;Sen Gupta et al., 2020). Finally, ivermectin also binds to the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), thereby inhibiting viral replication (Swargiary, 2020).

Arevalo et al investigated in a murine model infected with a type 2 family RNA coronavirus similar to SARS-CoV-2, (mouse hepatitis virus), the response to 500 mcg/kg of ivermectin vs. placebo (Arevalo et al., 2020). The study included 40 infected mice, with 20 treated with ivermectin, 20 with phosphate buffered saline, and then 16 uninfected control mice that were also given phosphate buffered saline. At day 5, all the mice were euthanized to obtain tissues for examination and viral load assessment. The 20 non-ivermectin treated infected mice all showed severe hepatocellular necrosis surrounded by a severe lymphoplasmacytic inflammatory infiltration associated with a high hepatic

viral load (52,158 AU), while in the ivermectin treated mice a much lower viral load was measured (23,192 AU; $p<0.05$), with only few livers in the ivermectin treated mice showing histopathological damage such that the differences between the livers from the uninfected control mice were not statistically significant.

Dias De Melo and colleagues recently posted the results of a study they did with golden hamsters that were intranasally inoculated with SARS-CoV-2 virus, and at the time of the infection, the animals also received a single subcutaneous injection of ivermectin at a dose of 0.4mg/kg on day 1 (de Melo et al., 2020). Control animals received only the physiologic solution. They found the following among the ivermectin treated hamsters; a dramatic reduction in anosmia (33.3% vs 83.3%, p=.03) which was also sex-dependent in that the male hamsters exhibited a reduction in clinical score while the treated female hamsters failed to show any sign of anosmia. They also found significant reductions in cytokine concentrations in the nasal turbinate's and lungs of the treated animals despite the lack of apparent differences in viral titers.

Despite these mounting insights into the existing and potential mechanisms of action of ivermectin both as a prophylactic and treatment agent, it must be emphasized that significant research gaps remain and that many further *in vitro* and animal studies should be undertaken to better define not only these mechanisms but also to further support ivermectin's role as a prophylactic agent, especially in terms of the optimal dose and frequency required.

Pre-Clinical studies of ivermectin's anti-inflammatory properties

Given that little viral replication occurs in the later phases of COVID-19, nor can virus be cultured, and only in a minority of autopsies can viral cytopathic changes be found (Perera et al., 2020;Polak et al., 2020;Young et al., 2020), the most likely pathophysiologic mechanism is that identified by Li et al. where they showed that the non-viable RNA fragments of SARS-CoV-2 leads to a high mortality and morbidity in COVID-19 via the provocation of an overwhelming and injurious inflammatory response (Li et al., 2013). Based on these insights and the clinical benefits of ivermectin in late phase disease to be reviewed below, it appears that the increasingly well described *in vitro* properties of ivermectin as an inhibitor of inflammation are far more clinically potent than previously recognized. The growing list of studies demonstrating the anti-inflammatory properties of ivermectin include its ability to; inhibit cytokine production after lipopolysaccharide exposure, downregulate transcription of NF-kB, and limit the production of both nitric oxide and prostaglandin E_2 (Zhang et al., 2008;Ci et al., 2009;Zhang et al., 2009).

Exposure prophylaxis studies of ivermectin's ability to prevent transmission of COVID-19

Data is also now available showing large and statistically significant decreases in the transmission of COVID-19 among human subjects based on data from three randomized controlled trials (RCT) and five observational controlled trials (OCT) with four of the eight (two of them RCT's) published in peer-reviewed journals (Behera et al., 2020;Bernigaud et al., 2020;Carvallo et al., 2020b;Chala, 2020;Elgazzar et al., 2020;Hellwig and Maia, 2020;Shouman, 2020).

Elgazzar and colleagues at Benha University in Egypt randomized 200 health care and households contacts of COVID-19 patients where the intervention group consisted of 100 patients given a high dose of 0.4mg/kg on day 1 and a second dose on day 7 in addition to wearing personal

protective equipment (PPE), while the control group of 100 contacts wore PPE only (Elgazzar et al., 2020). They reported a large and statistically significant reduction in contacts testing positive by RT-PCR when treated with ivermectin vs. controls, 2% vs 10%, p<.05.

Shouman conducted an RCT at Zagazig University in Egypt, including 340 (228 treated, 112 control) family members of patients positive for SARS-CoV-2 via PCR (Shouman, 2020). Ivermectin, (approximately 0.25mg/kg) was administered twice, on the day of the positive test and 72 hours later. After a two-week follow up, a large and statistically significant decrease in COVID-19 symptoms among household members treated with ivermectin was found, 7.4% vs. 58.4%, p<.001.

Recently Alam et al from Bangladesh performed a prospective observational study of 118 patients that were evenly split into those that volunteered for either the treatment or control arms, described as a persuasive approach. Although this method, along with the study being unblinded likely led to confounders, the differences between the two groups were so large (6.7% vs. 73.3%, p <.001) and similar to the other prophylaxis trial results that confounders alone are unlikely to explain such a result (Alam et al., 2020). Carvallo et al also performed a prospective observational trial where they gave healthy volunteers ivermectin and carrageenan daily for 28 days and matched them to similarly healthy controls who did not take the medicines (Carvallo et al., 2020b). Of the 229 study subjects, 131 were treated with 0.2mg of ivermectin drops taken by mouth five times per day. After 28 days, none of those receiving ivermectin prophylaxis group had tested positive for SARS-COV-2 versus 11.2% of patients in the control arm (p<.001). In a much larger follow-up observational controlled trial by the same group that included 1,195 health care workers, they found that over a 3-month period, there were no infections recorded among the 788 workers that took weekly ivermectin prophylaxis while 58% of the 407 controls had become ill with COVID-19. This study demonstrates that protection against transmission can be achieved among high-risk health care workers by taking 12mg once weekly (Carvallo et al., 2020b). The Carvallo IVERCAR protocol was also separately tested in a prospective RCT by the Health Ministry of Tucuman, Argentina where they found that among 234 health care workers, the intervention group that took 12 mg once weekly, only 3.4% contracted COVID-19 vs. 21.4% of controls, p<.0001(Chala, 2020).

The need for weekly dosing in the Carvallo study over a 4 month period may not have been necessary given that, in a recent RCT from Dhaka, Bangladesh, the intervention group (n=58) took 12mg only once monthly for a similar 4 month period and also reported a large and statistically significant decrease in infections compared to controls, 6.9% vs. 73.3%, p<.05 (Alam et al., 2020). Then, in a large retrospective observational case-control study from India, Behera et al. reported that among 186 case-control pairs (n=372) of health care workers, they identified 169 participants that had taken some form of prophylaxis, with 115 that had taken ivermectin prophylaxis (Behera et al., 2020). After matched pair analysis, they reported that in the workers who had taken two dose ivermectin prophylaxis, the odds ratio for contracting COVID-19 was markedly decreased (0.27, 95% CI, 0.15–0.51). Notably, one dose prophylaxis was not found to be protective in this study. Based on both their study finding and the Egyptian prophylaxis study, the All-India Institute of Medical Sciences instituted a prophylaxis protocol for their health care workers where they now take two 0.3mg/kg doses of ivermectin 72 hours apart and repeat the dose monthly.

Data which further illuminates the protective role of ivermectin against COVID-19 comes from a study of nursing home residents in France which reported that in a facility that suffered a scabies outbreak where all 69 residents and 52 staff were treated with ivermectin (Behera et al., 2020), they found that during the time period surrounding this event, 7/69 residents fell ill with COVID-19 (10.1%). In this group with an average age of 90 years, only one resident required oxygen support and

no resident died. In a matched control group of residents from surrounding facilities, they found 22.6% of residents fell ill and 4.9% died.

Likely the most definitive evidence supporting the efficacy of ivermectin as a prophylaxis agent was published recently in the International Journal of Anti-Microbial agents where a group of researchers analyzed data using the prophylactic chemotherapy databank administered by the WHO along with case counts obtained by Worldometers, a public data aggregation site used by among others, the Johns Hopkins University (Hellwig and Maia, 2020). When they compared the data from countries with active ivermectin mass drug administration programs for the prevention of parasite infections, they discovered that the COVID-19 case counts were significantly lower in the countries with recently active programs, to a high degree of statistical significance, p<.001.

Figure 1 below presents a meta-analysis performed by the study authors of the controlled ivermectin prophylaxis trials in COVID-19.

Figure 1. Meta-analysis of ivermectin prophylaxis trials in COVID-19

Group by Type	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Symptomatic Infection / Total: Group-Ivermectin	Symptomatic Infection / Total: Group-Control
Obs	Behera	0.127	0.069	0.232	-6.704	0.000	15 / 91	171 / 281
Obs	Carvallo -1	0.029	0.002	0.497	-2.441	0.015	0 / 131	11 / 98
Obs	Carvallo- 2	0.000	0.000	0.007	-5.426	0.000	0 / 788	237 / 407
Obs	Alam	0.027	0.008	0.086	-6.077	0.000	4 / 58	44 / 60
Obs		0.073	0.044	0.123	-9.900	0.000		
RCT	Elgazzar	0.184	0.039	0.861	-2.150	0.032	2 / 100	10 / 100
RCT	Shouman	0.057	0.029	0.110	-8.542	0.000	15 / 203	59 / 101
RCT	Chala	0.130	0.044	0.388	-3.662	0.000	4 / 117	25 / 117
RCT		0.079	0.047	0.135	-9.385	0.000		

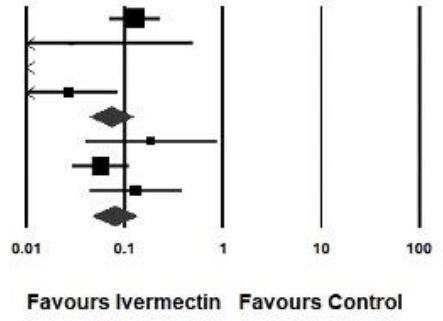


Figure 1 legend – OBS: Observational study, RCT: Randomized Controlled Trial

Symbols – Squares: indicate treatment effect of an individual study. Large diamond: reflect summary of study design immediately above. Small diamond: sum effect of all trial designs. Size of each symbol correlates with the size of the confidence interval around the point estimate of treatment effect with larger sizes indicating a more precise confidence interval.

Further data supporting a role for ivermectin in decreasing transmission rates can be found from South American countries where, in retrospect, large "natural experiments" appear to have occurred. For instance, beginning as early as May, various regional health ministries and governmental authorities within Peru, Brazil, and Paraguay initiated "ivermectin distribution" campaigns to their citizen populations (Chamie, 2020). In one such example from Brazil, the cities of Itajai, Macapa, and Natal distributed massive amounts of ivermectin doses to their city's population, where, in the case of Natal, 1 million doses were distributed.[7] The distribution campaign of Itajai began in mid-July, and in Natal they began on June 30th , and in Macapa, the capital city of Amapa and others nearby incorporated ivermectin into their treatment protocols in late May after they were particularly hard hit in April. The data in Table 1 below was obtained from the official Brazilian government site and the national press

[7] https://trialsitenews.com/an-old-drug-tackles-new-tricks-ivermectin-treatment-in-three-brazilian-towns/

consortium and show large decreases in case counts in the three cities soon after distribution began compared to their neighboring cities without such campaigns.

The decreases in case counts among the three Brazilian cities shown in Table 1 was also associated with reduced mortality rates as seen in Table 2 below.

