SUBMISSIONS TO THE AUSTRALIAN GOVERNMENT DEPARTMENT OF HEALTH – THERAPEUTIC GOODS ADMINISTRATION

TO

AMEND THE SCHEDULING OF IVERMECTIN - DELETION OF APPENDIX D, ITEM 10 FROM THE CURRENT S4 POISONS SCHEDULING

26 September 2022

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EXECUTIVE SUMMARY OF THE SUBMISSIONS

1. On 1 September 2022, the Secretary of the Australian Department of Health invited public submissions on scheduling proposals referred to the November 2022 meetings of the Advisory committees on Medicines and Chemical Scheduling including specific reference to ivermectin[1]. These submissions are in response to that invitation.

2. These Submissions to amend the Poisons Scheduling of ivermectin are submitted in the National interest. The evidence submitted in support of the proposed deletion of Appendix D, Item 10 in the ivermectin Poisons Scheduling is, arguably, the most important Poison Scheduling change ever considered by the Australian Government as it seeks to remove historically unprecedented restrictions on the prescribing of ivermectin which were primarily introduced during a pandemic response to encourage, rightly or wrongly, COVID-19 vaccine uptake as, in part, specifically stated by the Australian Therapeutic Goods Administration (TGA).

3. It is the view of the Co-Signatories that the introduction of Appendix D, Item 10 to the listing of ivermectin did not take into proper account the extensive existing documentation regarding the safety and efficacy of ivermectin used alone and in combination in relation to the potential management of COVID-19 and various parasitic indications. Since the restrictive scheduling change for ivermectin introduced on September 10 2021, considerable additional clinical safety and efficacy data has become available which adds weight to the compelling body of evidence which demonstrates that ivermectin restrictive scheduling should be normalised to return professional discretion to doctors in relation to off-label prescribing as is the conventional and accepted practice for other drugs.

4. Given the unique nature of the current COVID pandemic and the short time frame to construct these important Submissions, a diverse body of evidence

[1] Australian Government Department of Health, Therapeutic Goods Administration: Consultation: proposed amendments to the Poisons Standard – ACCS, ACMS and Joint ACCS/ACMS meetings, November 2022. 1 Sept. 2022.
https://www.tga.gov.au/resources/consultation/consultation-proposed-amendments-poisons-standard-accs-acms-and-joint-accsacms-meetings-november-2022

and both local and international expert opinion, (including commentary on certain published literature emanating from arguably vested and opposing interests) has been assembled. An attempt has been made to assemble all relevant literature in these Submissions. The Co-Signatories rely heavily upon the impressive historical world-wide safety record of ivermectin including the TGA's own safety assessments prior to the pandemic. These Submissions provide compelling evidence to support the impressive safety record of ivermectin which is matched by few, if any, widely used therapeutic agents in use today.

5. Rightly or wrongly, the Decision to apply Appendix D, Item 10 by the TGA regarding the scheduling change for ivermectin was not made solely upon normal considerations of safety and efficacy of this therapeutic agent. Other logistical and vaccine-centric reasons formed the basis of this unprecedented scheduling change which emanated from the national COVID pandemic policies. Now that the complexion of the pandemic has changed and considerable knowledge has been gained, it is the view of the Co-Signatories that the TGA's invitation for "Consultation" represents an admirable, encouraging and long-awaited sign of reflection and review in the national interest to improve Australia's COVID health policy which must involve the removal of unprecedented and restrictive Poison Scheduling currently impacting the prescribing of ivermectin.

6. Justification for removing Appendix D, Item 10 in the current Poison Scheduling for ivermectin may be summarised as follows:

a. The restrictive Poison Scheduling of ivermectin was introduced, in part, due to misconceived and inappropriate safety concerns. Worldwide use has demonstrated that ivermectin is among the safest drugs available and has a known and established high therapeutic index (or therapeutic ratio).
b. There are no reported and/or credible evidence to suggest that off-label prescribing of ivermectin, for any indication, is associated with an unacceptable incidence of adverse effects or consequences.
c. There have been no reported supply issues relating to ivermectin which may impact public health.

d. There are unintended consequences of the current restrictive prescribing regulations including the elevation of interest in obtaining and using ivermectin which may be counterfeit or of unsuitable quality (eg. veterinary products).
e. With more than 95% of the adult population now considered fully vaccinated, wider ivermectin availability would not be expected to impact the government's COVID vaccine policies.
f. With the introduction of early anti-viral drugs, molnupiravir and Paxlovid, it now appears timely to review the previously restrictive vaccine-only policy which formed the basis of the current restrictive scheduling of ivermectin.

7. SUBMISSION CORRESPONDENCE DETAILS:

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8. DECLARATION:

The factual matters stated in the report are, as far as I know, are true.
I have made all inquiries, consisting of literature review, considered appropriate.
There are no readily ascertainable additional facts which would assist me in reaching more reliable conclusions.
The opinions stated in the report are genuinely held by myself, and
The report contains reference to all matters I consider significant.

Signature 26 September 2022

Phillip M. Altman
Clinical Trial & Regulatory Affairs Consultant
Submitted for and on behalf of the Co-Signatories

INTRODUCTION

9. The Poison Scheduling change for ivermectin announced 10 September 2021 to effectively ban its off-label prescribing for the management of COVID-19 was part of a sweeping suite of harsh and extreme public health policies introduced or permitted to meet the challenges of the SARS-CoV-2 pandemic.

10. In retrospect, many of the health policies adopted by Australia and elsewhere have either been shown to have failed (eg. COVID-19 vaccination to stop the spread of the virus) or have attracted widespread and ongoing expert criticism.

11. One of the health policies which has been the focus of considerable criticism relates to the surprising lack of government advice, for the first time ever, that a potentially serious infectious disease should be treated as early as possible. Rather, the government advised, if one was infected, to isolate and wait for either eventual recovery or, if the infection became serious, affected individuals should be directed to hospital for management. The government essentially ruled out early treatment of the infection in deference to a "vaccine-only" policy to meet the challenges of COVID-19. Many clinicians did not agree with this policy and, as history has shown, it is possibly one of the biggest errors of judgement in relation to COVID-19 public health policy.

12. As it turns out, the health policies developed by the U.S. CDC under the leadership of Dr. Fauci and Dr. Birx, which formed a template for a global pandemic response including that of Australia, were not based on data and science. This was recently admitted:

13. In Washington D.C. on 18th of August the US Center for Disease Control Director, Dr. Walensky, told employees: "*To be frank, we are responsible for some pretty dramatic, pretty public mistakes from testing, to data, to communications".*

14. Dr. Deborah Birx, coordinator of the White House coronavirus task force, who set the strategies for early U.S. Covid responses, which were copied by much of the world, has publicly admitted to the poor quality of U.S. Covid data and

said "*it was a pandemic driven by assumptions and perceptions, rather than data and science*"

15. It is apparent now that the change to restrictive ivermectin Poison Scheduling was part of the mistaken assumptions and perceptions in government COVID health policy.

16. One of the most regrettable statements ever made by the U.S. Food and Drug Administration (FDA) was made on 21 August 2021 when it posted a link on Twitter saying "Why you should not use ivermectin" webpage with the message "You are not a horse. You are not a cow. Seriously, y'all. Stop it"[2].

17. This FDA public statement was made despite the well-known safety record of ivermectin. In fact, the Chief Medical Officer for England, Professor Sir Christopher Whitty, has previously stated "*The drug has proven to be safe. Doses up to 10 times the approved limit are well tolerated by healthy volunteers. Adverse reactions are few and usually mild.*" [3]

18. Some Australian Chief Health Officers publicly used exaggerated claims of ivermectin toxicity, calling it a dangerous horse de-worming medication unsuitable for human use. It is inconceivable that these senior health officials could be so ill-informed of the safety record and importance of ivermectin in modern medicine. The most generous and likely interpretation of this regrettable statement is that this claim was made to encourage vaccination uptake. Statements like this have never been retracted or corrected despite the fact that ivermectin is considered to be one of the safest and most valuable drugs used in medicine and is nominated by the World Health Organisation (WHO) to be an essential drug, with billions of doses used worldwide over several decades.

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[2] U.S. FDA, Twitter, https://twitter.com/us_fda/status/1429050070243192839?lang=en

[3] Chaccour, C., Lines, J. & Whitty, C. J. M. (2010). Effect of Ivermectin on Anopheles gambiae Mosquitoes Fed on Humans: The Potential of Oral Insecticides in Malaria Control. *Journal of Infectious Diseases*, **202**, 113-116. doi: 10.1086/653208. https://academic.oup.com/jid/article/202/1/113/888773

19. However, if it was the intent of the TGA to pause the availability of ivermectin for early treatment until more recognised anti-viral agents became available, then the change in scheduling, by all accounts, has achieved its goal with the current availability of both molnupiravir and Paxlovid and the scheduling of ivermectin should now revert to its previous pre-pandemic listing with the removal of Appendix D, Item 10.

20. The invitation represents a laudable step to remedy a serious error in health policy. Whether the highly restrictive but ill-advised prescribing of ivermectin via the addition of Amendment D, Item 10 to the Poison Scheduling was made, primarily, in good faith to drive COVID-19 vaccination uptake by the population using an ill-founded claim relating to the lack of safety or whether this change was made under international pressure by the pharmaceutical industry to develop and market new oral agents at higher costs and to harmonise with a similar ban or restriction on ivermectin prescribing in the U.S and elsewhere, remains a matter of speculation. The important thing is that this review of the restrictive prescribing of ivermectin is now being made by the Australian Government and should be applauded.

21. Any casual observer of the official TGA Consultation invitation might be misled into assuming this initiative to review the Poison Scheduling of ivermectin was initiated in response to a single recent submission by general practitioner doctor. This is incorrect.

22. In fact, there have been a large number of written communications and submissions by many experts, including some of Australia's most eminent clinicians, over the course of the pandemic which have sought to place evidence before the health authorities regarding the safety of ivermectin, to argue for the removal of restrictive prescribing and to reinstate the long-standing principles embodied in the sanctity of the doctor-patient relationship.

23. Examples of previous attempts to urge a change in the restrictive prescription policy for ivermectin consist of two open letters directed to the Australian National Covid Clinical Evidence Taskforce dated 21 August 2021 and 14

October 2021 which form part of these submissions. In addition, there was an Australian Government Parliamentary Petition to normalise the Poison Scheduling of ivermectin which attracted more than 100,000 signatures (Petition EN3364 – The Ivermectin Ban – An Authoritarian Threat to Public Health) – none of which have been seen to warrant a response to date.

24. In addition, there have been appeals for a return to a common-sense approach regarding ivermectin prescribing directed to head of the TGA in multiple private communications including those from Prof. Wendy Hoy AO FAA FRACP, Professor of Medicine, University of Queensland and authoritative public statements made in the print media by Emeritus Professor Robert Clancy AM DSc FRACP FRS(N). An "Ivermectin Statement" signed by a large number of medical and scientific experts which supported the removal of extreme restrictions on ivermectin prescribing was also widely distributed to Australia's health officials.

25. It is hoped that these Submissions will be received and treated with the respect it deserves as it presents a compelling case, supported by many health professionals, to reverse the extreme restrictions on the prescribing of ivermectin and normalise its Poisons Scheduling consistent with its important place in medicine.

PROPOSED AMENDMENT TO THE SCHEDULING OF IVERMECTIN

26. It is proposed to delete Appendix D, Item 10 listing in Schedule 4 for ivermectin.

All other listing details for ivermectin in Schedules 5 and 7 to remain the same.

Appendix D, Item 10 currently reads as follows:

10. Poisons available only when prescribed or authorised for:

(1)	an indication that is accepted by the Secretary of the Australian Government Department of Health in relation to the inclusion of ivermectin in tablet dosage form in the Australian Register of Therapeutic Goods (an approve***d*** indication); or Note: Approved indications are shown in the public summary of the Australian Register of Therapeutic Goods on the Therapeutic Goods Administration website at www.tga.gov.au.
(2)	an indication that is not an approved indication, when the preparation is prescribed or authorised by a medical practitioner registered under State or Territory legislation that forms part of the Health Practitioner Regulation National Law, as a specialist in any of the following specialties or fields of specialty practices: (a) dermatology; (b) gastroenterology and hepatology; (c) infectious diseases; (d) paediatric gastroenterology and hepatology; I paediatric infectious diseases; or
(3)	use in a clinical trial that is approved by, or notified to, the Secretary of the Australian Government Department of Health under the Therapeutic Goods Act 1989.
	IVERMECTIN in preparations for oral administration for human use

REGULATORY BACKGROUND TO THE INTRODUCTION OF APPENDIX D, ITEM 10 RESTRICTION TO THE PRESCRIBING OF IVERMECTIN

27. At the 35th meeting of the Advisory Committee on Medicines Scheduling (8 September 2021, TRIM Reference no. D21-3074411), the Minister's Delegate presented a discussion paper detailing concerns regarding the increased off-label prescribing of oral ivermectin for the prevention and treatment of COVID-19 and requested an urgent scheduling amendment to place prescribing controls on the supply of oral ivermectin[4]. Certain observers to this meeting included individuals with a stated conflict of interest but were allowed to participate in the meeting. The meeting minutes retrieved under Freedom of Information were heavily redacted. The subsequent Decision to restrict the off-label prescribing of oral ivermectin was issued on 10 September 2021[5,6].

28. The stated reasons for the Scheduling change to introduce restrictive prescribing of ivermectin were as follows:

a) "persons taking ivermectin in an effort to prevent COVID-19 consider themselves to be protected against the disease, elect not to be vaccinated as part of the national COVID-19 vaccination program"…..
b) "it is possible that oral ivermectin will be in shortage in Australia" [if used to manage COVID-19].
and
c) "Oral ivermectin also has the potential to cause severe adverse events in persons, particularly when taken in high doses that have recently been described in social media and other sources for the prevention or treatment of COVID-19 infection".

29. The stated Scheduling change was **not** made because ivermectin was considered ineffective in the treatment of COVID-19 but rather because such

[4] Record of the 35th meeting of the Advisory Committee on Medicines Scheduling 08 September 2021. Confidential – Official use only: Information retrieved under Freedom of Information (redacted to remove names of participants)
[5] Poisons Standard Amendment (Ivermectin) instrument 2021 – Authorised Version Explanatory Statement registered 10/09/2021 to F2021L01253
[6] Notice of an amendment to the current Poisons Standard under paragraph 52D(2)(a) of the Therapeutic Goods Act 1989

use might dissuade vaccine uptake by the community, a shortage of ivermectin for approved uses might eventuate and because of a potential but unsubstantiated belief that ivermectin might cause serious adverse effects if used in high doses.

30. The logic and rationale in relation to a) and b) remain in the domain of hypothetical and strategic government health policy and are not directly related to the usual safety and efficacy issues which would normally underpin a review of the use of any therapeutic in sofar as Poisons Scheduling is concerned. Introduction of Poison Scheduling Appendix D, item 10 represented a clear historical departure from conventional scheduling considerations where decisions were made primarily on safety and efficacy and not primarily intended to restrict the prescribers ability to employ off-label prescribing where it was considered justifiable and appropriate.

SCOPE OF THE SUBMISSIONS

31. These Submissions will focus on the safety aspects of ivermectin as this relates to public health. Published documents and references regarding the clinical efficacy of ivermectin in the management of COVID-19 are submitted for background purposes due to their relevance in relation to safety. It should be recognised that reasons a) and b) (above) underpinning the change in ivermectin scheduling no longer apply as the government claims[7] more than 95% of the over 18 years of age population in Australia have now been vaccinated and ivermectin supply has not been reported to be a problem in Australia or world-wide.

32. While these Submissions will focus upon the safety aspects of ivermectin (the one remaining reason why Appendix D, Item 10 was introduced), pivotal clinical trial studies, meta-analyses and commentary on such studies have been included as this information provides valuable background information which impacts any consideration of ivermectin safety.

[7] Australian Government Department of Health and Aged Care: Covid-19 vaccines

33. These Submissions are not intended to be a comprehensive or systematic review of the literature but focuses on key papers and reviews which should assist the TGA in evaluating the proposed normalisation of the Poison Scheduling for ivermectin.

34. In addition, these Submissions will not address the related, but extremely important, ethical and professional considerations regarding the sacred doctor-patient relationship as this was not stated as a reason for the restrictions placed on ivermectin prescribing.

RATIONALE FOR DELETING APPENDIX D, ITEM 10 FROM THE CURRENT SCHEDULING

35. Initially, little was known about the aetiology and pathophysiology of COVID-19. Clinicians were presented with a new, rapidly spreading pathogenic virus which was predicted to have a dramatic impact on the world's population.

36. The potential usefulness of revolutionary, but unproven mRNA gene-based vaccines was believed to be the best answer to the pandemic. Rightly or wrongly, a "vaccine-only" policy was promulgated worldwide which excluded early potential treatment with any existing therapeutics including ivermectin and other therapeutics despite considerable published evidence that ivermectin could be used safety and effectively. Surprisingly, it was the only time it has ever been officially recommended that a serious infection not be treated as soon as possible. The off-label use of ivermectin, according to government policy makers, presented a threat to the implementation of the vaccine-only policy.

37. In an attempt to dissuade the use of ivermectin, a media-wide campaign was commenced to suggest that ivermectin posed serious toxicological concerns which would outweigh any potential benefit. However, documented evidence over decades of usage showed that ivermectin was a drug with a wide therapeutic margin of safety – in fact, much safer than commonly used non-prescription drugs such as paracetamol. Previously, the TGA itself has acknowledged this wide margin of safety.

38. However, for completeness and with some reluctance, the Co-Signatories need to mention the medical literature has become a battleground with vested commercial interests behind various publications aiming to undermine the perceptions of safety and efficacy of ivermectin. The Co-Signatories have made a special point of including such publications in these Submissions and has provided comment so as to enable a proper and balanced appraisal of the safety and efficacy of ivermectin as it relates to Poisons Scheduling.

39. In these Submissions, the Co-Signatories will rely upon the following:

a) extensive toxicological and clinical safety data in relation to ivermectin
b) meta-analyses and reviews of the published medical literature concerning clinical trials of ivermectin
c) individual important clinical studies of ivermectin (several of these studies have become available subsequent to the imposition of restrictive ivermectin prescribing
d) accounts of the successful national ivermectin programs used by several countries in relation to COVID-19
e) specific rebuttals in response to key publications which purport to argue against the safe and effective use of ivermectin

40. The evidence will show that ivermectin is a particularly safe therapeutic agent and its restrictive Poisons Scheduling embodied in Appendix D, Item 10 is unwarranted and needs to be amended in the national interest as soon as possible. These Submissions focus on the safety aspects of ivermectin and have not been designed as Submissions to support any additional therapeutic indication, however, a number of key clinical studies and meta-analyses have been included in these Submissions insofar as they also relate to safety and provide some guidance in relation to common dosages employed.

41. Apart from the evidence presented in these Submissions regarding the intrinsic and relative safety of ivermectin, it needs to be recognised that there is both substantial clinical interest and public awareness of the potential use of ivermectin. The effective denial of supply, rightly or wrongly, has driven many to consider alternative sources of ivermectin (veterinary products, counterfeit

products and overseas therapeutic products) which carry undetermined safety risks of their own. The Co-Signatories argue that removal of Appendix D, Item 10 of the Poison Scheduling will assist in the provision of medically supervised use by doctors and pharmacists to ensure patients receive adequate patient information and a product of reliable quality suitable for human use.

IVERMECTIN – HISTORICAL PERSPECTIVE AND CLINICAL USE

42. Professor Satoshi Omura, of the Kitasato Institute, discovered a group of pharmacologically active compounds in 1975 called 'avermectins" from an unusual *Streptomyces* bacterium from the soil near a golf course along the Southeast coast of Honshu, Japan. One of these compounds was ivermectin.

43. Ivermectin became one of the most revolutionary drugs ever to be introduced into medicine. Although first introduced to treat parasites in animals, ivermectin has been used in humans since the 1980s[8]. Since then, ivermectin has dramatically improved the health and well-being of hundreds of millions of people mainly in relation to the effective management of parasitic diseases including river blindness and lymphatic filariasis – two of the most disfiguring diseases afflicting the world's poor. Later the use of ivermectin was expanded to include the treatment of scabies and lice.

44. Ivermectin has long since been approved as an antiparasitic by the World Health Organisation (WHO) and the U.S. Food and Drug Administration (FDA). The WHO has also included ivermectin on its list of "Essential Medicines"[9]. The importance of the drug to mankind was recognised by the award of the Nobel Prize in Medicine to the discovers in 2015[10].

45. In the decade leading up to the COVID-19 pandemic, studies showed that ivermectin possessed wide-ranging pharmacological activity including antiviral

[8] Andy Crump & Satoshi Omura, Ivermectin: enigmatic multifaceted 'wonder' drug continues to surprise and exceed expectations, 70 The Journal Antibiotics 495, 495 (2017), available at https://www.nature.com/articles/ja201711.pdf (hereinafter, "Crump, ivermectin")
[9] World Health Organisation. 2021 List of Essential Medicines. https://list.essentialmeds.org Last visited 15.9.22
[10] 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 15.9.22

activity against several RNA viruses[11]. In addition, ivermectin was also reported to possess useful anti-inflammatory activity[12]. Subsequently, doctors 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[13]. The potential usefulness of ivermectin in the management of inflammatory airway disease was also recognised[14]. In more recent times, there has been intense interest and research regarding the potential use of ivermectin in the management of COVID-19.