Table 1. Comparison of case count decreases among Brazilian cities with and without ivermectin distribution campaigns (bolded cities distributed ivermectin, neighboring regional city below did not)

REGION	NEW CASES	JUNE	JULY	AUGUST	POPULATION 2020 (1000)	% DECLINE IN NEW CASES BETWEEN JUNE AND AUGUST 2020
South	**Itajaí**	**2123**	**2854**	**998**	**223**	**– 53 %**
	Chapecó	1760	1754	1405	224	– 20 %
North	**Macapá**	**7966**	**2481**	**2370**	**503**	**– 70 %**
	Ananindeua	1520	1521	1014	535	– 30 %
North East	**Natal**	**9009**	**7554**	**1590**	**890**	**– 82 %**
	João Pessoa	9437	7963	5384	817	– 43 %

Table 2. Change in death rates among neighboring regions in Brazil (bolded regions contained a major city that distributed Ivermectin to its citizens, the other regions did not)

REGION	STATE	% CHANGE IN AVERAGE DEATHS/ WEEK COMPARED TO 2 WEEKS PRIOR
South	**Santa Catarina**	**– 36 %**
	PARANÁ	– 3 %
	Rio Grande do Sul	– 5 %
North	**Amapá**	**– 75 %**
	AMAZONAS	– 42 %
	Pará	+ 13 %
North East	**Rio Grande do Norte**	**– 65 %**
	CEARÁ	+ 62 %
	Paraíba	– 30 %

Clinical studies on the efficacy of ivermectin in treating mildly ill outpatients

Currently, seven trials which include a total of over 3,000 patients with mild outpatient illness have been completed, a set comprised of 7 RCT's and four case series (Babalola et al.;Cadegiani et al., 2020;Carvallo et al., 2020a;Chaccour et al., 2020;Chowdhury et al., 2020;Espitia-Hernandez et al., 2020;Gorial et al., 2020;Hashim et al., 2020;Khan et al., 2020;Mahmud, 2020;Podder et al., 2020;Ravikirti et al., 2021).

The largest, a double blinded RCT by Mahmud et al. was conducted in Dhaka, Bangladesh and targeted 400 patients with 363 patients completing the study (Mahmud, 2020). In this study, as in many other of the clinical studies to be reviewed, either a tetracycline (doxycycline) or macrolide antibiotic (azithromycin) was included as part of the treatment. The importance of including antibiotics such as doxycycline or azithromycin is unclear, however, both tetracycline and macrolide antibiotics have recognized anti-inflammatory, immunomodulatory, and even antiviral effects (*58-61*). Although the posted data from this study does not specify the amount of mildly ill outpatients vs. hospitalized patients treated, important clinical outcomes were profoundly impacted, with increased rates of early improvement (60.7% vs. 44.4% p<.03) and decreased rates of clinical deterioration (8.7% vs 17.8%, p<.02). Given that mildly ill outpatients mainly comprised the study cohort, only two deaths were observed (both in the control group).

Ravikirti performed a double-blind RCT of 115 patients, ang although the primary outcome of PCR positivity on Day 6 was no different, the secondary outcome of mortality was 0%vs. 6.9%, p=.019 (Ravikirti et al., 2021). Babalola in Nigeria also performed a double blind-RCT of 62 patients, and, in contrast to Ravikirti, they found a significant difference in viral clearance between both the low and high dose treatment groups and controls in a dose dependent fashion, p=.006 (Babalola et al.).

Another RCT by Hashim et al. in Baghdad, Iraq included 140 patients equally divided; the control group received standard care, the treated group included a combination of both outpatient and hospitalized patients (Hashim et al., 2020). In the 96 patients with mild-to-moderate outpatient illness, they treated 48 patients with a combination of ivermectin/doxycycline and standard of care and compared outcomes to the 48 patients treated with standard of care alone. The standard of care in this trial included many elements of the MATH+ protocol, such as dexamethasone 6mg/day or methyl-prednisolone 40mg twice per day if needed, Vitamin C 1000mg twice/day, Zinc 75–125mg/day, Vitamin D3 5000 IU/day, azithromycin 250mg/day for 5 days, and acetaminophen 500mg as needed. Although no patients in either group progressed or died, the time to recovery was significantly shorter in the ivermectin treated group (6.3 days vs 13.7 days, p<.0001).

Chaccour et al conducted a small, double-blinded RCT in Spain where they randomized 24 patients to ivermectin vs placebo and although they found no difference in PCR positivity at day 7, they did find statistically significant decreases in viral loads, patient days of anosmia (76 vs 158, p<.05), and patient days with cough (68 vs 98, p<.05) (Chaccour et al., 2020).

Another RCT of ivermectin treatment in 116 outpatients was performed by Chowdhury et al. in Bangladesh where they compared a group of 60 patients treated with the combination of ivermectin/ doxycycline to a group of 60 patients treated with hydroxychloroquine/doxycycline with a primary outcome of time to negative PCR (Chowdhury et al., 2020). Although they found no difference in this outcome, in the treatment group, the time to symptomatic recovery approached statistical significance (5.9 days vs. 7.0 days, p=.07). In another smaller RCT of 62 patients by Podder et al., they also found a shorter time to symptomatic recovery that approached statistical significance (10.1 days vs 11.5 days, p>.05, 95% CI, 0.86−3.67) (Podder et al., 2020).

A medical group in the Dominican Republic reported a case series of 2,688 consecutive symptomatic outpatients seeking treatment in the emergency room, the majority of whom were diagnosed using a clinical algorithm. The patients were treated with high dose ivermectin of 0.4mg/kg for one dose along with five days of azithromycin. Only 16 of the 2,688 patients (0.59%) required subsequent hospitalization with one death recorded (Morgenstern et al., 2020).

In another case series of 100 patients in Bangladesh, all treated with a combination of 0.2mg/kg ivermectin and doxycycline, they found that no patient required hospitalization nor died, and all patients' symptoms improved within 72 hours (Robin et al., 2020).

A case series from Argentina reported on a combination protocol which used ivermectin, aspirin, dexamethasone and enoxaparin. In the 135 mild illness patients, all survived (Carvallo et al., 2020a). Similarly, a case series from Mexico of 28 consecutively treated patients with ivermectin, all were reported to have recovered with an average time to full recovery of only 3.6 days (Espitia-Hernandez et al., 2020).

Clinical studies of the efficacy of ivermectin in hospitalized patients

Studies of ivermectin amongst more severely ill hospitalized patients include 6 RCT's, 5 OCTs, and a database analysis study (Ahmed et al., 2020;Budhiraja et al., 2020;Camprubi et al., 2020;Chachar et al., 2020;Elgazzar et al., 2020;Gorial et al., 2020;Hashim et al., 2020;Khan et al., 2020;Niaee et al., 2020;Portmann-Baracco et al., 2020;Rajter et al., 2020;Soto-Becerra et al., 2020;Spoorthi V, 2020).

The largest RCT in hospitalized patients was performed concurrent with the prophylaxis study reviewed above by Elgazzar et al (Elgazzar et al., 2020). 400 patients were randomized amongst 4 treatment groups of 100 patients each. Groups 1 and 2 included mild/moderate illness patients only, with Group 1 treated with one dose 0.4mg/kg ivermectin plus standard of care (SOC) and Group 2 received hydroxychloroquine (HCQ) 400mg twice on day 1 then 200mg twice daily for 5 days plus standard of care. There was a statistically significant lower rate of progression in the ivermectin treated group (1% vs. 22%, p<.001) with no deaths and 4 deaths respectively. Groups 3 and 4 all included only severely ill patients, with group 3 again treated with single dose of 0.4mg/kg plus SOC while Group 4 received HCQ plus SOC. In this severely ill subgroup, the differences in outcomes were even larger, with lower rates of progression 4% vs. 30%, and mortality 2% vs 20% (p<.001).

The one largely outpatient RCT done by Hashim reviewed above also included 22 hospitalized patients in each group. In the ivermectin/doxycycline treated group, there were 11 severely ill patients and 11 critically ill patients while in the standard care group, only severely ill patients (n=22) were included due to their ethical concerns of including critically ill patients in the control group (*45*). This decision led to a marked imbalance in the severity of illness between these hospitalized patient groups. However, despite the mismatched severity of illness between groups and the small number of patients included, beneficial differences in outcomes were seen, but not all reached statistical significance. For instance, there was a large reduction in the rate of progression of illness (9% vs. 31.8%, p=0.15) and, most importantly, there was a large difference in mortality amongst the severely ill groups which reached a borderline statistical significance, (0% vs 27.3%, p=.052). Another important finding was the surprisingly low mortality rate of 18% found among the subset of critically ill patients, all of whom were treated with ivermectin.

A recent RCT from Iran found a dramatic reduction in mortality with ivermectin use (Niaee et al., 2020). Among multiple ivermectin treatment arms (different ivermectin dosing strategies were used in the intervention arms), the average mortality was reported as 3.3% while the average mortality within the standard care and placebo arms was 18.8%, with an OR of 0.18 (95% CI 0.06-0.55, p<.05).

Spoorthi and Sasanak performed a prospective RCT of 100 hospitalized patients whereby they treated 50 with ivermectin and doxycycline while the 50 controls were given a placebo consisting of Vitamin B6 (Spoorthi V, 2020). Although no deaths were reported in either group, the ivermectin treatment group had a shorter hospital LOS 3.7 days vs 4.7 days, p=.03, and a shorter time to complete resolution of symptoms, 6.7 days vs 7.9 days, p=.01.

The largest OCT (n=280) in hospitalized patients was done by Rajter et al. at Broward Health Hospitals in Florida and was recently published in the major medical journal *Chest* (*43*). They

performed a retrospective OCT with a propensity matched design on 280 consecutive treated patients and compared those treated with ivermectin to those without. 173 patients were treated with ivermectin (160 received a single dose, 13 received a 2nd dose at day 7) while 107 were not (Rajter et al., 2020). In both unmatched and propensity matched cohort comparisons, similar, large, and statistically significant lower mortality was found amongst ivermectin treated patients (15.0% vs. 25.2%, p=.03). Further, in the subgroup of patients with severe pulmonary involvement, mortality was profoundly reduced when treated with ivermectin (38.8% vs. 80.7%, p=.001).

Another large OCT in Bangladesh compared 115 pts treated with ivermectin to a standard care cohort consisting of 133 patients (Khan et al., 2020). Despite a significantly higher proportion of patients in the ivermectin group being male (i.e., with well-described, lower survival rates in COVID), the groups were otherwise well matched, yet the mortality decrease was statistically significant (0.9% vs. 6.8%, p<.05). The largest OCT is a study from Brazil which included almost 1,500 patients (Portmann-Baracco et al., 2020). Although the primary data was not provided, they reported that in 704 hospitalized patients treated with a single dose of 0.15mg/kg ivermectin compared to 704 controls, overall mortality was reduced (1.4% vs. 8.5%, HR 0.2, 95% CI 0.12-0.37, p<.0001). Similarly, in the patients on mechanical ventilation, mortality was also reduced (1.3% vs. 7.3%). A small study from Baghdad, Iraq compared 16 ivermectin treated patients to 71 controls (Gorial et al., 2020). This study also reported a significant reduction in length of hospital stay (7.6 days vs. 13.2 days, p<.001) in the ivermectin group. In a study reporting on the first 1000 patients treated in a hospital in India, they found that in the 34 patients treated with ivermectin alone, all recovered and were discharged, while in the over 900 patients treated with other agents, there was an overall mortality of 11.1% (Budhiraja et al., 2020).

One retrospective analysis of a database of hospitalized patients compared responses in patients receiving ivermectin, azithromycin, hydroxychloroquine or combinations of these medicines. In this study, no benefit for ivermectin was found, however the treatment groups in this analysis all included a number of patients who died on day 2, while in the control groups no early deaths occurred, thus the comparison appears limited (Soto-Becerra et al., 2020).

Meta-analyses of the above controlled treatment trials were performed by the study authors focused on the two important clinical outcomes: time to clinical recovery and mortality (Figures 2 and 3). The consistent and reproducible signals leading to large overall statistically significant benefits from within both study designs is remarkable, especially given that in several of the studies treatment was initiated late in the disease course.