IVERMECTIN SAFETY AND TOXICOLOGICAL INFORMATION

46. The U.S. National Institute of Health (NIH) has recognised that "ivermectin has been widely used and is generally well tolerated"[15]. A recent systematic review stated "ivermectin at the usual doses…is considered extremely safe for use in humans"[16]. Ivermectin was added to the 2018 Essential Medicine list for use in scabies and in supporting the application for inclusion in the list, the WHO concluded that the adverse events associated with ivermectin are "primarily minor and transient"[17]. The most recent Australian Public Assessment Report for Ivermectin regarding the safety and efficacy of ivermectin by the TGA in relation to use in scabies found no safety concerns at even 10 times the (then) current approved dose of 200ug/kg[18]. The report said:

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[11] 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 15.9.22

[12] Crump, ivermectin, supra, at 499

[13] 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 15.9.22

[14] Crump, ivermectin, supra at 499

[15] National Institutes of Health, COVID-19 Treatment Guidelines: ivermectin, https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ivermectin/ Last visited 15.9.22

[16] 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 15.9.22. Hereafter "Bryant ivermectin".

[17] 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)

[18] Australian Public Assessment Report for Ivermectin – October 2013 https://www.tga.gov.au/auspar/auspar-ivermectin

47. *"The sponsors have only provided one new study (066) in 40 healthy subjects which showed good tolerability and no safety concerns at doses ranging from 30 to 120 mg, that is, up to 10 times the proposed dose of 200 µg/kg for treatment of scabies."*

48. *"Ivermectin has been used extensively to treat 6 million people in 30 countries for onchocerciasis caused by the filarial worm Onchocerca volvulus. Ivermectin also has proven effective for the human diseases, loiasis, strongyloidiasis, bancroftian filariasis and cutaneous larva migrans. Several studies have now evaluated ivermectin for human scabies. There were no significant safety concerns reported with the use of ivermectin in any of the scabies studies to date, except for one report of fatal complications in patients from a long-term care facility but these were not confirmed in other studies."*

and

49. "*The most comprehensively reported safety data came from the PK study conducted in healthy volunteers (Study 066). In this study oral ivermectin administered in multiple doses of up to 60 mg given 3 times a week or in single doses of up to 120 mg (which is approximately 10 times the proposed dose of 200 µg/kg for treatment of scabies) was generally well tolerated, with no evidence of mydriatic effect or other neurological toxicity. The most commonly reported clinical AE was headache, which occurred in equal proportions of ivermectin and placebo treated subjects. Other AEs, reported in single subjects in each group, were nausea, dizziness and rash.* ***No serious AEs were reported in the study. The clinical evaluator found there were no significant safety concerns reported with the use of ivermectin*** *in any of the published scabies studies, except for one report of fatal complications in elderly patients from a long-term care facility. However, Barkwell's findings were not confirmed in subsequent studies, some of which used even higher doses of ivermectin. Overall, the adverse event profile for ivermectin use in treatment of scabies appeared to be similar to that observed for other indications for which it is approved. In the published randomised clinical trials the main adverse events were headache, abdominal pain, mild diarrhoea and rash. Post marketing data were also provided in the form of a PSUR, covering the period*

April 2010 to April 2011. ***During the reporting period an estimated 1,423,010 patient treatment courses were administered for all indications***." (bolding added for emphasis).

50. An expert toxicological review report based on over 500 articles up to February 2021[19] stated the following:

51. *"The present extensive review of adverse events reportedly associated with ivermectin treatment for therapeutic or prophylactic purpose did not reveal any significant cause for concern. Indeed, with the notable exception of patients with parasitic diseases such as Onchocerciasis or Loa-Loa microfiliaris, serious adverse events temporarily associated with ivermectin were very infrequent. In fact, adverse events were mainly mild to moderate and infrequent. This is confirmed by results reported in patients with scabies or human beings without any ongoing parasitic disease."*

and

52. *"Hundreds of millions of human subjects have been treated with ivermectin for curative or prophylactic purposes worldwide over the last 3 decades. The reference list of this report demonstrates that a large body of data is available, which allows for a detailed analysis of ivermectin medical safety. Undoubtedly, uncertainties remain regarding ivermectin pharmacological effects and mechanisms of action, but when removed, this is not anticipated to alter the main conclusions of this report in any significant way as they rely on an extensive and consistent body of medical publications."*

53. *"Taking into account all the above, the author of the present analysis of the available medical data concludes that the safety profile of ivermectin has so far been excellent in the majority of treated human patients so that ivermectin human toxicity cannot be claimed to be a serious cause for concern."*

[19] Descotes, J. Expert Review Report – Medical Safety of Ivermectin. 3 March 2021 https://www.medincell.com/wp-content/uploads/2021/03/Clinical_Safety_of_Ivermectin-March_2021.pdf

54. An Opinion written by the U.S. Nebraska State Attorney General's Office (14 October 2021) provided a detailed analysis of the arguments regarding ivermectin and off-label prescribing which are instructive[20], a copy of which forms Annexure 1 to these Submissions, which Opinion the Co-Signatories wish to rely upon in full as it pertains to ivermectin.

55. The opinion stated in part:

"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[21]. One recent systematic review similarly states that "ivermectin" at the usual doses….is considered extremely safe for use in humans[22]. Other studies have noted that the medicine "has an established safety profile for human use"[23] and it "provide[s] a high margin of safety for a growing number of indications"[24]. 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"[25].

and

56. *"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. The largest reported categories for ivermectin include skin issues, headaches, dizziness and gastrointestinal disturbances such as diarrhea and nausea. The NIH confirms that ivermectin's primary adverse side effects "include dizziness, pruritis [itchy skin], nausea or diarrhea". And a recent review of ivermectin similarly describes*

[20] U.S. State of Nebraska, Office of the Attorney General. Prescription of Ivermectin or Hydroxychloroquine as Off-Label Medicines for the Prevention or Treatment of Covid-19. 14 October 2021. No. 21-017
[21] National Institutes of Health, COVID-19 Treatment Guidelines: Ivermectin, https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ivermectin/ (last visited 18 Sept. 2022)
[22] Bryant, Ivermectin, supra, at 435
[23] U.S. Nebraska State Attorney General opinion. Prescription of Ivermectin or hydroxychloroquine as Off-Label medicines for the Prevention or Treatment of Covid-19. 14 October 2021 https://ago.nebraska.gov/sites/ago.nebraska.gov/files/docs/opinions/21-017_0.pdf
[24] Kircik, Ivermectin, supra, at 325
[25] 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)

the common side effects as "itching, rash, swollen lymph nodes, joint pain, fever and headache."

and

57. *"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[26]. This number is incredibly low considering that "more than 3.7 billion doses" of ivermectin have been administered to humans worldwide since the 1980s."*

and

58. *"To illustrate the safety of ivermectin, compare its VigiAccess report to that of remdesivir, an FDA-approved treatment for COVID-19. 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. 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. Since that safety profile is sufficient to retain FDA approval, ivermectin's safety record cannot reasonably be questioned."*

59. The safety and pharmacokinetics of ivermectin, administered in higher and/or more frequent doses than currently approved for human use, were evaluated in a double-blind, placebo-controlled, dose escalation study in 2002[27].

[26] VigiAccess, Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, http://vigiaccess.org/

[27] Guzzo, C.A. et al. Safety, Tolerability, and Pharmacokinetics of Escalating High Doses of Ivermectin in Healthy Adult Subjects. J Clin Pharmacol 2002;42:1122-1133. https://pubmed.ncbi.nlm.nih.gov/12362927/ (last visited 18 Sept. 2022)

60. In contrast to the current recommended single doses of ivermectin for parasitic indications (about 200ug/kg), this study employed both single and multiple doses with an upper single dose of 120mg. Safety assessments addressed both known ivermectin CNS effects and general toxicity. The report stated:

61. "The primary safety endpoint was mydriasis, accurately quantitated by pupillometry. *Ivermectin was generally well tolerated, with no indication of associated CNS toxicity for doses up to 10 times the highest FDA-approved dose of 200ug/kg." …"This study demonstrated that ivermectin is generally well tolerated at these higher doses and more frequent regimens."*

62. An important systematic review including a meta-analysis of the safety of ivermectin for various parasitic infections following single high dose ivermectin (up to 800ug/kg or four times the recommended dose) has provided evidence of the wide margin of safety of this widely used drug[28]. The results and conclusions were summarised as follows:

63. "Results: The systematic search identified six studies for inclusion, revealing no differences in the number of individuals experiencing adverse events. A descriptive analysis of these clinical trials for a variety of indications showed no difference in the severity of the adverse events between standard (up to 400 lg/kg) and higher doses of ivermectin. Organ system involvement only showed an increase in ocular events in the higher-dose group in one trial for the treatment of onchocerciasis, all of them transient and mild to moderate in intensity."

64. "Conclusions: Although within this review the safety of high-dose ivermectin appears to be comparable to standard doses, there are not enough data to support a recommendation for its use in higher-than-approved doses. Ocular adverse events, despite being transient, are of concern in onchocerciasis patients. These data can inform programme managers and guide operational

[28] Navarro, M. et al: Safety of high-dose ivermectin: a systematic review and meta-analysis. J Antimicrob Chemother 2020; 75: 827–834 doi:10.1093/jac/dkz524 Advance Access publication 20 January 2020. https://academic.oup.com/jac/article/75/4/827/5710696

research activities as new approaches for the use of ivermectin are evaluated. "

65. A recent clinical trial using ivermectin for the management of 34 severe hypoxic COVID-19 patients warrants special mention as it provides both useful high dose ivermectin safety data as well as impressive oxygen saturation data[29]. Remarkably, all but three of these 34 patients had significantly increased SpO2 values within 24 hours after the first ivermectin dose. However, in relation to safety the authors stated:

66. *"As evidence of IVM safety and tolerability accrued following its use beginning in August 2020, its stat dose of 10 mg as used for the earliest patients was increased on 11 September 2020 to 10–12 mg every four days for three doses. Subsequently, the dosage was further increased to 12 mg IVM on the day of admission and then on Days 4 and 8 plus doxycycline (100 mg b.i.d.) and zinc sulfate (60 mg/day). The latter regimen was used up through December 2020, when the second pandemic wave emerged in Zimbabwe. At that time, additional evidence of the safety and tolerability of this regimen supported further dose escalation to a standard IVM dose regimen of 12 mg daily for five consecutive days, with adjunct use of doxycycline and zinc sulfate continued at the doses noted. In some cases, for which this standard treatment regimen did not yield significant clinical gains within a few days, even higher doses of IVM were used, in some cases as high as 100 mg for a single dose. Transient adverse effects (Aes) such as blurred vision characteristic of high-dose IVM often occurred at those dose levels, but no serious AEs [adverse effects] associated with IVM were manifested in any patient. "*