Figure 2. Meta-analysis of the outcome of time to clinical recovery from controlled trials of ivermectin treatment in COVID-19

Group by Days	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Ivermectin	Control
		Statistics for each study							Sample size	
Multi	Elgazzar -Mild	-6.638	0.421	0.177	-7.462	-5.814	-15.783	0.000	100	50
Multi	Elgazzar -Severe	-6.108	0.337	0.113	-6.767	-5.448	-18.149	0.000	100	100
Multi	Niaee	-0.607	0.161	0.026	-0.923	-0.291	-3.761	0.000	120	60
Multi	Hashim	-1.197	0.184	0.034	-1.557	-0.838	-6.524	0.000	70	70
Multi		-1.820	0.110	0.012	-2.036	-1.604	-16.540	0.000		
Single	Chowdhury	-0.602	0.190	0.036	-0.975	-0.230	-3.171	0.002	60	56
Single	Podder	-0.295	0.256	0.065	-0.796	0.206	-1.154	0.248	32	30
Single	Rezai	-0.692	0.200	0.040	-1.084	-0.300	-3.461	0.001	53	53
Single	Spoorthi	-0.444	0.202	0.041	-0.841	-0.048	-2.195	0.028	50	50
Single		-0.534	0.104	0.011	-0.738	-0.330	-5.134	0.000		
Overall		-1.141	0.076	0.006	-1.289	-0.993	-15.093	0.000		

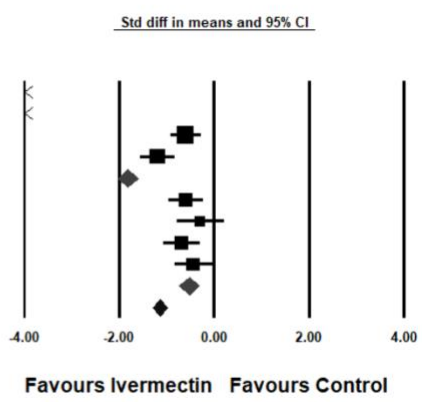


Figure 2 legend — Multi: multiple day dosing regimen. Single: single dose regimen.

Symbols — Squares: indicate treatment effect of an individual study. Large diamond: reflect summary of study design immediately above. Small diamond: sum effect of all trial designs. Size of each symbol correlates with the size of the confidence interval around the point estimate of treatment effect with larger sizes indicating a more precise confidence interval.

Figure 3. Meta-analysis of the outcome of mortality from controlled trials of ivermectin treatment in COVID-19

Group by RCT-Obs	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Dead / Total Ivermectin	Dead / Total Control
		Statistics for each study						
OBS	Rajter	0.524	0.287	0.958	-2.099	0.036	26 / 173	27 / 107
OBS	Khan	0.121	0.015	0.969	-1.990	0.047	1 / 115	9 / 133
OBS	Gorial	0.842	0.039	18.393	-0.109	0.913	0 / 16	2 / 71
OBS	Budhiraja	0.118	0.007	1.932	-1.499	0.134	0 / 34	103 / 942
OBS		0.451	0.258	0.789	-2.793	0.005		
RCT	Mahmud	0.138	0.007	2.694	-1.306	0.192	0 / 183	3 / 180
RCT	Hashim	0.314	0.061	1.611	-1.389	0.165	2 / 70	6 / 70
RCT	Elgazzar	0.074	0.017	0.318	-3.502	0.000	2 / 200	24 / 200
RCT	Niaee	0.154	0.047	0.506	-3.080	0.002	4 / 120	11 / 60
RCT	Cadegiani	0.046	0.002	0.970	-1.980	0.048	0 / 585	2 / 137
RCT	Ravikirti	0.107	0.006	2.038	-1.486	0.137	0 / 55	4 / 57
RCT		0.134	0.065	0.277	-5.413	0.000		
Overall		0.288	0.185	0.448	-5.509	0.000		

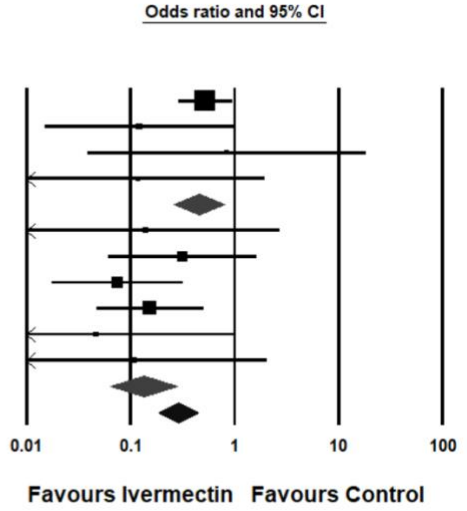


Figure 3 legend — OBS: Observational study, RCT: Randomized Controlled Trial.

Symbols — Squares: indicate treatment effect of an individual study. Large diamond: reflect summary of study design immediately above. Small diamond: sum effect of all trial designs. Size of each symbol correlates with the size of the confidence interval around the point estimate of treatment effect with larger sizes indicating a more precise confidence interval.

Details of the prophylaxis, early, and late treatment trials of ivermectin in COVID-19 can be found in Table 3 below.

Table 3. Clinical studies assessing the efficacy of ivermectin in the prophylaxis and treatment of COVID-19

Prophylaxis Trials					
AUTHOR, COUNTRY, SOURCE	**STUDY DESIGN, SIZE**	**STUDY SUBJECTS**	**IVERMECTIN DOSE**	**DOSE FREQUENCY**	**CLINICAL OUTCOMES REPORTED**
Shouman W, Egypt *www.clinicaltrials.gov* NCT04422561	RCT N=340	Household members of pts with +COVID-19 PCR test	40–60kg: 15mg 60–80kg: 18mg > 80kg: 24mg	Two doses, 72 hours apart	7.4% vs. 58.4% developed COVID-19 symptoms, p<.001
Elgazzar A, Egypt ResearchSquare doi.org/10.21203/rs.3.rs-100956/v1	RCT N=200	Health care and Household contacts of pts with +COVID-19 PCR test	0.4mg/kg	Two doses, Day 1 and Day 7	2% vs. 10% tested positive for COVID-19 p<.05
Chala R. Argentina NCT04701710 *Clinicaltrials.gov*	RCT N=234	Health Care Workers	12mg	Every 7 days	3.4% vs. 21.4%, p=.0001.
Carvallo H, Argentina *Journal of Biochemical Research and Investigation* doi.org/10.31546/2633-8653.1007	OCT N=229	Healthy patients negative for COVID-19 PCR	0.2mg drops	1 drop five times a day x 28 days	0.0% vs. 11.2% contracted COVID-19 p<.001
Alam MT. Bangladesh *European J Med Hlth Sciences* 10.24018/ejmed.2020.2.6.599	OCT N=118	Health Care Workers	12mg	Monthly	6.9% vs. 73.3%, p<.05
Carvallo H. Argentina *Journal of Biochemical Research and Investigation* doi.org/10.31546/2633-8653.1007	OCT N=1,195	Health Care Workers	12 mg	Once weekly for up to ten weeks	0.0% of the 788 workers taking ivermectin vs. 58% of the 407 controls contracted COVID-19.
Behera P, India *medRxiv* doi.org/10.1101/2020.10.29.20222661	OCT N=186 case control pairs	Health Care Workers	0.3 mg/kg	Day 1 and Day 4	2 doses reduced odds of contracting COVID-19 (OR 0.27 95% CI 0.16–0.53)
Bernigaud C. France *Annales de Dermatologie et de Venereologie* doi.org/10.1016/j.annder.2020.09.231	OCT N=69 case control pairs	Nursing Home Residents	0.2 mg/kg	Once	10.1% vs. 22.6% residents contracted COVID-19 0.0% vs 4.9% mortality
Hellwig M. USA *J Antimicrobial Agents* doi.org/10.1016/j.ijantimicag.2020.106248	OCT N=52 countries	Countries with and without IVM prophylaxis programs	Unknown	Variable	Significantly lower-case incidence of COVID-19 in African countries with IVM prophylaxis programs p<.001
Clinical Trials – Outpatients					% Ivermectin vs. % Controls
AUTHOR, COUNTRY, SOURCE	**STUDY DESIGN, SIZE**	**STUDY SUBJECTS**	**IVERMECTIN DOSE**	**DOSE FREQUENCY**	**CLINICAL OUTCOMES REPORTED**
Mahmud R, Bangladesh *www.clinicaltrials.gov* NCT0452383	DB-RCT N=363	Outpatients and hospitalized	12mg + doxycycline	Once, within 3 days of PCR+ test	Early improvement 60.7% vs. 44.4%, p<.03, deterioration 8.7% vs 17.8%, p<.02
Chowdhury A, Bangladesh *Research Square* doi.org/10.21203/rs.3.rs-38896/v1	DB-RCT N=116	Outpatients	0.2 mg//kg + doxycycline	Once	Recovery time 5.9 vs 9.3 days (p=.07)

Ravikirti, India *medRxiv* doi.org/10.1101/2021.01.05.21249310	DB-RCT N=115	Mild-moderate illness	12mg	Daily for 2 days	No diff in day 6 PCR+ 0% vs 6.9% mortality, p=.019
Babalola OE, Nigeria medRxiv doi.org/10.1101/2021.01.05.21249131	DB-RCT N=62	Mild-moderate illness	6mg and 12 mg	Every 48h x 2 weeks	Time to viral clearance: 4.6 days high dose vs 6.0 days low dose vs 9.1 days control (p=.006)
Podder CS, Bangladesh *IMC J Med Sci 2020;14(2)*	RCT N=62	Outpatients	0.2 mg/kg	Once	Recovery time 10.1 vs 11.5 days (NS), average time 5.3 vs 6.3 (NS)
Chaccour C. Spain *Research Square* doi.org/10.21203/rs.3.rs-116547/v1	RCT N=24	Outpatients	0.4mg/kg	Once	No diff in PCR+ Day 7, lower viral load days 4 and 7, (p<.05), 76 vs 158 pt. days of anosmia (p<.05), 68 vs 98 pt. days of cough (p<.05)
Morgenstern J, Dominican Republic *medRxiv* doi.org/10.1101/2020.10.29.20222505	Case Series N=3,099	Outpatients and hospitalized	Outpatients: 0.4mg/kg Hospital Patients: 0.3mg/kg	Outpatients:0.3 mg/kg x 1 dose Inpatients: 0.3mg/kg, Days 1,2,6,7	Mortality = 0.03% in 2688 outpatients, 1% in 300 non-ICU hospital patients, 30.6% in 111 ICU patients
Carvallo H, Argentina *medRxiv* doi.org/10.1101/2020.09.10.20191619	Case Series N=167	Outpatients and hospitalized	24mg=mild, 36mg=moderate, 48mg=severe	Days 0 and 7	All 135 with mild illness survived, 1/32 (3.1% of hospitalized patients died
Alam A, Bangladesh, *J of Bangladesh College Phys and Surg*, 2020;38:10-15 doi.org/10.3329/jbcps.v38i0.47512	Case series N=100	Outpatients	0.2 mg/kg/kg + doxycycline	Once	All improved within 72 hours
Espatia-Hernandez G, Mexico *Biomedical Research* www.biomedres.info/biomedi..-proof-of-concept-study-14435.html	Case Series N=28	Outpatients	6mg	Days 1,2, 7, 8	All pts recovered Average recovery time 3.6 days

Clinical Trials – Hospitalized Patients					% Ivermectin vs. % Controls
AUTHOR, COUNTRY, SOURCE	**STUDY DESIGN, SIZE**	**STUDY SUBJECTS**	**IVERMECTIN DOSE**	**DOSE FREQUENCY**	**CLINICAL OUTCOMES REPORTED**
Elgazzar A, Egypt *ResearchSquare* doi.org/10.21203/rs.3.rs-100956/v1	OL-RCT N=400	Hospitalized Patients	0.4 mg/kg	Once	Moderately Ill: worsened 1% vs 22%, p<.001. Severely ill: worsened 4% vs 30% mortality 2% vs 20% both with p<.001
Niaee S. M. *Research Square* doi.org/10.21203/rs.3.rs-109670/v1	DB-RCT N=180	Hospitalized Patients	0.2, 0.3, 0.4 mg/kg (3 dosing strategies)	Once vs. Days 1,3,5	Mortality 3.3% vs. 18.3%. OR 0.18, (.06-0.55, p<.05)
Hashim H, Iraq *medRxiv* doi.org/10.1101/2020.10.26.20219345	SB-RCT N=140	2/3 outpatients, 1/3 hospital pts	0.2 mg/kg + doxycycline	Daily for 2–3 days	Recovery time 6.3 vs 13.6 days (p<.001), 0% vs 27.3% mortality in severely ill (p=.052)

Spoorthi S, India *AIAM, 2020; 7(10):177-182*	RCT N=100	Hospitalized Patients	0.2mg/kg+ Doxycycline	Once	Shorter Hospital LOS, 3.7 vs. 4.7 days, p=.03, faster resolution of symptoms, 6.7 vs 7.9 days, p=.01
Ahmed S. Dhaka, Bangladesh *International Journal of Infectious Disease* doi.org/10.1016/j.ijid.2020.11.191	DB-RCT N=72	Hospitalized Patients	12mg	Daily for 5 days	Faster viral clearance 9.7 vs 12.7 days, p=.02
Chachar AZK, Pakistan *Int J Sciences* doi.org/10.18483/ijSci.2378	DB-RCT N=50	Hospitalized Patients-Mild	12mg	Two doses Day 1, one dose Day 2	64% vs 60% asymptomatic by Day 7
Portman-Baracco A, Brazil *Arch Bronconeumol. 2020* doi.org/10.1016/j.arbres.2020.06.011	OCT N=1408	Hospitalized patients	0.15 mg/kg	Once	Overall mortality 1.4% vs. 8.5%, HR 0.2, 95% CI 0.12-0.37, p<.0001
Soto-Beccerra P, Peru *medRxiv* doi.org/10.1101/2020.10.06.20208066	OCT N=5683, IVM, N=563	Hospitalized patients, database analysis	Unknown dose <48hrs after admission	Unknown	No benefits found
Rajter JC, Florida *Chest 2020* doi.org/10.1016/j.chest.2020.10.009	OCT N=280	Hospitalized patients	0.2 mg/kg + azithromycin	Day 1 and Day 7 if needed	Overall mortality 15.0% vs. 25.2%, p=.03, Severe illness mortality 38.8% vs. 80.7%, p=.001
Khan X, Bangladesh *Arch Bronconeumol. 2020* doi.org/10.1016/j.arbres.2020.08.007	OCT N=248	Hospitalized patients	12 mg	Once on admission	Mortality 0.9% vs. 6.8%, p<.05, LOS 9 vs. 15 days, p<.001
Gorial FI, Iraq *medRxiv* doi.org/10.1101/2020.07.07.20145979	OCT N=87	Hospitalized patients	0.2 mg/kg + HCQ and azithromycin	Once on admission	LOS 7.6 vs. 13.2 days, p<.001, 0/15 vs. 2/71 died
Budiraja S. India *medRxiv* doi.org/10.1101/2020.11.16.20232223	OCT N=1000 IVM=34	Hospitalized Patients	n/a	n/a	100% IVM pts recovered 11.1% mortality in non-IVM treated pts

Legend: DB-RCT = double-blind randomized controlled trial, HCQ = hydroxychloroquine, IVM = ivermectin, LOS = Length of stay, NS = non-statistically significant, p>.05, OCT = observational controlled trial, OL = open label, PCR – polymerase chain reaction, RCT = randomized controlled trial, SB-RCT =single blind, randomized controlled trial

Ivermectin in post-COVID-19 syndrome

Increasing reports of persistent, vexing, and even disabling symptoms after recovery from acute COVID-19 have been reported and which many have termed the condition as “long Covid” and patients as “long haulers”, estimated to occur in approximately 10% of cases (Callard and Perego, 2020;Rubin, 2020;Siegelman, 2020). Generally considered as a post-viral syndrome consisting of a chronic and sometimes disabling constellation of symptoms which include, in order, fatigue, shortness of breath, joint pains and chest pain. Many patients describe their most disabling symptom as impaired memory and concentration, often with extreme fatigue, described as “brain fog”, and are highly suggestive of the condition myalgic encephalomyelitis/chronic fatigue syndrome, a condition well-reported to begin after viral infections, in particular with Epstein-Barr virus. Although no specific

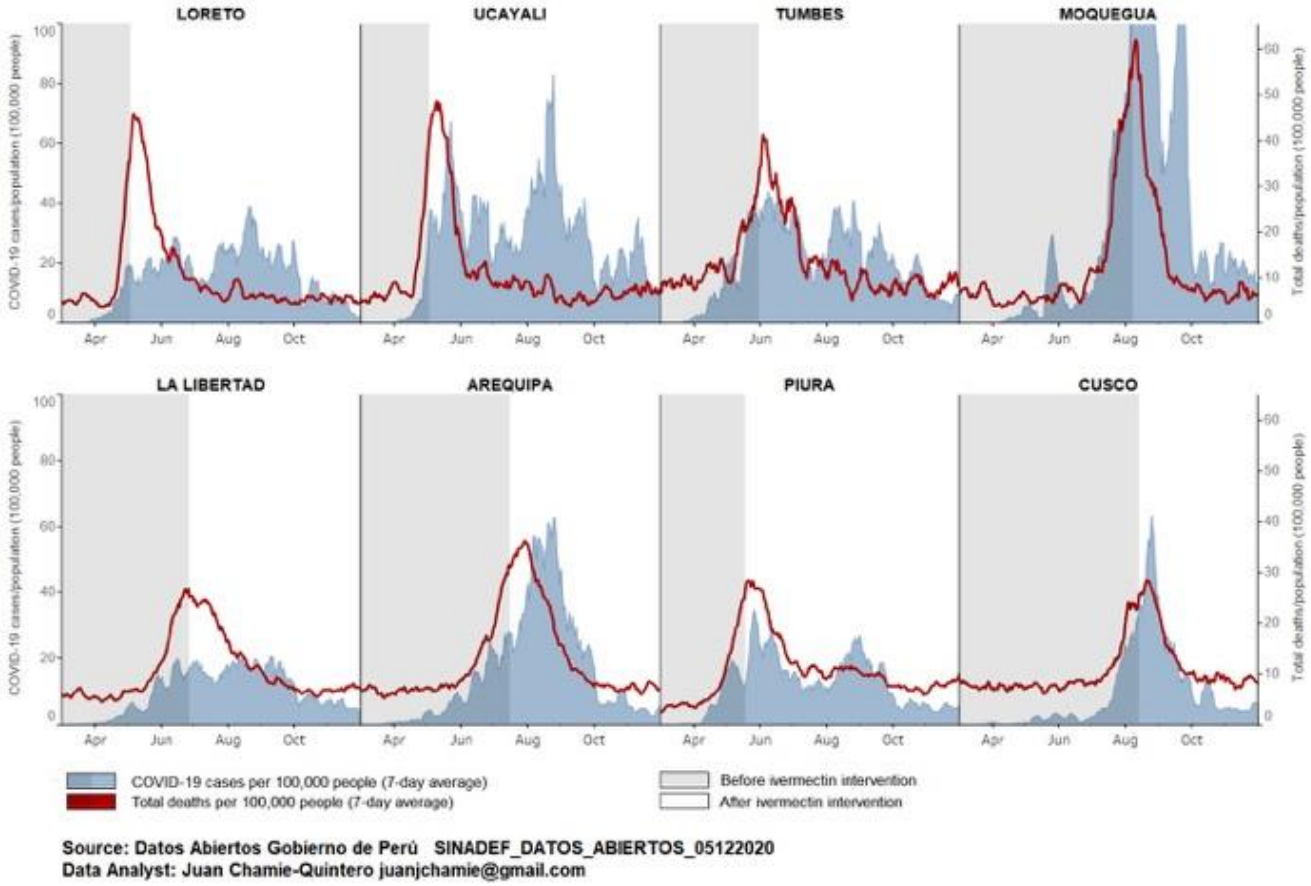
treatments have been identified for long COVID, a recent manuscript by Aguirre-Chang et al from the National University of San Marcos in Peru reported on the experience with ivermectin in such patients (Aguirre-Chang, 2020). They treated 33 patients who were between 4 and 12 weeks from the onset of symptoms with escalating doses of ivermectin; 0.2mg/kg for 2 days if mild, 0.4mg/kg for 2 days if moderate, with doses extended if symptoms persisted. They found that in 87.9% of the patients, resolution of all symptoms was observed after two doses with an additional 7% reporting complete resolution after additional doses. Their experience suggests the need for controlled studies to better test efficacy in this vexing syndrome.

Epidemiological data showing impacts of widespread ivermectin use on population case counts and case fatality rates

Similar to the individual cities in Brazil that measured large decreases in case counts soon after distributing ivermectin in comparison to neighboring cities without such campaigns, in Peru, the government approved the use of ivermectin by decree on May 8, 2020, solely based on the *in vitro* study by Caly et al. from Australia (Chamie, 2020).[8] Soon after, multiple state health ministries initiated ivermectin distribution campaigns in an effort to decrease what was at that time some of the highest COVID-19 morbidity and mortality rates in the world. Juan Chamie, a data analyst and member of the FLCCC Alliance recently posted a paper based on two critical sets of data that he compiled and compared; first he identified the timing and magnitude of each region's ivermectin interventions via a review of official communications, press releases, and the Peruvian Situation Room database in order to confirm the dates of effective delivery, and second, he extracted data on the total all-cause deaths from the region along with COVID-19 case counts in selected age groups over time from the registry of the National Computer System of Deaths (SINADEF), and from the National Institute of Statistics and Informatics (Chamie, 2020). It should be noted that he restricted his analyses to only those citizens over 60 years old in order to avoid the confounding of rises in the numbers of infected younger patients. With these data, he was then able to compare the timing of major decreases in this age group of both total COVID-19 cases and total deaths per 1000,000 people among 8 states in Peru with the initiation dates of their respective ivermectin distribution campaigns as shown in Figure 4 below.

[8] https://trialsitenews.com/trialsite-news-original-documentary-in-peru-about-ivermectin-and-covid-19/

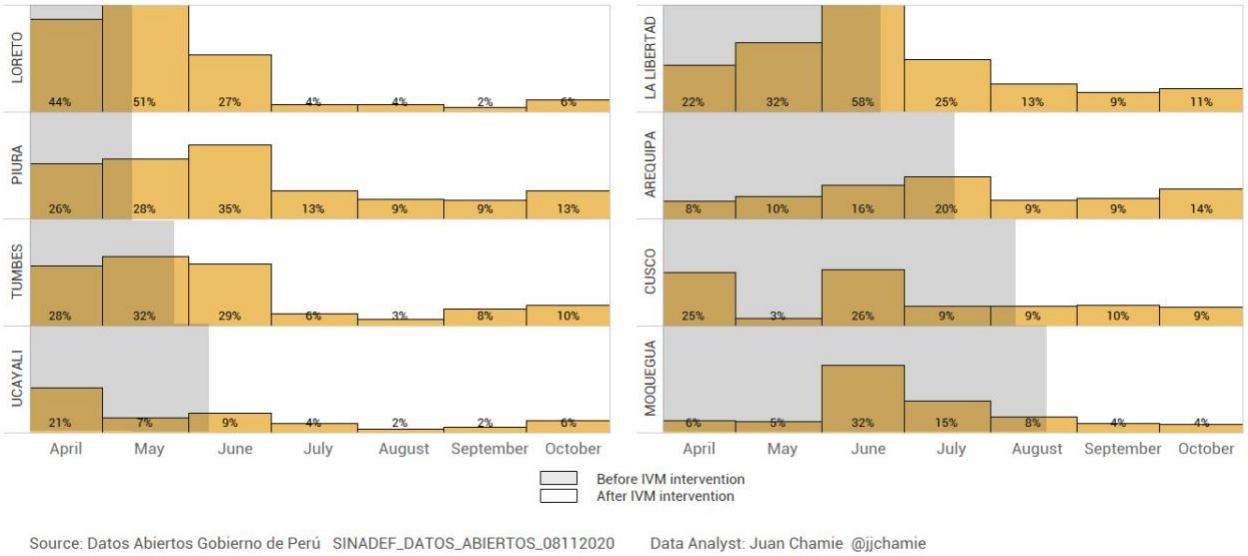
Figure 4. Decrease in total case incidences and total deaths/population of COVID-19 in the over 60 population among 8 Peruvian states after deploying mass ivermectin distribution campaigns



Source: Datos Abiertos Gobierno de Perú SINADEF_DATOS_ABIERTOS_05122020
Data Analyst: Juan Chamie-Quintero juanjchamie@gmail.com