[29] Stone, J.C. et al: Changes in SpO2 on Room Air for 34 Severe COVID-19 Patients after Ivermectin-Based Combination Treatment: 62% Normalization within 24 Hours. *Biologics* **2022**, *2*, 196–210. https://doi.org/10.3390/biologics2030015 . https://www.mdpi.com/2673-8449/2/3/15

67. *Similarly* impressive clinical efficacy results using ivermectin for the management of COVID-19 were reported in another study[30]. In relation to the important issue of ivermectin safety the authors commented:

68. *"Five such studies for IVM treatment of COVID-19 recently published in top-tier medical journals have all shown multiple clinical benefits for IVM versus controls, most of these with high statistical significance on the order of p < 0.002 [6–10]. At much greater than the standard single anti-parasite dose of 200 µg/kg, IVM is well tolerated [11,12] and has been used in RCTs for COVID-19 treatment at cumulative doses of 1500 µg/kg [13] and 3000 µg/kg [14,15] over 4 or 5 days either without or with mild and transient adverse effects. Not surprisingly, IVM has become extensively used in the prevention and early disease management of COVID-19, particularly in non-Western countries."*[references omitted]

COMPARATIVE SAFETY INFORMATION REGARDING MOLNUPIRAVIR AND PAXLOVID

69. *Any* consideration of the normalisation of Poison Scheduling of ivermectin would be incomplete without regard to the clinical juxtaposition of an assessment of the safety of the recently "Provisionally Approved" anti-virals, molnupiravir and Paxlovid, which have a vastly inferior and uncertain safety record by comparison to ivermectin[31].

70. *Molnupiravir* is an old drug which has been repurposed to treat COVID-19. Previously, commercial interest was abandoned in this drug due to concerns regarding its mutagenic potential[32] (cancer risk or transgenerational pathology)

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[30] Hazan, S. et al: Effectiveness of ivermectin-based multidrug therapy in severely hypoxic, ambulatory COVID-19 patients. Future Microbiol. 2022 Mar;17:339-350. doi: 10.2217/fmb-2022-0014. Epub 2022 Feb 9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8826831/

[31] Clancy, R.: The Suppression of Useful COVID-19 Treatments. Quadrant, 8 August 2022. https://quadrant.org.au/opinion/public-health/2022/08/the-suppression-of-useful-covid-19-treatments/

[32] Zhou, S. et al: β-d-N^4-hydroxycytidine Inhibits SARS- CoV-2 Through Lethal Mutagenesis but Is Also Mutagenic to Mammalian Cells. Journal of Infectious Diseases, 2021:224 (1 August) pp415-419. https://pubmed.ncbi.nlm.nih.gov/33961695/

and concerns regarding disappointing clinical efficacy; both resulting in the failure to achieve registration approval in a number of countries.

71. Paxlovid, containing a combination of the antiviral nirmatrelvir, a protease inhibitor, and ritonavir, a cytochrome P450 pathway inhibitor, was also Provisionally Approved for the treatment of COVID-19. However, initial clinical efficacy claims could not be supported, rebound infection was reported and ritonavir is associated with serious toxicity including known toxicity to the liver[33] and fatalities have been reported[34].

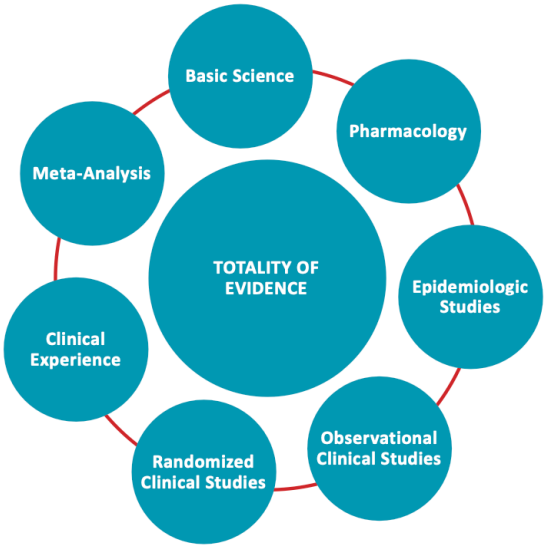
72. Ivermectin, in contrast to these two antiviral medications, has a much wider therapeutic index and has a relatively high level of safety following many years of use in many millions of individuals treated for parasitic infections such as river blindness. It should also be noted, in contrast to ivermectin, that these two "Provisionally Approved" antivirals have been used in COVID-19 based on relatively limited clinical safety and efficacy data.

IVERMECTIN CLINICAL STUDIES AND META-ANALYSES FOR UNAPPROVED INDICATIONS – SUBMITTED AS EVIDENCE OF CLINICAL SAFETY

73. The circumstances surrounding the amended Poison Scheduling of ivermectin were as unprecedented as was the level of clinical interest and research in the use of ivermectin since the COVID-19 pandemic began.

74. Since 2012, numerous in-vitro and in-vivo studies began to report the anti-viral and anti-inflammatory efficacy of ivermectin. A review of the totality of evidence supporting ivermectin safety and efficacy derived from diverse sources was published in 2021[35]

[33] Australian Product Information - Paxlovid. Version: pfppaxlt10122. https://www.tga.gov.au/sites/default/files/auspar-nirmatrelvir-ritonavir-220124-pi.pdf
[34] U.S. Prescribing Information - Norvir. Revised June 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209512lbl.pdf
[35] Kory, P. et al: review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19. American Journal of Therapeutics: May/June 2021 - Volume 28 - Issue 3 - p e299-e318doi: 10.1097/MJT.0000000000001377



75. The dosages of ivermectin varied in relation to the dose per day and the number of days of dosing. Generally, the most common dose was about 12mg or 200ug/kg administered daily for up to about 5 days.

76. This Kory et al meta-analysis concluded:

"Meta-analyses based on 18 randomized controlled treatment trials of ivermectin in COVID-19 have found large, statistically significant reductions in mortality, time to clinical recovery, and time to viral clearance. Furthermore, results from numerous controlled prophylaxis trials report significantly reduced risks of contracting COVID-19 with the regular use of ivermectin. Finally, the many examples of ivermectin distribution campaigns leading to rapid population-wide decreases in morbidity and mortality indicate that an oral agent effective in all phases of COVID-19 has been identified."

77. Another significant meta-analysis appeared mid-2021[36]. Twenty-four randomized controlled trials involving 3406 participants met the review criteria for inclusion. The authors concluded:

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https://journals.lww.com/americantherapeutics/fulltext/2021/06000/review_of_the_emerging_evidence_demonstrating_the.4.aspx

[36] see previously "Bryant ivermectin".

78. *"Moderate-certainty evidence finds that large reductions in COVID-19 deaths are possible using ivermectin. Using ivermectin early in the clinical course may reduce numbers progressing to severe disease. The apparent safety and low cost suggest that ivermectin is likely to have a significant impact on the SARS-CoV-2 pandemic globally."*

79. Following Bryant's publication of his team's review, the Elgazzar study, one of the randomised controlled trials included in the meta-analysis, was questioned and placed under review. This issue has attracted considerable attention by the detractors of ivermectin in the literature. This prompted the Bryant's authors to reanalyze the data without the Elgazzar study but the review still found a clear result showing a 49% reduction in mortality in favour of ivermectin[37]. The dosages of ivermectin again varied but were generally either similar to the current recommended single dose for parasitic infection or a multiple of two or three times higher with daily dosing up to 9 days implying a relatively wide margin of safety.

80. A more recent meta-analysis of the clinical safety and efficacy may be found at ivmmeta.com which includes an analysis of 91 studies (of which 41 were randomized controlled trials involving 11,141 patients) as at 9 September 2022[38]. This resource illustrates the high level of international interest in the clinical application of ivermectin for potential use in COVID-19.

81. When taken in totality, the clinical data presented at ivmmeta.com presents a compelling case for the safety and efficacy of ivermectin and more than 20 countries (including India, Mexico, regions of Peru, Argentina, Japan, Dominican Republic and Brazil) have adopted ivermectin for the management of COVID-19. Collectively, the studies strongly suggest that *"ivermectin reduces the risk for COVID-19 with very high confidence for mortality, ventilation, ICU admission, hospitalization, progression, recovery, [number of] cases, viral clearance, and in pooled analysis."* Meta-analysis using the most

[37] Bryant, A 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

[38] Ivermectin for COVID-19: real-time meta analysis of 91 studies. Covid Analysis, Sept. 9 2022 Version 198. www.Ivmmeta.com

serious outcome measure shows 62% [57-70%] and 83% [74-89%] improvement for early treatment and prophylaxis".

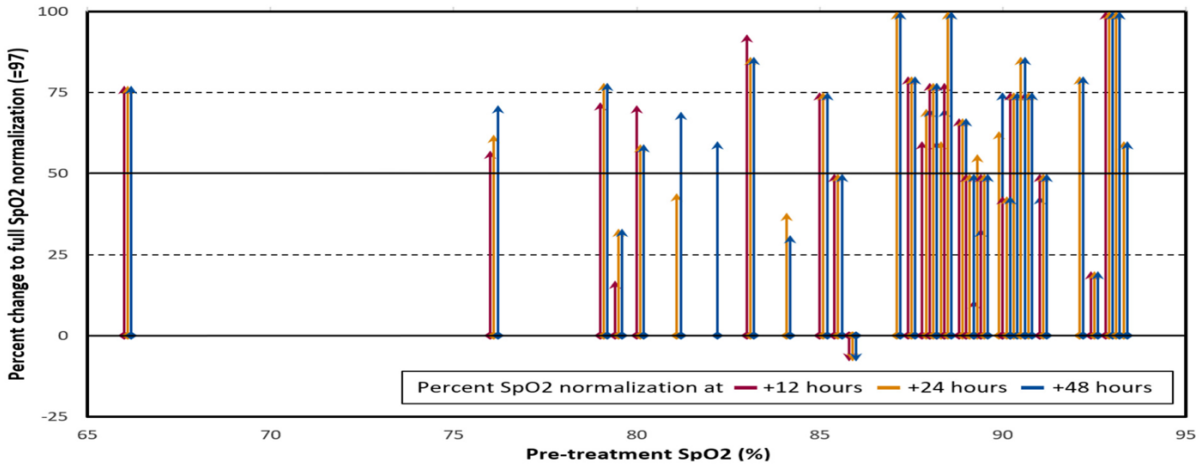
82. In a mini-review of ivermectin safety in the treatment of COVID-19 it was concluded that ivermectin "has been safely used in 3.7 billion doses since 1987" and that the medicine has been "used without serious [adverse effects] in multiple COVID-19 studies[39].