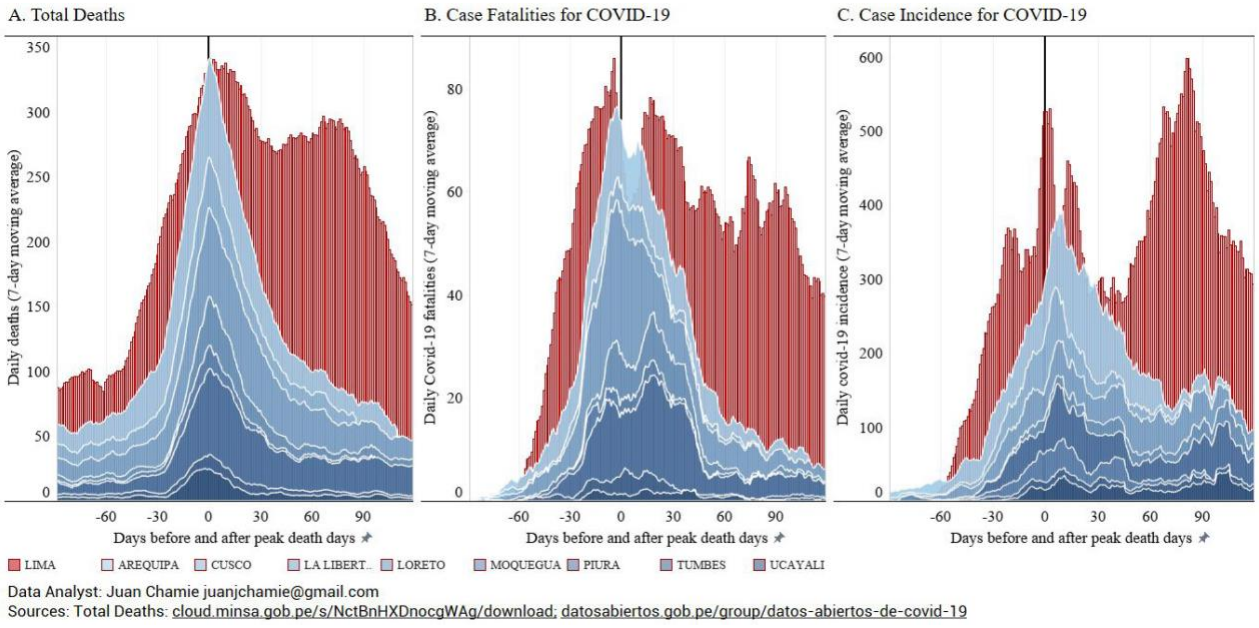
Figure 5 below from the same study presents data on the case fatality rates in patients over 60, again among the 8 states in Peru. Note the dramatically decreased case fatality rates among older patients with COVID-19 after ivermectin became widely distributed in those areas.

Figure 5. Monthly reported case fatality rates among patients over 60 in eight Peruvian states after deploying mass ivermectin treatment.



In an even more telling example, Chamie compared the case counts and fatality rates of the 8 states above with the city of Lima, where ivermectin was not distributed nor widely used in treatment during the same time period. Figure 6 below compares the lack of significant or sustained reductions in case counts or fatalities in Lima with the dramatic reductions in both outcomes among the 8 states with widespread ivermectin distribution.

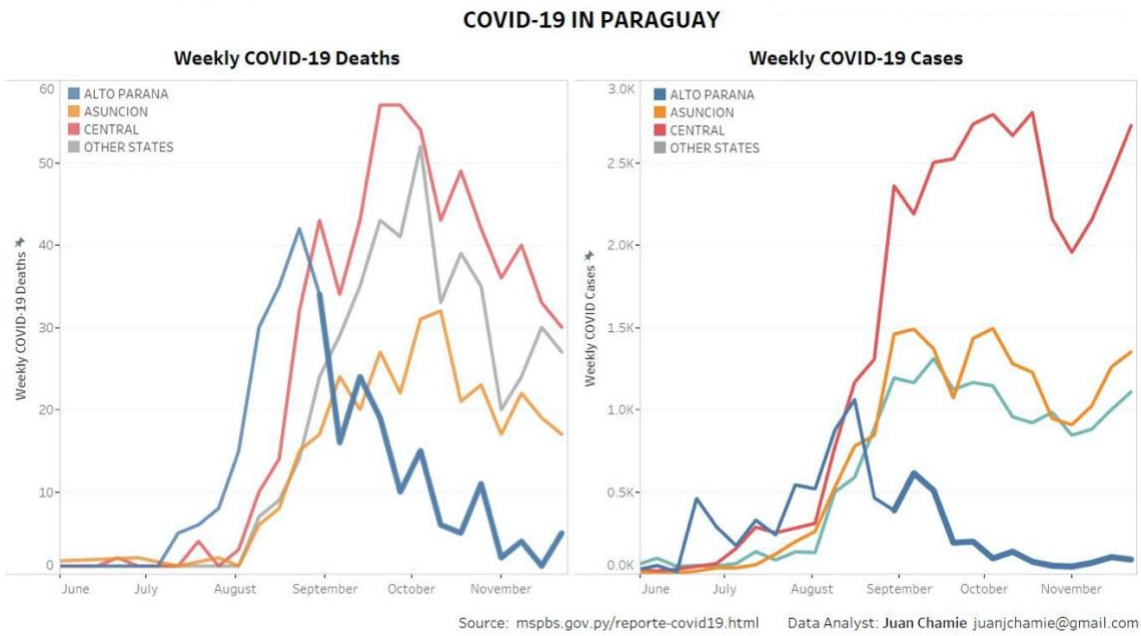
Figure 6. Covid-19 case fatalities and total deaths with and without mass ivermectin in different states of Peru



Legend: Daily total deaths, case fatalities and case incidence for COVID-19 in populations of patients age 60 and above for eight states in Peru deploying early mass ivermectin treatments vs. the state of Lima, including the capital city, where ivermectin treatment was applied months later.

Another compelling example can be seen from the data compiled from Paraguay, again by Chamie, who noted that the government of the state of Alto Parana had launched an ivermectin distribution campaign in early September. Although the campaign was officially described as a "de-worming" program, this was interpreted as a guise by the region's governor to avoid reprimand or conflict with the National Ministry of Health that recommended against use of ivermectin to treat COVID-19 in Paraguay.[9] The program began with a distribution of 30,000 boxes of ivermectin and by October 15, the governor declared that there were very few cases left in the state as can be seen in Figure 5 below.[10]

Figure 7. Paraguay – COVID-19 case counts and deaths in Alto Parana (bolded blue line) after ivermectin distribution began compared to other regions.



The clinical evidence base for ivermectin against COVID-19

A summary of the statistically significant results from the above controlled trials are as follows:

Controlled trials in the prophylaxis of COVID-19 (8 studies)

- All 8 available controlled trial results show statistically significant reductions in transmission
- 3 RCT's with large statistically significant reductions in transmission rates, N=774 patients (Chala, 2020;Elgazzar et al., 2020;Shouman, 2020)
- 5 OCT's with large statistically significant reductions in transmission rates, N=2052 patients (Alam et al., 2020;Behera et al., 2020;Bernigaud et al., 2020;Carvallo et al., 2020b;Hellwig and Maia, 2020)

[9] https://public.tableau.com/profile/jchamie#!/vizhome/COVID-19PARAGUAY/Paraguay
[10] https://public.tableau.com/profile/jchamie#!/vizhome/COVID-19PARAGUAY/Paraguay

Controlled trials in the treatment of COVID-19 (19 studies)

- 5 RCT's with statistically significant impacts in time to recovery or hospital length of stay (Elgazzar et al., 2020;Hashim et al., 2020;Mahmud, 2020;Niaee et al., 2020;Spoorthi V, 2020)
- 1 RCT with a near statistically significant decrease in time to recovery, p=.07, N=130 (Chowdhury et al., 2020)
- 1 RCT with a large, statistically significant reduction in the rate of deterioration or hospitalization, N=363 (Mahmud, 2020)
- 2 RCT's with a statistically significant decrease in viral load, days of anosmia and cough, N=85 (Chaccour et al., 2020;Ravikirti et al., 2021)
- 3 RCT's with large, statistically significant reductions in mortality (N=695) (Elgazzar et al., 2020;Niaee et al., 2020;Ravikirti et al., 2021)
- 1 RCT with a near statistically significant reduction in mortality, p=0.052 (N=140) (Hashim et al., 2020)
- 3 OCT's with large, statistically significant reductions in mortality (N=1,688) (Khan et al., 2020;Portmann-Baracco et al., 2020;Rajter et al., 2020)

Safety of Ivermectin

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 the parasites and include itching, rash, swollen lymph nodes, joint paints, fever and headache (Kircik et al., 2016). 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 (Gardon et al., 1997). 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 *drugs.com* database, 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 escalating high doses of ivermectin, toxicity is unlikely although a reduced efficacy due to decreased levels may be a concern (Guzzo et al., 2002).

Concerns of safety in the setting of liver disease are unfounded given that, to our knowledge, only two cases of liver injury have ever been reported in association with ivermectin, with both cases rapidly resolved without need for treatment. (Sparsa et al., 2006;Veit et al., 2006). Further, no dose adjustments are required in patients with liver disease. Some have described ivermectin as potentially neurotoxic, yet one study performed a search of a global pharmaceutical database and found only 28 cases of serious neurological adverse events such as ataxia, altered consciousness, seizure, or tremor (Chandler, 2018). Potential explanations included the effects of concomitantly administered drugs which increase absorption past the blood brain barrier or polymorphisms in the mdr-1 gene. However, the total number of reported cases suggests that such events are rare. Finally, ivermectin has been used safely in pregnant women, children, and infants.

Discussion

Currently, as of December 14, 2020, the accumulating evidence demonstrating the safety and efficacy of ivermectin in COVID-19 strongly supports its immediate use on a risk/benefit calculation in the context of a pandemic. Large-scale epidemiologic analyses validate the findings of *in vitro*, animal, prophylaxis, and clinical studies. Regions of the world with widespread ivermectin use have demonstrated a sizable reduction in case counts, hospitalizations, and fatality rates. This approach should be urgently considered in the presence of an escalating COVID-19 pandemic and as a bridge to vaccination. A recent systematic review of eight RCTs by Australian researchers, published as a pre-print, similarly concluded that ivermectin treatment led to a reduction in mortality, time to clinical recovery, the incidence of disease progression, and duration of hospital admission in patients across all stages of clinical severity (Kalfas et al., 2020). Our current review includes a total of 6,612 patients from 27 controlled studies [16 of them were RCTs, 5 double blinded, one single blinded, (n= 2,503)]; 11 published in peer-reviewed journals including 3,900 patients.

Pre-print publications have exploded during the COVID-19 pandemic. Except for hydroxychloroquine and convalescent plasma that were widely adopted before availability of any clinical data to support, almost all subsequent therapeutics were adopted after pre-print publication and *prior to peer review*. Examples include remdesivir, corticosteroids, and monoclonal antibodies. An even more aggressive example of rapid adoption was the initiation of inoculation programs using novel mRNA vaccines prior to review of either pre-print or peer-reviewed trials data by physicians ordering the inoculations for patients.[11] In all such situations, both academia and governmental health care agencies relaxed their standard to rise to the needs dictated by the pandemic.

In the context of ivermectin's long standing safety record, low cost, and wide availability along with the consistent, reproducible, large magnitude findings on transmission rates, need for hospitalization, mortality, and population-wide control of COVID-19 case and fatality rates in areas with widespread ivermectin distribution, insisting on the remaining studies to pass peer review prior to widespread adoption appears to be imprudent and to deviate from the now established standard approach towards adoption of new therapeutics during the pandemic. In fact, insisting on such a barrier to adoption would actually violate this new standard given that 12 of the 24 controlled trials have already been published in peer reviewed journals.