83. An Australian perspective referred to as the "Ivermectin Statement", supported by several concerned health professionals, supported the use of ivermectin both alone and in combination with other therapeutic agents[40]. The Statement concluded:

"The information presented in this statement clearly shows the benefit of ivermectin for a prophylactic role in Covid-19, and the value of using ivermectin for early and established Covid-19 infections."

84. The published report of Stone et al[41] (previously referred to above in relation to safety at paragraphs 64-65) warrants repeated mention in that this highly monitored clinical study eloquently illustrates why there is continued and justifiable clinical interest in ivermectin. Dramatic overall improvement in oxygen saturation, an important recovery metric, in 34 ivermectin treated COVID-19 patients, as presented in the figure below, underscores the legitimacy of clinician interest in exploring alternate therapeutic approaches to COVID.

[39] 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) at https://pubmed.ncbi.nlm.nih.gov/34466270/
[40] Morris, P.: Repurposed drugs to treat Covid-19: Ivermectin. July 22, 2022. www.drphilipmorris.com
[41] Stone, J.C. et al (supra) at footnote 27



85. Despite more than 90 clinical trials being reported in the literature, there are no credible reports of serious or significant adverse events which would argue against the view that ivermectin, compared to almost all other drugs, should be considered a safe therapeutic agent with a wide therapeutic index.

INTERNATIONAL REAL WORLD IVERMECTIN EXPERIENCE IN RELATION TO THE TREATMENT OF COVID-19

86. In light of the very limited amount of controlled clinical trial safety data, international drug regulatory agencies have acknowledged as relevant and frequently referred to "real world" experience to support claims of safety relating to COVID-19 vaccination in children. "Real world" data can, indeed, be useful given the obvious large sample sizes inherent in such data collection.

87. In an early report of correlation between prophylactic ivermectin use and the suppression of COVID-19 incidence[42], data was collected from countries which routinely deploy prophylactic chemotherapy (PCT) using various drugs including ivermectin. The countries could be grouped into two categories: those which include ivermectin in their PCT and those which do not. Data sources included

[42] Hellwig, A and Maia, A: A COVID-19 prophylaxis? Lower incidence associated with prophylactic administration of ivermectin. International Journal of Antimicrobial Agents 57 (2021 106248. https://pubmed.ncbi.nlm.nih.gov/33259913/

the WHO and the COVID-19 portal published by Johns Hopkins University via the aggregated Worldometer database. All data was current as of 20 October 2020.

88. The authors concluded:

"Here, we show that countries with routine mass drug administration of prophylactic chemotherapy including ivermectin have a significantly lower incidence of COVID-19. Prophylactic use of ivermectin against parasitic infections is most common in Africa and we hence show that the reported correlation is highly significant both when compared among African nations as well as in a worldwide context."

89. Peru deployed mass ivermectin-based COVID-19 treatments from April 2020 through November 2020 throughout its 25 States[43]. An analysis of the impact of ivermectin on excess deaths related to the pandemic showed the following:

"The 25 states of Peru were grouped by extent of IVM distributions: maximal (mass IVM distributions through operation MOT, a broadside effort led by the army); medium (locally managed IVM distributions); and minimal (restrictive policies in one state, Lima). The mean reduction in excess deaths 30 days after peak deaths was 74% for the maximal IVM distribution group, 53% for the medium group and 25% for Lima. Reduction of excess deaths correlated with extent of IVM distribution by state with $p<0.002$ using the Kendall τ_b test. Nationwide, excess deaths decreased 14-fold over four months through December 1, 2020, after which deaths then increased 13-fold when IVM use was restricted under a new president."

90. A retrospective statistical analysis study of the impact of ivermectin against COVID-19 between the 31 onchocerciasis-endemic countries using the community-directed treatment with ivermectin (CDTI) and the non-endemic 22

[43] Chamie-Quintero J.J. 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). https://osf.io/9egh4/

countries in Africa. The morbidity, mortality, recovery rate, and fatality rate caused by COVID-19 were calculated from the WHO situation report in Africa[44].

The authors concluded:

91. *"The morbidity and mortality were statistically significantly less in the 31 countries using CDTI. The recovery and fatality rates were not statistically significant difference. The average life expectancy was statistically significantly higher in the non-endemic countries. The morbidity and mortality in the onchocerciasis endemic countries are lesser than those in the non-endemic ones. The community-directed onchocerciasis treatment with ivermectin is the most reasonable explanation for the decrease in morbidity and fatality rate in Africa. In areas where ivermectin is distributed to and used by the entire population, it leads to a significant reduction in mortality."*

92. Real world data derived from Ivermectin National Treatment Programmes were also described in the Altman open letter of 14 October 2021 to the National Covid Clinical Evidence Taskforce (NCCET) in Appendix 1.

93. In this open letter it was stated:

"In addition to the successful national treatment programmes in countries such as Mexico, Argentina and Peru, the NCCET should now be aware of the success in treating COVID-19 individuals with ivermectin in the Indian State of Uttar Pradesh."

94. *"Ivermectin based combination therapy was administered as early and preventative treatment in all family contacts as part of the "Uttar Pradesh Covid Control Model". Using this therapeutic approach, COVID-19 was virtually eliminated in a population of 230 million people with a vaccination rate of less than 6% (compares to the US fully vaccinated rate at the same time of 54%). This result is in direct contrast to the comparable State of Kerala, a small state*

[44] Tanioka, H et al: Why COVID-19 is not so spread in Africa: How does Ivermectin affect it? Preprint. Europe PMC. 26 March 2021.
DOI: 10.1101/2021.03.26.21254377 https://europepmc.org/article/PPR/PPR303143

located in Southern India that is over-dependent on vaccines and restricted ivermectin use to more severe cases and late treatment if used at all."

95. *The* inescapable conclusion provided by the national ivermectin prophylactic campaigns is that ivermectin use correlates closely and consistently across many countries with a beneficial impact on COVID-19. This important observation has been largely ignored to date in favour of highly restrictive ivermectin prescription policies in Australia and elsewhere which do not appear to be justifiable based on the known safety of this well-established therapeutic agent. A strictly controlled ambitious city-wide program in the Southern Brazilian city of Itajai involving 223,128 subjects, the relationship between progressive dose and regularity of dosing of reported reductions in COVID-19 infection, hospitalization and mortality rates previously observed by these same researchers, was explored[45]. The study is of importance from both a safety and efficacy point of view in that the current recommended single dose of ivermectin of 0.2mg/kg/day was used but on two consecutive days every 15 days which represents a total drug exposure well beyond that commonly employed and a dose-response efficacy relationship was observed.

The researchers concluded:

96. *"The non-use of ivermectin was associated with a 10-times increase in mortality risk and a 7-times increased risk of dying from COVID-19, compared to strictly regular use of ivermectin in a dose of 0.2mg/kg for two consecutive days every 15 days, in a prospectively, strictly controlled population. A progressive, dose- and regularity-response pattern for protection from COVID-19 related outcomes was observed and consistent across levels of ivermectin use and all outcomes, except for reduction in infection rate, that was significant and consistent, but irrespective of level of ivermectin use."*

[45] Kerr, L. et al: Regular Use of Ivermectin as Prophylaxis for COVID-19 led up to a 92% Reduction in COVID-19 Mortality Rate in a Dose-Response Manner: Results of a Prospective Observational Study of a Strictly Controlled Population of 88,012 Subjects. **DOI:** 10.7759/cureus.28624. https://www.cureus.com/articles/82162-ivermectin-prophylaxis-used-for-covid-19-a-citywide-prospective-observational-study-of-223128-subjects-using-propensity-score-matching

CONTROVERSIAL EVIDENCE/REVIEWS NOT SUPPORTING THE CLINICAL EFFICACY OF IVERMECTIN FOR COVID-19

97. *Any* review of matters relating to the amendment to the current Poisons Scheduling of ivermectin would not be complete without reference to meta-analyses and papers which are not supportive in relation to the use of ivermectin in COVID-19 which have received considerable attention and warrant comment. It is important to note that this information focused on clinical efficacy and in no case was there material evidence suggestive of any safety concern.

The TOGETHER TRIAL

98. The efficacy of ivermectin in preventing hospitalization or extended observation in an emergency setting among outpatients with acutely symptomatic COVID-19 was studied in 679 ivermectin treated patients and 679 placebo treated patients at a dose level of 400ug per kg for 3 days[46]. The authors concluded that ivermectin did not result in a lower incidence of a composite outcome defined as medical admissions to a hospital due to progression of Covid-19 or, alternatively, prolonged emergency department observation. This “composite" outcome measure was rejected as “inadequate” by both the FDA and NIH in the USA. However, when the study was analysed “per protocol” (that is counting those who completed the trial according to the protocol), protection against admission to hospital was a statistically significant 60%. This result demonstrating clinical efficacy was not reported in the published paper. The critically important outcome of mortality is reported only for an Intention-To-Treat (ITT) group, for which meaningful comparison is invalidated by a wholly anomalous "apparent dropout rate" of 58% in the placebo arm, when per protocol compliance is considered. Anomalies of this magnitude essentially invalidate an ITT analysis and demand primary attention to the per protocol groups. Multiple requests for mortality data in the per protocol groups have however been denied; though clearly available, the data informing the effect on mortality remains unreported.

[46] Reis, G. et al: Effect of Early Treatment with ivermectin among Patients with Covid-19. N Engl J Med 386;18 nejm.org may 5, 2022 https://www.nejm.org/doi/pdf/10.1056/NEJMoa2115869?articleTools=true

99. The authors of the TOGETHER TRIAL have thus far refused to provide de-identified patient-level data, though promised in their Data Sharing Statement "immediately after publication" (30 March 2022), and have for several months mis-directed enquiries to a data repository (ICODA) which denies holding the data. The journal (*NEJM*) which published the study has not to date responded to a letter requesting information from 66 senior international physicians and scientists[47] and has declined to publish any of the many short (< 175 words) Letters to the Editor raising questions about this study. The study appears fraught with data irregularities, the lack of transparency and conflicts of interests which remain to be clarified.

100. It is of some note that even at this relatively high dose, the incidence of all grades of adverse events for ivermectin were lower or about the same compared to placebo, raising the possibility of self-medication with over-the-counter (OTC) ivermectin which is freely available in the study locale. Conducted in the midst of the emergence of the clinically aggressive "Gamma" or "Brazilian" variant, silent non-compliance with protocol by participants would be understandable, and a valid comparison with placebo requires concurrent recruitment, for which insufficient data are yet available to confirm.