In regard to concerns over the validity of observational trial findings, it must be recognized that in the case of ivermectin; 1) half of the trials employed a randomized, controlled trial design (12 of the 24 reviewed above), and 2) that observational and randomized trial designs reach equivalent conclusions on average in nearly all diseases studied, as reported in a large Cochrane review of the topic from 2014 (Anglemyer et al., 2014). In particular, OCTs that employ propensity-matching techniques (as in the Rajter study from Florida), find near identical conclusions to later-conducted RCTs in many different disease states, including coronary syndromes, critical illness, and surgery (Dahabreh et al., 2012;Lonjon et al., 2014;Kitsios et al., 2015). Similarly, as evidenced in the prophylaxis (Figure 1) and treatment trial (Figures 2 and 3) meta-analyses as well as the summary trials table (Table 3), the entirety of the benefits found in both OCT and RCT trial designs align in both direction and magnitude of benefit. Such a consistency of benefit amongst numerous trials of varying designs from multiple different countries and centers around the world is both unique in the history of evidence-based medicine and provides strong, additional support to the conclusions reached in this review. All must consider Declaration 37 of the World Medical Association's "Helsinki Declaration on the Ethical Principles for Medical Research Involving Human Subjects," first established in 1964, which states:

[11] https://www.wsj.com/articles/u-k-begins-rollout-of-pfizers-covid-19-vaccine-in-a-first-for-the-west-11607419672

> *In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, 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, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.*

The continued challenges faced by health care providers in deciding on appropriate therapeutic interventions in patients with COVID-19 would be greatly eased if more updated and definitive evidence-based guidance came from the leading governmental health care agencies. Currently, in the United States, the treatment guidelines for COVID-19 are issued by the National Institutes of Health (NIH). Unfortunately, the NIH's recommendation on the use of ivermectin in COVID-19 patients was last updated on August 27, 2020. At that time, ivermectin received a recommendation of A-III *against* use outside of a clinical trial. An A-III recommendation, per the NIH recommendation scheme, means that it was a strong opinion (A), and based on expert opinion only (III) given that presumably little clinical evidence existed at the time to otherwise inform that recommendation.

Based on the totality of the clinical and epidemiologic evidence presented in this review, and in the context of a worsening pandemic in parts of the globe where ivermectin is not widely used, the authors believe the recommendation must be immediately updated to support and guide the nation's health care providers. One aspect that the NIH expert panel may debate is on the grade of recommendation that should be assigned to ivermectin. Based on the NIH rating scheme, the strongest recommendation possible would be an A-I in support of ivermectin which requires "one or more randomized trials with clinical outcomes and/or laboratory endpoints." Given that data from 16 randomized controlled trials (RCT's) demonstrate consistent and large improvements in "clinical outcomes" such as transmission rates, hospitalization rates, and death rates, it appears that the criteria for an A-I level recommendation has been exceeded. However, although troubling to consider, if experts somehow conclude that the entirety of the available RCT data should be invalidated and dismissed given that either; they were conducted outside of US shores and not by US pharmaceutical companies or academic research centers, that some studies were small or of "low quality", or that such data from foreign countries are not generalizable to American patients, an A-II level recommendation would then have to be considered. In the context of worsening pandemic conditions, when considering a safe, low-cost, widely available early treatment option, even an A-II would result in immediate, widespread adoption by providers in the treatment of COVID-19. The criteria for an A-II requires supportive findings from "one of more well-designed non-randomized, or observational cohort studies". Fortunately, there are many such studies on ivermectin in COVID-19, with one of the largest and best designed being Dr. Rajter's study from Florida, published in the major peer-reviewed medical journal *Chest*, where they used propensity matching, a technique accorded by many to be as valid a design as RCT's. Thus, at a minimum, an A-II recommendation is met, which again would and should lead to immediate and widespread adoption in early outpatient treatment, an area that has been little investigated and is devoid of any highly effective therapies at the time of this writing. Further, it is clear that these data presented far exceed any other NIH strength or quality level such as moderate strength (B), weak strength (C) or grade III quality. To merit the issuance of these lower grades of recommendation would require both a dismissal of the near entirety of the evidence presented in this review in addition to a risk benefit calculation resulting in the belief that the risks of widespread ivermectin use would far exceed any possible benefits in the context of rising case counts, deaths, lockdowns, unemployment, evictions, and bankruptcies.

It is the authors opinion, that based on the totality of these data, the use of ivermectin as a prophylactic and early treatment option should receive an A-I level recommendation by the NIH in support of use by the nation's health care providers. When, or if, such a recommendation is issued, the Front Line COVID-19 Critical Care Alliance has developed a prophylaxis and early treatment protocol for COVID-19 (I-MASK+), centered around ivermectin combined with masking, social distancing, hand hygiene, Vitamin D, Vitamin C, quercetin, melatonin, and zinc, with all components known for either their anti-viral, anti-inflammatory, or preventive actions (Table 4). The I-MASK+ protocol suggests treatment approaches for prophylaxis of high-risk patients, post-exposure prophylaxis of household members with COVID-19, and an early treatment approach for patients ill with COVID-19.

Table 4. I-MASK+ Prophylaxis & Early Outpatient Treatment Protocol for COVID-19

Prophylaxis Protocol	
MEDICATION	RECOMMENDED DOSING
Ivermectin	*Prophylaxis for high-risk individuals*: 0.2 mg/kg per dose* — one dose today, 2nd dose in 48 hours, then one dose every 2 weeks
	*Post COVID-19 exposure prophylaxis****: 0.2 mg/kg per dose, one dose today, 2nd dose in 48 hours
Vitamin D3	1,000–3,000 IU/day
Vitamin C	1,000 mg twice daily
Quercetin	250 mg/day
Melatonin	6 mg before bedtime (causes drowsiness)
Zinc	50 mg/day of elemental zinc
Early Outpatient Treatment Protocol******	
MEDICATION	RECOMMENDED DOSING
Ivermectin	0.2 mg/kg per dose – one dose daily for minimum of 2 days, continue daily until recovered (max 5 days)
Vitamin D3	4,000 IU/day
Vitamin C	2,000 mg 2–3 times daily and **Quercetin** 250 mg twice a day
Melatonin	10 mg before bedtime (causes drowsiness)
Zinc	100 mg/day elemental zinc
Aspirin	325 mg/day (unless contraindicated)

* Example for a person of 60 kg body weight: 60 kg × 0.2 mg = 12 mg (1 kg = 2.2 lbs) = 4 tablets (3mg/tablet). To convert pounds, divide weight in pounds by 11: example for a person of 165 pounds: 165 ÷ 11 = 15 mg
** The dosing may be updated as further scientific studies emerge.
*** To use if a household member is COVID-19 positive, or if you have had prolonged exposure to a COVID-19+ patient without wearing a mask
**** For late phase – hospitalized patients – see the FLCCC's "MATH+" protocol on www.flccc.net

In summary, based on the existing and cumulative body of evidence, we recommend the use of ivermectin in both prophylaxis and treatment for COVID-19. In the presence of a global COVID-19 surge, the widespread use of this safe, inexpensive, and effective intervention would lead to a drastic reduction in transmission rates and the morbidity and mortality in mild, moderate, and even severe disease phases. The authors are encouraged and hopeful at the prospect of the many favorable public health and societal impacts that would result once adopted for use.

Acknowledgements

None

Contribution to the field statement

COVID-19 has caused a worldwide pandemic that has caused over 1.5 million global deaths along with continued rising case counts, lockdowns, unemployment and recessions in multiple countries. In response, the Front Line COVID-19 Critical Care Alliance (FLCCC), formed early in the pandemic, began to review the rapidly emerging basic science, translational, and clinical data to develop effective treatment protocols. The supportive evidence and rationale for their highly effective hospital treatment protocol called "MATH+" was recently published in a major medical journal. More recently, during their ongoing review of the studies on a wide range of both novel and repurposed drugs, they identified that ivermectin, a widely used anti-parasitic medicine with known anti-viral and anti-inflammatory properties is proving a highly potent and multi-phase effective treatment against COVID-19. This manuscript comprehensively reviews the diverse and increasing amount of available evidence from studies on ivermectin which then concludes with the FLCCC consensus recommendation that ivermectin for both the prophylaxis and treatment of COVID-19 should be systematically and globally adopted with the achievable goal of saving countless lives and reversing the rising and persistent transmission rates in many areas of the world.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Study conception and design: Pierre Kory, G. Umberto Meduri, Howard Kornfeld, Keith Berkowitz. Acquisition of data: Scott Mitchell, Eivind Norjevoll, Paul Marik, Fred Wagshul Analysis and interpretation of data: Paul Marik, Pierre Kory Drafting of manuscript: Pierre Kory Critical revision: Umberto Meduri, Joseph Varon.

Funding

There was no funding involved for this project.

Acknowledgments

None.

References

Agarwal, A., Mukherjee, A., Kumar, G., Chatterjee, P., Bhatnagar, T., Malhotra, P., and Collaborators, P.T. (2020). Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ* 371**,** m3939.

Aguirre-Chang, G. (2020). Post-Acute or prolonged COVID-19: treatment with ivermectin for patietns with persistent, or post-acute symptoms *ResearchGate*.

Ahmed, S., Karim, M.M., Ross, A.G., Hossain, M.S., Clemens, J.D., Sumiya, M.K., Phru, C.S., Rahman, M., Zaman, K., and Somani, J. (2020). A five day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *International Journal of Infectious Diseases*.

Alam, M., R, M., Pf, G., Md, M.Z., S, S., and Ma, C. (2020). Ivermectin as Pre-exposure Prophylaxis for COVID 19 among Healthcare Providers in a Selected Tertiary Hospital in Dhaka An Observational Study. *European Journal of Medical and Health Sciences*.

Anglemyer, A., Horvath, H.T., and Bero, L. (2014). Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database Syst Rev***,** MR000034.

Arevalo, A.P., Pagotto, R., Porfido, J., Daghero, H., Segovia, M., Yamasaki, K., Varela, B., Hill, M., Verdes, J.M., and Vega, M.D. (2020). Ivermectin reduces coronavirus infection in vivo: a mouse experimental model. *bioRxiv*.

Atkinson, S.C., Audsley, M.D., Lieu, K.G., Marsh, G.A., Thomas, D.R., Heaton, S.M., Paxman, J.J., Wagstaff, K.M., Buckle, A.M., Moseley, G.W., Jans, D.A., and Borg, N.A. (2018). Recognition by host nuclear transport proteins drives disorder-to-order transition in Hendra virus V. *Scientific Reports* 8**,** 358.

Babalola, O.E., Bode, C.O., Ajayi, A.A., Alakaloko, F.M., Akase, I.E., Otrofanowei, E., Salu, O.B., Adeyemo, W.L., Ademuyiwa, A.O., and Omilabu, S.A. Ivermectin shows clinical benefits in mild to moderate Covid19 disease: A randomised controlled double blind dose response study in Lagos. *medRxiv***,** 2021.2001. 2005.21249131.

Behera, P., Patro, B.K., Singh, A.K., Chandanshive, P.D., Ravikumar, S., Pradhan, S.K., Pentapati, S.S.K., Batmanabane, G., Padhy, B.M., and Bal, S. (2020). Role of ivermectin in the prevention of COVID-19 infection among healthcare workers in India: A matched case-control study. *medRxiv*.

Bernigaud, C., Guillemot, D., Ahmed-Belkacem, A., Grimaldi-Bensouda, L., Lespine, A., Berry, F., Softic, L., Chenost, C., Do-Pham, G., and Giraudeau, B. (Year). "Bénéfice de l'ivermectine: de la gale à la COVID-19, un exemple de sérendipité", in: *Annales de Dermatologie et de Vénéréologie*: Elsevier), A194.

Bray, M., Rayner, C., Noël, F., Jans, D., and Wagstaff, K. (2020). Ivermectin and COVID-19: a report in Antiviral Research, widespread interest, an FDA warning, two letters to the editor and the authors' responses. *Antiviral Research*.

Budhiraja, S., Soni, A., Jha, V., Indrayan, A., Dewan, A., Singh, O., Singh, Y., Chugh, I., Arora, V., and Pandey, R. (2020). Clinical Profile of First 1000 COVID-19 Cases Admitted at Tertiary Care Hospitals and the Correlates of their Mortality: An Indian Experience. *medRxiv*.

Cadegiani, F.A., Goren, A., Wambier, C.G., and Mccoy, J. (2020). Early COVID-19 Therapy with Azithromycin Plus Nitazoxanide, Ivermectin or Hydroxychloroquine in Outpatient Settings Significantly Reduced Symptoms Compared to Known Outcomes in Untreated Patients. *medRxiv*.

Callard, F., and Perego, E. (2020). How and why patients made Long Covid. *Social Science & Medicine***,** 113426.

Caly, L., Druce, J.D., Catton, M.G., Jans, D.A., and Wagstaff, K.M. (2020a). The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res* 178**,** 104787.

Caly, L., Druce, J.D., Catton, M.G., Jans, D.A., and Wagstaff, K.M. (2020b). The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Research* 178**,** 104787.

Carvallo, H.E., Hirsch, R.R., and Farinella, M.E. (2020a). Safety and Efficacy of the combined use of ivermectin, dexamethasone, enoxaparin and aspirin against COVID-19. *medRxiv*.

Carvallo, H.E., Roberto, H., Psaltis, A., and Veronica, C. (2020b). Study of the Efficacy and Safety of Topical Ivermectin+ Iota-Carrageenan in the Prophylaxis against COVID-19 in Health Personnel.

Chaccour, C., Casellas, A., Blanco-Di Matteo, A., Pineda, I., Fernandez-Montero, A., Castillo, P.R., Richardson, M.-A., Mateos, M.R., Jordan-Iborra, C., and Brew, J. (2020). The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with mild COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial.

Chachar, A.Z.K., Khan, K.A., Asif, M., Tanveer, K., Khaqan, A., and Basri, R. (2020). Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients. *International Journal of Sciences* 9**,** 31-35.

Chala (2020). Prophylaxis Covid-19 in Healthcare Agents by Intensive Treatment With Ivermectin and Iota-carrageenan (Ivercar-Tuc). *ClinicalTrials.gov* NCT04701710.

Chamie, J. (2020). *Real-World Evidence: The Case of Peru. Causality between Ivermectin and COVID-19 Infection Fatality Rate.*

Chandler, R.E. (2018). Serious neurological adverse events after ivermectin—do they occur beyond the indication of onchocerciasis? *The American journal of tropical medicine and hygiene* 98**,** 382-388.

Chowdhury, A.T.M.M., Shahbaz, M., Karim, M.R., Islam, J., Guo, D., and He, S. (2020). A Randomized Trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients.

Ci, X., Li, H., Yu, Q., Zhang, X., Yu, L., Chen, N., Song, Y., and Deng, X. (2009). Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway. *Fundam Clin Pharmacol* 23**,** 449-455.

Consortium, W.S.T. (2020). Repurposed antiviral drugs for COVID-19—interim WHO SOLIDARITY trial results. medRxiv. *Preprint posted online* 15.

Crump, A., and Omura, S. (2011). Ivermectin,'wonder drug'from Japan: the human use perspective. *Proceedings of the Japan Academy, Series B* 87**,** 13-28.

Dahabreh, I.J., Sheldrick, R.C., Paulus, J.K., Chung, M., Varvarigou, V., Jafri, H., Rassen, J.A., Trikalinos, T.A., and Kitsios, G.D. (2012). Do observational studies using propensity score methods agree with randomized trials? A systematic comparison of studies on acute coronary syndromes. *European Heart Journal* 33**,** 1893-1901.

Dasgupta J, S.U., Bakshi a, Dasgupta a, Manna K, Saha, C De, Rk, Mukhopadhyay S, Bhattacharyya Np (2020). Nsp7 and Spike Glycoprotein of SARS-CoV-2 Are Envisaged as Potential Targets of Vitamin D and Ivermectin. *Preprints*.

Dayer, M.R. (2020). Coronavirus (2019-nCoV) Deactivation via Spike Glycoprotein Shielding by Old Drugs, Bioinformatic Study.

De Melo, G.D., Lazarini, F., Larrous, F., Feige, L., Kergoat, L., Marchio, A., Pineau, P., Lecuit, M., Lledo, P.-M., Changeux, J.-P., and Bourhy, H. (2020). Anti-COVID-19 efficacy of ivermectin in the golden hamster. *bioRxiv***,** 2020.2011.2021.392639.

Elgazzar, A., Hany, B., Youssef, S.A., Hafez, M., and Moussa, H. (2020). Efficacy and Safety of Ivermectin for Treatment and prophylaxis of COVID-19 Pandemic.

Entrenas Castillo, M., Entrenas Costa, L.M., Vaquero Barrios, J.M., Alcala Diaz, J.F., Lopez Miranda, J., Bouillon, R., and Quesada Gomez, J.M. (2020). "Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study". *J Steroid Biochem Mol Biol* 203**,** 105751.

Espitia-Hernandez, G., Munguia, L., Diaz-Chiguer, D., Lopez-Elizalde, R., and Jimenez-Ponce, F. (2020). Effects of Ivermectin-azithromycin-cholecalciferol combined therapy on COVID-19 infected patients: a proof of concept study.

Gardon, J., Gardon-Wendel, N., Demanga, N., Kamgno, J., Chippaux, J.-P., and Boussinesq, M. (1997). Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection. *The Lancet* 350**,** 18-22.

Gorial, F.I., Mashhadani, S., Sayaly, H.M., Dakhil, B.D., Almashhadani, M.M., Aljabory, A.M., Abbas, Hassan M, Ghanim, M., and Rasheed, J.I. (2020). Effectiveness of Ivermectin as add-on Therapy in COVID-19 Management (Pilot Trial). *medRxiv*.

Götz, V., Magar, L., Dornfeld, D., Giese, S., Pohlmann, A., Höper, D., Kong, B.-W., Jans, D.A., Beer, M., Haller, O., and Schwemmle, M. (2016). Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. *Scientific Reports* 6**,** 23138.

Guzzo, C., Furtek, C., Porras, A., Chen, C., Tipping, R., Clineschmidt, C., Sciberras, D., Hsieh, J., and Lasseter, K. (2002). Safety, Tolerability, and Pharmacokinetics of Escalating High Doses of Ivermectin in Healthy Adult Subjects. *Journal of clinical pharmacology* 42**,** 1122-1133.

Hashim, H.A., Maulood, M.F., Rasheed, A.M., Fatak, D.F., Kabah, K.K., and Abdulamir, A.S. (2020). Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq. *medRxiv*.

Hellwig, M.D., and Maia, A. (2020). A COVID-19 Prophylaxis? Lower incidence associated with prophylactic administration of Ivermectin. *Int J Antimicrob Agents***,** 106248.

Hermine, O., Mariette, X., Tharaux, P.L., Resche-Rigon, M., Porcher, R., Ravaud, P., and Group, C.-C. (2020). Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med*.

Horby, P., Lim, W.S., Emberson, J.R., Mafham, M., Bell, J.L., Linsell, L., Staplin, N., Brightling, C., Ustianowski, A., and Elmahi, E. (2020). Dexamethasone in hospitalized patients with Covid-19-preliminary report. *The New England journal of medicine*.

Hussien, M.A., and Abdelaziz, A.E. (2020). Molecular docking suggests repurposing of brincidofovir as a potential drug targeting SARS-CoV-2 ACE2 receptor and main protease. *Network Modeling Analysis in Health Informatics and Bioinformatics* 9**,** 1-18.

Jehi, L., Ji, X., Milinovich, A., Erzurum, S., Rubin, B.P., Gordon, S., Young, J.B., and Kattan, M.W. (2020). Individualizing Risk Prediction for Positive Coronavirus Disease 2019 Testing: Results From 11,672 Patients. *Chest* 158**,** 1364-1375.

Kalfas, S., Visvanathan, K., Chan, K., and Drago, J. (2020). THE THERAPEUTIC POTENTIAL OF IVERMECTIN FOR COVID-19: A REVIEW OF MECHANISMS AND EVIDENCE. *medRxiv*.

Khan, M.S.I., Khan, M.S.I., Debnath, C.R., Nath, P.N., Mahtab, M.A., Nabeka, H., Matsuda, S., and Akbar, S.M.F. (2020). Ivermectin Treatment May Improve the Prognosis of Patients With COVID-19. *Archivos de Bronconeumología*.

King, C.R., Tessier, T.M., Dodge, M.J., Weinberg, J.B., and Mymryk, J.S. (2020). Inhibition of Human Adenovirus Replication by the Importin α/β1 Nuclear Import Inhibitor Ivermectin. *Journal of Virology* 94.

Kircik, L.H., Del Rosso, J.Q., Layton, A.M., and Schauber, J. (2016). Over 25 Years of Clinical Experience With Ivermectin: An Overview of Safety for an Increasing Number of Indications. Journal of drugs in dermatology : JDD 15, 325-332.

Kitsios, G.D., Dahabreh, I.J., Callahan, S., Paulus, J.K., Campagna, A.C., and Dargin, J.M. (2015). Can We Trust Observational Studies Using Propensity Scores in the Critical Care Literature? A Systematic Comparison With Randomized Clinical Trials. *Crit Care Med* 43**,** 1870-1879.

Kory, P., Meduri, G.U., Iglesias, J., Varon, J., and Marik, P.E. (2020). Clinical and Scientific Rationale for the "MATH+" Hospital Treatment Protocol for COVID-19. *Journal of Intensive Care Medicine*.

Lehrer, S., and Rheinstein, P.H. (2020). Ivermectin Docks to the SARS-CoV-2 Spike Receptor-binding Domain Attached to ACE2. *In Vivo* 34**,** 3023-3026.

Li, Y., Chen, M., Cao, H., Zhu, Y., Zheng, J., and Zhou, H. (2013). Extraordinary GU-rich single-strand RNA identified from SARS coronavirus contributes an excessive innate immune response. *Microbes Infect* 15**,** 88-95.

Lonjon, G., Boutron, I., Trinquart, L., Ahmad, N., Aim, F., Nizard, R., and Ravaud, P. (2014). Comparison of treatment effect estimates from prospective nonrandomized studies with propensity score analysis and randomized controlled trials of surgical procedures. *Ann Surg* 259**,** 18-25.

Lv, C., Liu, W., Wang, B., Dang, R., Qiu, L., Ren, J., Yan, C., Yang, Z., and Wang, X. (2018). Ivermectin inhibits DNA polymerase UL42 of pseudorabies virus entrance into the nucleus and proliferation of the virus in vitro and vivo. *Antiviral Research* 159**,** 55-62.

Mahmud, R. (2020). A Randomized, Double-Blind Placebo Controlled Clinical Trial of Ivermectin plus Doxycycline for the Treatment of Confirmed Covid-19 Infection.

Marik, P.E., Kory, P., Varon, J., Iglesias, J., and Meduri, G.U. (2020). MATH+ protocol for the treatment of SARS-CoV-2 infection: the scientific rationale. *Expert Review of Anti-infective Therapy***,** 1-7.

Mastrangelo, E., Pezzullo, M., De Burghgraeve, T., Kaptein, S., Pastorino, B., Dallmeier, K., De Lamballerie, X., Neyts, J., Hanson, A.M., Frick, D.N., Bolognesi, M., and Milani, M. (2012). Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. *Journal of Antimicrobial Chemotherapy* 67**,** 1884-1894.

Maurya, D.K. (2020). A combination of ivermectin and doxycycline possibly blocks the viral entry and modulate the innate immune response in COVID-19 patients.

Morgenstern, J., Redondo, J.N., De Leon, A., Canela, J.M., Torres, N., Tavares, J., Minaya, M., Lopez, O., Placido, A.M., and Castillo, A. (2020). The use of compassionate Ivermectin in the management of symptomatic outpatients and hospitalized patients with clinical diagnosis of COVID-19 at the Medical Center Bournigal and the Medical Center Punta Cana, Rescue Group, Dominican Republic, from may 1 to august 10, 2020. *medRxiv*.

Nadkarni, G.N., Lala, A., Bagiella, E., Chang, H.L., Moreno, P.R., Pujadas, E., Arvind, V., Bose, S., Charney, A.W., Chen, M.D., Cordon-Cardo, C., Dunn, A.S., Farkouh, M.E., Glicksberg, B.S., Kia, A., Kohli-Seth, R., Levin, M.A., Timsina, P., Zhao, S., Fayad, Z.A., and Fuster, V. (2020). Anticoagulation, Bleeding, Mortality, and Pathology in Hospitalized Patients With COVID-19. *J Am Coll Cardiol* 76**,** 1815-1826.

Nallusamy, S., Mannu, J., Ravikumar, C., Angamuthu, K., Nathan, B., Nachimuthu, K., Ramasamy, G., Muthurajan, R., Subbarayalu, M., and Neelakandan, K. (2020). Shortlisting Phytochemicals Exhibiting Inhibitory Activity against Major Proteins of SARS-CoV-2 through Virtual Screening.