101. Similar concerns regarding data integrity and conflicts of interest in the literature with regard to generic drugs with potential therapeutic efficacy in the management of COVID-19 also occurred in the Surgisphere saga which resulted in an embarrassing retraction by The Lancet[48] and parallel papers in NEJM. Unless and until the promised de-identified data set is openly released, this study violates too many norms of scientific conduct to be considered reliable.

[47] Letter from 66 scientists and physicians to the co-authors of Reis et al. 2022 and to others as identified in the correspondence, as emailed on May 10 2022, together with the email thread of follow-up correspondence through July 19, 2022, with all but certain publicly available email addresses redacted at https://drive.google.com/file/d/1eSez1YNIf26PHAPX6oHpw-UFg-QY1cfd/preview

[48] Mehra, M. et al. Retraction-Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: A multinational registry analysis. The Lancet, Vol 395, Issue 10240, P1820, June 13 2020. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31324-6/fulltext

102. THE COCHRANE REVIEW OF IVERMECTIN

Another meta-analysis known as the Popp review[49] has reached more skeptical conclusions which have been subsequently been challenged. The analysis excluded some of the randomised clinical trials that Bryant considered and evaluated only 14 studies with 1,678 participants and determined that the "completed studies are small and few are considered of high quality". The authors expressed "uncertainty about the efficacy and safety of ivermectin used to treat or prevent COVID-19" but Bryant and others[50] contend most of the relevant evidence was excluded from analysis and the Popp analysis suffered from numerous flaws including unsupported assertions and inconsistencies in design which exemplify the literature battleground.

Additional critical comments on the Cochrane Review appears on the extensive online ivermectin data website ivmmeta.com[51] which also is critical of the Popp et al analytical approach including the impact of splitting up studies for analysis (fragmentation of data) which reduced the chance of demonstrating statistical significance and selecting arbitrary time points for outcome measures.

103. THE ROMAN REVIEW

Another meta-analysis, the Roman review[52], restricted the selection of randomised clinical trials for analysis even further and considered only 10 trials and concluded that ivermectin does not reduce all-cause mortality or viral clearance. But since its publication the Roman review has drawn some harsh criticism. The authors of the Bryant review have highlighted four categories of flaws with the Roman analysis: mis-reporting of source data, highly selective study inclusion, "cherry picking" of data and conclusions that do not follow from

[49] Maria Popp et al., Ivermectin for preventing and treating COVID-19, Cochrane Database of Systematic Reviews (July 28, 2021) available at https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD015017.pub2/full

[50] Edmund J. Fordham et al, The uses and abuses of systematic reviews: the case of ivermectin in Covid-19, OSF Preprints (Oct. 7, 2021) at https://osf.io/mp4f2/

[51] Ivmmeta.com (supra)

[52] 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 (June 28, 2021) at https://pubmed.ncbi.nlm.nih.gov/34181716/

the evidence[53] and requested a retraction of the Roman et al meta-analysis. Another report[54] reaffirms the Bryant meta-analysis results and concluded:

104. *"We show that there is overwhelming evidence to support a causal link between ivermectin, Covid-19 severity and mortality, and: i) for severe Covid-19 there is a 90.7% probability the risk ratio favours ivermectin; ii) for mild/moderate Covid-19 there is an 84.1% probability the risk ratio favours ivermectin. Also, from the Bayesian meta-analysis for patients with severe Covid-19, the mean probability of death without ivermectin treatment is 22.9%, whilst with the application of ivermectin treatment it is 11.7%. The paper also highlights advantages of using Bayesian methods over classical statistical methods for meta-analysis."*

THE NCCET RECOMMENDATION ON IVERMECTIN

105. The National Covid Clinical Evidence Taskforce (NCCET) conducted a review of the clinical data (Communique Ed. 48 – 5.8.21) regarding the use of ivermectin in the management of COVID-19 and concluded:

106. *"The available research evidence does not yet provide reasonable certainty to recommend for or against the use of ivermectin and therefore the Taskforce recommends ivermectin not be used outside of randomised trials. The certainty of the current evidence base varies from low to very low depending which on outcome is being measured, as a result of serious risk of bias and serious imprecision in the 18 included studies."*

107. Two fully documented and comprehensive responses were submitted to the NCCET by Dr. Phillip Altman dated 21 August 2021 (together with a Commentary by Dr. Tess Lawrie and Dr. Edmund Fordham) and 14 October 2021 which were also published in the Quadrant Magazine as Open Letters, however, no reply was ever received. A copy of these letters and commentary is attached as Annexure 2 for the record.

[53] Letter from Andrew Bryant et al to Robert T. Schooley, Editor in Chief, Clinical infectious Diseases at https://bird-group.org/letter-to-editor-of-journal-requesting-retraction-of-roman-et-al-meta-analysis/
[54] Neil, M et al: Bayesian meta Analysis of Ivermectin confirms Bryant et al study that ivermectin works for Covid. July 13, 2021 published on the BIRD website. https://bird-group.org/bayesian-meta-analysis-of-ivermectin-confirms-bryant-et-al-study-that-ivermectin-works-for-covid/

The 21 August 2021 response, in part, commented:

108. *"The [NCCET] analysis reveals and details (with references) serious flaws in the selective NCCET interpretation of the 'cherry picked' literature. It ignores the broad sweep of clinical evidence from other randomised controlled clinical trials, observational trials and national treatment programs and demands (in the NCCET's own words) as a matter of high priority to review this recommendation in the national interest."*

109. This comment is even more applicable today as considerable clinical safety and efficacy data has been generated since the Altman submissions yet there has been no reconsideration of the position on ivermectin.

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ANNEXURE 1

STATE OF NEBRASKA
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DOUGLAS J. PETERSON
ATTORNEY GENERAL

No. 21-017
STATE OF NEBRASKA
OFFICIAL
OCT 14 2021
DEPT. OF JUSTICE

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

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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 Ron 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

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7 Bosoley & 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

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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(5), (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 those 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

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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(U).

22 *Curran v. Busse*, 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

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[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]

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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]

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[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, 496 (2017), *available at* https://www.nature.com/articles/ja201711.pdf (last visited Oct. 14, 2021) (hereinafter, "Crump, *Ivermectin*").

[43] *Id.*

[44] Andy Crump & Satoshi Omura, *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*, 26 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

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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*, 26 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 & Roza 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*, 58 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

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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

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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

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[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

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77 *Id.*

78 *Id.*

79 *Id.*

80 Priyamadhabo 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 Shakhs 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

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87 *Id.*

88 Bryant, *Ivermectin*, *supra*, at 461.

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://covid19critical care.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/pegcj/ (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

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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

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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. 7, 2021), *available at* https://arxiv.org/ftp/arxiv/papers/2109/2109.13739.pdf (last visited Oct. 14, 2021).

105 Ivermec.in: 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]

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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]

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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.

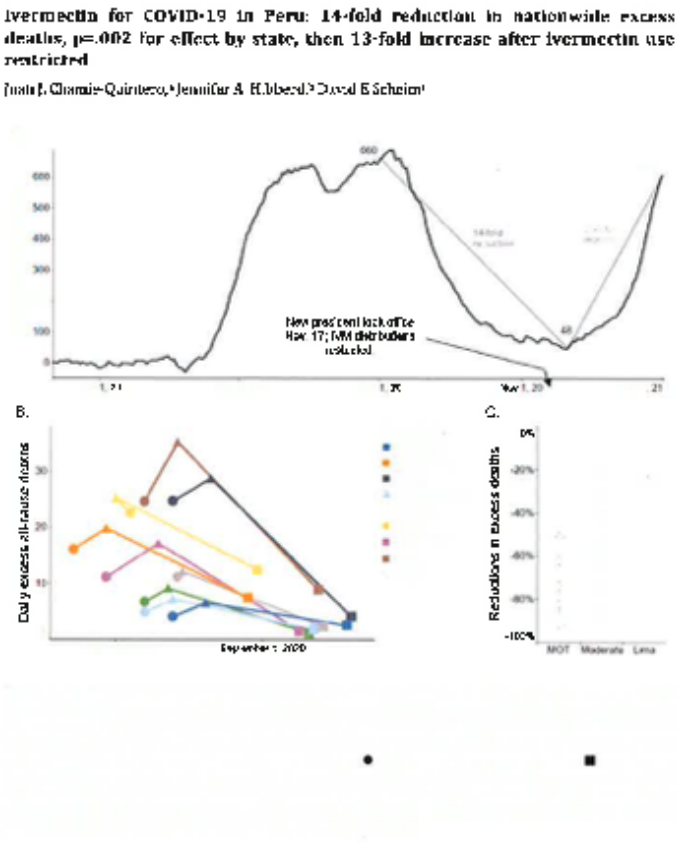
118 Santin, *supra*, at 3.

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

120 *Id.*

121 *Id.*

122 *Id.*



"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

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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

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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

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[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-sot-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.

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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]

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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

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

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

[153] 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,

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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).

156 *Id.*

157 *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

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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/a6a3f83e-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.[169] 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.

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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).

169 *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.*

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

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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."[164] The AAPS has thus publicly resisted these groups' call to "stop[] the off-label use of long-approved drugs."[165]

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.[166] 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.[167] 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,"[168] and it includes a five-day course of ivermectin as part of its COVID-19 early treatment protocol.[169] 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.[170]

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.

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164 *Id.*

165 *Id.*

166 Tokyo Metropolitan Medical Association recommends ivermectin administration to prevent aggravation, Nikkei (Feb. 9, 2021), https://www.nikkei.com/article/DGXZQOFB25AAL0V20C21A2000000/ (last visited Oct. 14, 2021).

167 *Id.*

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

169 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).

170 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

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[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] Elisa Laura Nirk et al., *Hydroxychloroquine in rheumatic autoimmune disorders and beyond*, EMBO Molecular Medicine, e: 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

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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 Haladyj 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 those 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

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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 (Jun. 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

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215 *Id.*

216 Eva Haras 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

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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, those 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 those 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.

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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

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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] Those 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]

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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 confoundor."[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

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251 Shivraj Padiyar & Deepshish Dandа, *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."[258] 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

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258 *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

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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]

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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

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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 Xueling 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 acqually decreasing hospitalization and mortality rates when used as an outpatient treatment. As we discussed above, many large observational studies strongly suggest that hydroxychloroquino 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 hydroxych'oroquine 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

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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."[290] 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

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290 FDA, Bringing Perspective, *supra*.

291 *Id.*

292 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).

293 *Id.*

294 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).

295 *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]

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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.

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

Very truly yours,

DOUGLAS J. PETERSON
Attorney General

James A. Campbell
Solicitor General

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Approved by:

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ANNEXURE 2

OPEN LETTER

21 August 2021

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Re: Call for an Urgent Review of the NCCET Recommendation regarding the use of ivermectin in the management of Covid-19 within 14 days

I refer to the current recommendation by the National Covid Clinical Evidence Taskforce (NCCET) regarding the use of the drug ivermectin for the management of Covid-19.

The NCCET serves an important role in reviewing and recommending treatment for Covid-19 to peak health professional bodies across Australia. The current recommendation (Communique Ed. 48 - 5.8.21) regarding the use of the drug ivermectin is as follows:

"The available research evidence does not yet provide reasonable certainty to recommend for or against the use of ivermectin and therefore the Taskforce recommends ivermectin not be used outside of randomised trials. The certainty of the current evidence base varies from low to very low depending which on outcome is being measured, as a result of serious risk of bias and serious imprecision in the 18 included studies.

In addition to uncertainty around benefits for patients with COVID-19, there are common side effects and harms associated with ivermectin, including diarrhoea, nausea and dizziness. Given this uncertainty of benefit, and concerns of harms; we recommend that ivermectin only be provided in research trials, where there is the potential to generate further evidence on the effectiveness, or otherwise, of ivermectin." ….

"This is a high priority recommendation and will be updated as soon as new evidence becomes available."

Ivermectin has been the subject of more than 60 clinical trials, including more than 30 randomised controlled trials and used successfully in national Covid-19 mass treatment campaigns in India, Mexico and several other countries to reduce the number of cases and prevent serious complications of the disease leading to hospitalisation and death.

Despite this, and in the absence of NCCET members' personal experience in treating COVID-19 patients with ivermectin, the NCCET has selected in an arbitrary and imprecise manner a small number of published clinical trials (18) upon which to base its current negative recommendation for ivermectin use. NCCET has failed to apply sophisticated, defined, and detailed meta-analysis techniques as employed in widely discussed published reviews on

ivermectin (see references attached). When lives are at risk, the highest standards of evaluation are required.

The emphasis on minor and generally uneventful "harms associated with ivermectin, including diarrhoea, nausea and dizziness" contained in the above NCCET statement demonstrates a total lack of therapeutic perspective in relation to the much more serious side effects of other drugs used to treat COVID-19. Including many over the counter non-prescription drugs and the dire consequences of a lack of effective therapeutic management of COVID-19 individuals.

The NCCET has sought to respond to critics of its recommendation on ivermectin in the Communique of 5 Aug. 2021 by justifying its limited consideration of the ivermectin literature by posing, and then, answering its own question in the following way:

NCCET: "But hasn't ivermectin been shown to be effective as an early COVID-19 treatment in randomised controlled trials overseas?":

NCCET: "Despite some early suggestions that ivermectin may provide both prophylactic and therapeutic benefit, the available research evidence does not yet provide reasonable certainty to recommend for or against the use of ivermectin. More robust, well-designed randomised controlled trials are needed to demonstrate whether or not ivermectin is effective."

"Some widely discussed meta-analyses of ivermectin studies (e.g. The British Ivermectin Research Development (BIRD) Group meta analysis) have significant weaknesses, for example they include a large trial which has been discredited and retracted (Elgazzar et al.). Even in these reviews, when patient populations are separated by severity and comparisons to active treatments removed, no meaningful effect is found."

Given the national importance of the NCCET advice on ivermectin, I invited internationally recognised and experienced literature review specialist (Tess Lawrie MBBCh PhD) and Edmund Fordham (PhD FlnstP) of Evidence Based Medicine Consultancy Ltd (UK) and EbMCsquared, a Community Interest Company located in Bath, England, to comment on the above NCCET interpretations of the literature. Their expert analysis is attached and entitled, "Commentary upon NCCET Statement" dated 7 August 2021.

The analysis reveals and details (with references) serious flaws in the selective NCCET interpretation of the 'cherry picked' literature. It ignores the broad sweep of clinical evidence from other randomised controlled clinical trials, observational trials and national treatment programs and demands (in the NCCET's own words) as a matter of high priority to review this recommendation in the national interest.

In addition, related to the current NCCET recommendation is the statement by the TGA (18 Aug 2021):

"There is currently insufficient evidence to support the safe and effective use of ivermectin, doxycycline and zinc (either separately, or in combination) for the prevention or treatment of COVID-19. More robust, well-designed clinical trials are needed before they could be considered an appropriate treatment option." requires immediate review in light of the information herein provided." In reality, there is insufficient evidence not to support the use of ivermectin while new and expensive drugs are being expedited through the regulatory process

and given provisional approval with far less clinical trial, efficacy and safety data supporting their use.

Australia is in the grip of a pandemic of enormous consequences. Every possible useful therapeutic approach is needed in this crisis. Ivermectin, especially in combination with zinc and doxycycline has shown to be effective in relation to COVID-19 management. Other new antiviral medications have been recently approved by the TGA with relatively minimal safety and efficacy data by comparison to ivermectin.

Ivermectin has been in use for more than three decades. Four billion doses have been administered, it is on the World Health Organisation List of Essential Drugs and is one of the world's most useful and well tolerated drugs available. Its breakthrough discovery is attributed to Prof. Satoshi Omura and Irish biologist William Campbell, who were awarded the Nobel Prize in Medicine in 2015, reflecting the magnitude of their achievement and the importance of ivermectin to medicine.

The current approach to symptomatic COVID-19 individuals is largely to do nothing and simply observe until they either get better or get worse, perhaps much worse, and need to go to hospital. The do-nothing approach places enormous strain on our health care system. Evidence for this 'do nothing, watch and observe' approach is lacking. Ivermectin offers a potentially effective, low cost, safe and rational approach to the management of such individuals with little or no disadvantage. The NCCET recommendation on ivermectin is considered to be misinformation by many experts and is viewed as contributing to needless hospitalisation – but for this recommendation, many Covid-19 infected individuals could be receiving early effective treatment.

Hon. Greg Hunt MP, Minister for Health and Aged Care, has written regarding ivermectin in a reply to Sen. Malcolm Roberts (27 July 2021)." It remains open for doctors to prescribe existing medicines 'off-label' based on their own clinical judgement". Indeed, this has always been the case previously.

Given the evidence available, doctors should be able to prescribe ivermectin as monotherapy or in combination without stigma or hindrance by a restrictive recommendation from the NCCET or the TGA. Both the NCCET and the TGA should re-examine the accumulating international experience with ivermectin from all sources supporting its safe and effective use and should actively support and encourage ongoing efforts by many to clarify the important role of ivermectin in the management of COVID-19.

I request the NCCET review and issue revised recommendations for the use of ivermectin within 14 days in light of the submitted information as a matter of urgent priority and national interest.

Please confirm receipt of this Open Letter by return email.

Regards,
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COMMENTARY UPON NCCET STATEMENT DATED 7 AUGUST 2021

SUBMITTED AND REFERRED TO IN SUPPORT OF DR. ALTMAN'S NCCET OPEN LETTER OF 21 AUG. 2021 BY DR. TESS LAWRIE AND DR. EDMUND FORDHAM

We have considered the extracts quoted below from the current National Covid Clinical Evidence Taskforce (NCCET) statement regarding the use of ivermectin in Covid-19. Our responses and commentary to these statements follow.

The current recommendation regarding ivermectin is as follows:

"Despite some early suggestions that ivermectin may provide both prophylactic and therapeutic benefit, the available research evidence does not yet provide reasonable certainty to recommend for or against the use of ivermectin."

And a specific critique asserts:

"Some widely discussed meta-analyses of ivermectin studies (e.g. The British Ivermectin Research Development (BIRD) Group meta analysis) have significant weaknesses, for example they include a large trial which has been discredited and retracted (Elgazzar et al.). Even in these reviews, when patient populations are separated by severity and comparisons to active treatments removed, no meaningful effect is found."

A. Overall assertion.

The available research evidence from **(i)** randomised controlled trials, **(ii)**observational trials, **(iii)** clinical success of multiple unrelated clinicians in many parts of the world, **(iv)** the phenomenology of whole country effects with both temporal correlation to introduction of ivermectin, and the contrasting experimental control of states or other administrative divisions with differing public health policies, all point overwhelmingly to the efficacy of ivermectin in both the prevention and management of Covid-19 [1].

The phrase "reasonable certainty" is undefined and vague, and no declaration as to what level of certainty would be regarded as "reasonable" is given. It is not a "level of certainty" recognised in formal meta-analysis.

The formal review of Bryant et al. [2] found "moderate certainty" evidence which is normally considered more than sufficient for regulatory approval of existing drugs in a new indication. For example, corticosteroids have become a standard of care for inflammatory stage Covid-19 on the basis of a single RCT of dexamethasone [3], on what is generally considered as "moderate certainty" evidence. The review of Bryant et al. [2] found "moderate certainty" evidence over 24 RCTs, not just one.

The prophylaxis trials were assessed as “low certainty” but report quantitative results in prophylaxis fully consistent with much larger observational trials, some very large [4].

“Low” certainty evidence in the past has been sufficient for the inclusion of ivermectin on the WHO Essential Medicines (Children) (EMLc) List in the indication of scabies [5] where measures of effect were in fact inferior to the previously recommended drugs.

On the basis of prior decisions in Covid-19, and for ivermectin in an anti-parasitic indication, the continued hesitancy of regulatory authorities worldwide with respect to ivermectin in Covid-19 is completely anomalous.

“Reasonable” is not recognised in formal meta-analysis, according to PRISMA guidelines [6], which recognise very low, low, moderate, and high certainty, typically from appraisals of Risk of Bias in contributing studies. There is always a measure of subjectivity in such appraisals but allocation of grades and conclusions of “levels of certainty” follow strict rules.

“High” certainty evidence is rare, confined to strong effects in very large clinical trials or meta-analyses pooling several such large studies.

“Moderate” certainty evidence is generally considered extremely powerful, and more than sufficient for regulatory approval of existing medicines in new indications.

“Low” certainty evidence has led to prior regulatory approvals to meet clear clinical needs. We address subsequent critiques of [2] below, under (B).

Much of the evidence was summarised as early as November 2020 by Kory *et al.* and now published in their narrative review in the *American Journal of Therapeutics* [1] (May- June issue).

The formal systematic review and meta-analysis by Bryant *et al.* [2] (July-August issue of same journal) was an exercise in support of the narrative review of Kory et al. [1], but restricted by deliberate choice to Randomised Controlled Trials (RCTs) only, as conventionally considered the highest quality of medical evidence.

For example, the review protocol excluded by policy notable studies such as the ICON study [7] demonstrating strong advantage in overall mortality in a large propensity-matched retrospective study, with obvious confounders addressed, simply because the patient allocation was not randomised. The most pronounced benefits were seen in severe disease.