Niaee, M.S., Gheibi, N., Namdar, P., Allami, A., Zolghadr, L., Javadi, A., Karampour, A., Varnaseri, M., Bizhani, B., and Cheraghi, F. (2020). Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial.

Perera, R.A., Tso, E., Tsang, O.T., Tsang, D.N., Fung, K., Leung, Y.W., Chin, A.W., Chu, D.K., Cheung, S.M., and Poon, L.L. (2020). SARS-CoV-2 virus culture from the upper respiratory tract: Correlation with viral load, subgenomic viral RNA and duration of illness. *MedRXiv*.

Podder, C.S., Chowdhury, N., Sina, M.I., and Haque, W. (2020). Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study. *IMC J. Med. Sci* 14.

Polak, S.B., Van Gool, I.C., Cohen, D., Von Der Thusen, J.H., and Van Paassen, J. (2020). A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. *Mod Pathol* 33**,** 2128-2138.

Portmann-Baracco, A., Bryce-Alberti, M., and Accinelli, R.A. (2020). Antiviral and Anti-Inflammatory Properties of Ivermectin and Its Potential Use in Covid-19. *Arch Bronconeumol*.

Rajter, J.C., Sherman, M.S., Fatteh, N., Vogel, F., Sacks, J., and Rajter, J.J. (2020). Use of Ivermectin is Associated with Lower Mortality in Hospitalized Patients with COVID-19 (ICON study). *Chest*.

Ravikirti, Roy, R., Pattadar, C., Raj, R., Agarwal, N., Biswas, B., Majhi, P.K., Rai, D.K., Shyama, Kumar, A., and Sarfaraz, A. (2021). Ivermectin as a potential treatment for mild to moderate COVID-19 – A double blind randomized placebo-controlled trial. *medRxiv***,** 2021.2001.2005.21249310.

Robin, R.C., Alam, R.F., Saber, S., Bhiuyan, E., Murshed, R., and Alam, M.T. (2020). A Case Series of 100 COVID-19 Positive Patients Treated with Combination of Ivermectin and Doxycycline. *Journal of Bangladesh College of Physicians and Surgeons***,** 10-15.

Rodriguez-Nava, G., Trelles-Garcia, D.P., Yanez-Bello, M.A., Chung, C.W., Trelles-Garcia, V.P., and Friedman, H.J. (2020). Atorvastatin associated with decreased hazard for death in COVID-19 patients admitted to an ICU: a retrospective cohort study. *Crit Care* 24**,** 429.

Rubin, R. (2020). As Their Numbers Grow, COVID-19 “Long Haulers” Stump Experts. *JAMA* 324**,** 1381-1383.

Salvarani, C., Dolci, G., Massari, M., Merlo, D.F., Cavuto, S., Savoldi, L., Bruzzi, P., Boni, F., Braglia, L., Turra, C., Ballerini, P.F., Sciascia, R., Zammarchi, L., Para, O., Scotton, P.G., Inojosa, W.O., Ravagnani, V., Salerno, N.D., Sainaghi, P.P., Brignone, A., Codeluppi, M., Teopompi, E., Milesi, M., Bertomoro, P., Claudio, N., Salio, M., Falcone, M., Cenderello, G., Donghi, L., Del Bono, V., Colombelli, P.L., Angheben, A., Passaro, A., Secondo, G., Pascale, R., Piazza, I., Facciolongo, N., Costantini, M., and Group, R.-T.-C.-S. (2020). Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med*.

Scheim, D. (2020). "From Cold to Killer: How SARS-CoV-2 Evolved without Hemagglutinin Esterase to Agglutinate, Then Clot Blood Cells in Pulmonary and Systemic Microvasculature". SSRN).

Schmith, V.D., Zhou, J., and Lohmer, L.R. (2020). The Approved Dose of Ivermectin Alone is not the Ideal Dose for the Treatment of COVID-19. *Clinical Pharmacology & Therapeutics*.

Sen Gupta, P.S., Biswal, S., Panda, S.K., Ray, A.K., and Rana, M.K. (2020). Binding mechanism and structural insights into the identified protein target of COVID-19 and importin-alpha with in-vitro effective drug ivermectin. *J Biomol Struct Dyn***,** 1-10.

Shouman, W. (2020). Use of Ivermectin as a Prophylactic Option in Asymptomatic Family Close Contact for Patient with COVID-19. *Clincal Trials.gov*.

Siegelman, J.N. (2020). Reflections of a COVID-19 Long Hauler. *JAMA*.

Soto-Becerra, P., Culquichicón, C., Hurtado-Roca, Y., and Araujo-Castillo, R.V. (2020). Real-world effectiveness of hydroxychloroquine, azithromycin, and ivermectin among hospitalized COVID-19 patients: results of a target trial emulation using observational data from a nationwide healthcare system in Peru. *Azithromycin, and Ivermectin Among Hospitalized COVID-19 Patients: Results of a Target Trial Emulation Using Observational Data from a Nationwide Healthcare System in Peru*.

Sparsa, A., Bonnetblanc, J., Peyrot, I., Loustaud-Ratti, V., Vidal, E., and Bedane, C. (Year). "Systemic adverse reactions with ivermectin treatment of scabies", in: *Annales de Dermatologie et de Venereologie*), 784-787.

Spoorthi V, S.S. (2020). Utility of Ivermectin and Doxycycline combination for the treatment of SARS-CoV2. *International Archives of Integrated Medicine* 7**,** 177-182.

Suravajhala, R., Parashar, A., Malik, B., Nagaraj, A.V., Padmanaban, G., Kishor, P.K., Polavarapu, R., and Suravajhala, P. (2020). Comparative Docking Studies on Curcumin with COVID-19 Proteins.

Swargiary, A. (2020). Ivermectin as a promising RNA-dependent RNA polymerase inhibitor and a therapeutic drug against SARS-CoV2: Evidence from in silico studies.

Tambo, E., Khater, E.I., Chen, J.H., Bergquist, R., and Zhou, X.N. Nobel prize for the artemisinin and ivermectin discoveries: a great boost towards elimination of the global infectious diseases of poverty.

Tay, M.Y.F., Fraser, J.E., Chan, W.K.K., Moreland, N.J., Rathore, A.P., Wang, C., Vasudevan, S.G., and Jans, D.A. (2013). Nuclear localization of dengue virus (DENV) 1–4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. *Antiviral Research* 99**,** 301-306.

Varghese, F.S., Kaukinen, P., Gläsker, S., Bespalov, M., Hanski, L., Wennerberg, K., Kümmerer, B.M., and Ahola, T. (2016). Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses. *Antiviral Research* 126**,** 117-124.

Veit, O., Beck, B., Steuerwald, M., and Hatz, C. (2006). First case of ivermectin-induced severe hepatitis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 100**,** 795-797.

Wagstaff, Kylie m., Sivakumaran, H., Heaton, Steven m., Harrich, D., and Jans, David a. (2012). Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. *Biochemical Journal* 443**,** 851-856.

Yang, S.N.Y., Atkinson, S.C., Wang, C., Lee, A., Bogoyevitch, M.A., Borg, N.A., and Jans, D.A. (2020). The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. *Antiviral Research* 177**,** 104760.

Young, B.E., Ong, S.W., Ng, L.F., Anderson, D.E., Chia, W.N., Chia, P.Y., Ang, L.W., Mak, T.-M., Kalimuddin, S., and Chai, L.Y.A. (2020). Viral dynamics and immune correlates of COVID-19 disease severity. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*.

Zhang, J., Rao, X., Li, Y., Zhu, Y., Liu, F., Guo, G., Luo, G., Meng, Z., De Backer, D., and Xiang, H. (2020a). High-dose vitamin C infusion for the treatment of critically ill COVID-19.

Zhang, X., Song, Y., Ci, X., An, N., Ju, Y., Li, H., Wang, X., Han, C., Cui, J., and Deng, X. (2008). Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. *Inflamm Res* 57**,** 524-529.

Zhang, X., Song, Y., Xiong, H., Ci, X., Li, H., Yu, L., Zhang, L., and Deng, X. (2009). Inhibitory effects of ivermectin on nitric oxide and prostaglandin E2 production in LPS-stimulated RAW 264.7 macrophages. *Int Immunopharmacol* 9**,** 354-359.

Zhang, X.-J., Qin, J.-J., Cheng, X., Shen, L., Zhao, Y.-C., Yuan, Y., Lei, F., Chen, M.-M., Yang, H., and Bai, L. (2020b). In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. *Cell metabolism* 32**,** 176-187. e174.

Exhibit C

Exhibit C

FLCCC's Level of Expertise

To assist in understanding the value FLCCC's work brings to covid-19 treatment, I include this brief introduction to the FLCCC physicians[1] and their efforts. FLCCC was founded by a group of highly published, world-renowned Critical Care physicians and scholars, many who have held leadership positions in large medical center ICUs. Its MATH+ Hospital Treatment Protocol[2] was introduced in March 2020 and has saved tens of thousands of patients who were critically ill with COVID-19.[3] This is a group of recognized leaders in critical care with expertise in therapies directed at severe infections.[4] The expertise in clinical research can be seen just in the fact FLCCC member physicians have nearly 2,000 published peer-reviewed publications among them. These eminent, well-recognized physicians have extensive experience with COVID-19, and, despite being overtime at bedside throughout this emergency, have put remarkable efforts into studying, documenting, and educating the professions and the public about the clinical value of ivermectin in COVID-19.

One of FLCCC's initial efforts, consistent with WHO guidelines, was to explore the re-purposing of existing drugs to treat COVID-19, an effort that received too little global effort as financial resources focused on developing new patented medications. This lead to its medical discovery of a rapidly growing published medical evidence base demonstrating ivermectin's unique and highly potent ability to inhibit SARS-CoV-2 replication and to suppress inflammation. This conclusion was based not only on multiple in-vitro and animal models, but numerous clinical trials from centers and countries around the world showing repeated, consistent, large magnitude improvements in clinical outcomes when ivermectin is used, not only as a prophylactic agent, but also in mild, moderate, but even has some positive effects even in severe disease states.

This discovery prompted the Alliance to aggressively pursue additional study and use of ivermectin for prevention and treatment in all stages of COVID-19. From months of such study and clinical experience, FLCCC developed consensus-based standards among its physician members, issued them for use by interested medical professionals world-wide, and advocated for their adoption and public discussion by physicians who recognize the need to inform the public about the value and availability of ivermectin.

The Alliance has the academic support of allied physicians from around the world to research and develop lifesaving protocols for the prevention and treatment of COVID-19 in all stages of illness. This protocol was painstakingly developed and advocated by FLCCC precisely because it shares, and is indeed more directly aware of the concern you express in your letter that COVID-19 poses serious consequences to public health. A fair consideration of the FLCCC website evaluated on its merits rather than presumptions drawn from the public narrative is that the website offers important and well-sourced information. The website, for example, cites a large number of peer-reviewed publications, some of which were authored by FLCCC's founding

---

[1] For information about the core group of physicians in the Alliance *see* https://covid19criticalcare.com/about/the-flccc-physicians/

[2] https://covid19criticalcare.com/covid-19-protocols/math-plus-protocol/

[3] *See* https://www.newswise.com/coronavirus/flccc-s-covid-19-hospital-treatment-protocol-published-in-the-journal-of-intensive-care-medicine2

[4] *See for e.g.*, Marik, P.E. Hydrocortisone, Ascorbic Acid and Thiamine (HAT Therapy) for the Treatment of Sepsis. Focus on Ascorbic Acid. *Nutrients*. 2018, 10, 1762. https://doi.org/10.3390/nu10111762

physicians.[5] Your cease and desist letters challenge information on the website as false and misleading even though these statements are supported by publications that have undergone peer review. I'm not sure what review your office conducted of the FLCCC website or of the evidence underlying the ivermectin recommendations prior to issuing these letters, but enforcement actions based on information from highly qualified physicians that has repeatedly passed journal peer review without even acknowledging that fact is highly irregular. That there are professional differences of opinion on the topic does not create a basis for such action.

[5] *See for e.g.* Kory P, Meduri GU, Varon J, Iglesias J, Marik PE. *Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19* [published correction appears in Am J Ther. 2021 Nov-Dec 01;28(6):e813]. Am J Ther. 2021;28(3):e299-e318. Published 2021 Apr 22. doi:10.1097/MJT.0000000000001377