Similarly in prophylaxis the very large trial of Behera *et al.* [4] with well over 3000 participants was excluded for the same reasons, though delivering quantitative measures of Risk Reduction (for infection) very close to the meta-analysis of the RCTs.

Including high-quality observational trials was found to lead to results just as reliable as RCTs in the synthesis of Anglemyer [15]. Adding the many known observational trials to the meta-analysis of Bryant *et al.* [2] is likely only to strengthen the findings further.

In any serious scientific appraisal, the evidence presented by these non-randomised trials cannot be dismissed as of no account, just because they lacked certain formal constraints, being part of the experience of hard-working clinicians in stressed circumstances.

(**Authorship note:** To pre-empt widespread misunderstandings, what is called "the BiRD group" or more accurately the British Ivermectin Recommendation Development panel (*not* "Research") was an *ad hoc* panel of clinicians, researchers and other stakeholders, with international representation, convened for an "Evidence to Decision" framework event on 20 February 2021 to hear the evidence summarised in an earlier version of reference [2].

The BiRD panel published its recommendation quite separately from Bryant *et al.* [2]. The authors of Bryant *et al.* [2] comprise: two members of the steering group (who did not vote), four ordinary members of the BiRD panel (consumer representative, health economist and two active clinicians), and one professional systematic reviewer who did not take part in the BiRD panel but contributed extensively to the research.

Hence the authors of Bryant *et al.* [2] are not congruent with the membership of the BiRD panel, a much larger group, and include one major contributor who remains uninvolved with BiRD.)

B. Subsequent critiques of [2]:

Some widely discussed meta-analyses of ivermectin studies (e.g. The British Ivermectin Research Development (BIRD) Group meta analysis) have significant weaknesses, for example they include a large trial which has been discredited and retracted (Elgazzar et al.). Even in these reviews, when patient populations are separated by severity and comparisons to active treatments removed, no meaningful effect is found.

These claims are categorically false, though regularly asserted by those with an agenda driven independently of the actual evidence.

1/ The claim of "*significant weakness*" in [2] is confined entirely to the inclusion of the disputed trial of Elgazzar [8]. The review of [2] was exhaustive of all RCTs found at the review closure and the first anywhere to follow strict PRISMA guidelines [6]. At the time of publication of [2], there was no reason to doubt the veracity of Elgazzar [8]; indeed it would have been a protocol violation to exclude it.

It is untrue to state that the study has been "retracted". Prof. Elgazzar has retracted nothing, asserts defamation and has intimated legal action. The server *ResearchGate* has withdrawn the preprint in response to a complaint, without giving Prof Elgazzar the right of reply. Whether or not the study is "discredited" remains to be determined.

Notwithstanding these uncertainties, a "Letter to the Editor" of *Am. J. Therap.* [9] concerning the Elgazzar dispute has been accepted for publication and should appear shortly. We show explicitly the consequences of deleting the disputed trial in the

leading mortality outcome, and in prophyalxis (Elgazzar [8] contributed arms to both outcomes). Whilst the quantitative result inevitably changes, the mortality outcome remains clear, demonstrating a 49% reduction in favour of ivermectin (aRR=0.51, 95% CI 0.27 – 0.95).

Similarly, the prophylaxis outcome remains in quantitative effect virtually unchanged, and in fact slightly improved in that the point estimate for reduction in Covid-19 infection increases from 86% to 87% (aRR=0.13, 95% CI 0.08 – 0.21), with similarly tight 95% Confidence Intervals again fully consistent with the larger observational trials of ivermectin prophylaxis.

NCCET: "W*hen patient populations are separated by severity and comparisons to active treatments removed, no meaningful effect is found*."

This assertion lacks any logic. Removing comparison to active treatments would be a pointless exercise. The pragmatic and pre-specified inclusion of "active" treatment comparators is a strength, not a weakness, of Bryant et al. [2] and would lead to *under*-estimation of the effect of ivermectin, not over-estimation. In other words, Bryant *et al.* [2] is conservative by design, **against** *t*he effect of ivermectin. The fact that consistent positive effects are observed makes the results *more* convincing, not less.

Separation by severity has been dealt with explicitly by Neil and Fenton [10] who apply a Bayesian meta-analysis to the full set of trials in Bryant *et al.* [2], with an explicit separation of disease severity between "severe" and "mild-moderate". The study of Niaee [11] was excluded because disease severity was not distinguished. A "leave one out" sensitivity analysis is performed systematically on the entire data set, including the disputed trial of Elgazzar [8]. Again the conclusions remain robust to the removal of particular studies. For some studies with known heterogeneity the results are actually improved.

Neil & Fenton [10] find for severe disease a 90.7% posterior probability that the risk ratio favours ivermectin, and for mild/moderate Covid-19 there is an 84.1% probability the risk ratio favours ivermectin. They conclude that the results support the conclusions of Bryant *et al.* [2] over other claims such as that of Roman *et* [12]. The removal of Elgazzar [8] (Niaee [11] already excluded) provides the worst reduction in evidence but still result in a Bayesian posterior probability of effective risk reduction of 77%.

Other meta-analyses have been accepted for publication [12], in spite of demonstrated reporting errors available at pre-print stage, with very similar titles to [2] but asserting the opposite conclusions. Roman *et al.* [12] make a limited selection (1173 patients over 10 trials compared to 3406 patients over 24 trials in [2]) of the trials reviewed in [2]. The assertions in [12] commit the elementary fallacy of supposing that lack of statistically significant evidence (in their highly selective survey) is the same thing as a positive demonstration of no benefit. These claims of Roman *et al.* [12] were dismissed by Neil & Fenton [13], an earlier version of [10].

Similar assertions have been made by propagandists in news media [14] but are simply untrue, as demonstrated explicitly in [9].

The context where essentially all studies are referenced to placebo (or non-pharmaceutical precautions) is prophylaxis. As previously mentioned, the

prophylaxis effect reported in [2] is actually slightly improved by the removal of Elgazzar [8], and consistent with large non-randomised trials of ivermectin prophylaxis. There is no question of categorising by severity in the prophylaxis context and virtually all studies are referenced against no active comparators. The reduction in infection risk by 87% cannot be said to constitute "no meaningful effect". It is a very strong effect, achieved with ivermectin alone (or in one trial, combined with topical iota-carageenan nasal sprays).

Moreover, there has been no credible challenge to the prophylaxis results. It is not credible that ivermectin should achieve a prophylactic effect (by whatever mechanism) and fail to achieve a therapeutic effect, at least in the initial (viremic) phase of the illness.

The authors are principals of Evidence Based Medicine Consultancy Ltd., in Bath, England

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OPEN LETTER

14 October 2021

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Re: SECOND CALL for an Urgent Review of the NCCET Recommendation regarding the use of ivermectin in the management of COVID-19

I refer to my previous Open Letter calling for an urgent review of the NCCET recommendations regarding the use of ivermectin in the management of COVID-19 (dated 21 August) which remains unanswered (see copy attached)

Recent Developments

Since the writing of Open Letter there have been several important developments with regard to the COVID-19 pandemic, including:

1. The issuance of TGA "New restrictions on prescribing ivermectin for COVID-19 (10 Sept. 2021) https://www.tga.gov.au/media-release/new-restrictions-prescribing-ivermectin-covid-19
2. Notice of an amendment to the current Poisons Standard under paragraph 52D(2)(a) of the Therapeutic Goods Act 1989 (10 Sept. 2021)
3. Reports of the near eradication of COVID-19 in the Indian State of Uttar Pradesh (230 million people) using ivermectin combination therapy despite a vaccination rate below 6%.
4. Multiple reports of diminishing mRNA "vaccine" protection against the Delta COVID-19 virus strain following calls for "vaccine" boosters
5. An orchestrated and irresponsible mainstream "media science" campaign aiming to discredit the use of ivermectin on safety grounds.

Additional Public Information on the Safety of Ivermectin

The current NCCET recommendation continues to question the safety of ivermectin despite its worldwide use (4 billion doses) for more than 3 decades and the inclusion of ivermectin on the World Health Organisation Model List of Essential Medicines.

In fact, ivermectin is known to have a wide margin of safety compared to most drugs including many non-prescription medications.

Prior to the pandemic, the Australian Therapeutics Goods Administration (TGA) previously had no significant concerns regarding the safety of ivermectin. According to the TGA Australian Public Assessment Report for Ivermectin – 2013 (see attached).

- Page 11: “Escalation to a single dose of 120 mg (up to 2 mg/kg), 10 times the approved dose and 5 times the anticipated head lice dose, also produced no mydriatic effect. This supports the safety of ivermectin at the proposed dose and provides a significant margin of safety.”

- Page 18: the drug “showed good tolerability and no safety concerns at doses ranging from 30 to 120 mg, that is, up to 10 times the proposed dose of 200 µg/kg for treatment of scabies”.

- Page 39: The TGA clinical evaluator found that there were no significant safety concerns reported with the use of ivermectin in any of the published studies.

There were 3 stated reasons for the TGA action in preventing ivermectin from being used in the treatment of COVID-19:

Reason 1. ivermectin use might dissuade people from being vaccinated
Reason 2. ivermectin was associated with serious adverse events including “severe nausea, vomiting, dizziness, neurological effects such as dizziness, seizures and coma”.
Reason 3. ivermectin prescribing for COVID-19 might lead to shortages of this medication for other approved indications.

Reasons 1 and 3 do not justify the prohibition of ivermectin prescribing for the treatment of COVID-19.

With regard to Reason 2 – this contradicts the TGA’s prior assessment of the safety of ivermectin (above).

Ivermectin National Treatment Programmes

Clinical trials are fundamentally designed to randomly select a relatively small group of individuals for specified treatments and observe safety and efficacy. The results, if statistically powered correctly, can then be extrapolated to the population at large. However, in the case of ivermectin, not only are there more than 60 published clinical trials available, but several countries have embraced the use of ivermectin for the treatment of COVID-19 with success and treatment data is available on huge populations which provide important efficacy data.

In addition to the successful national treatment programmes in countries such as Mexico, Argentina and Peru, the NCCET should now be aware of the success in treating COVID-19 individuals with ivermectin in the Indian State of Uttar Pradesh.

https://www.thegatewaypundit.com/2021/09/huge-uttar-pradesh-india-announces-state-covid-19-free-proving-effectiveness-deworming-drug-ivermectin/?utm_source=Twitter&utm_medium=PostTopSharingButtons&utm_campaign=websitesharingbuttons

https://www.thedesertreview.com/opinion/columnists/indias-ivermectin-blackout---part-v-the-secret-revealed/article_9a37d9a8-1fb2-11ec-a94b-47343582647b.html

https://osf.io/preprints/socarxiv/r93g4/

https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3765018

Ivermectin based combination therapy was administered as early and preventative treatment in all family contacts as part of the "Uttar Pradesh Covid Control Model". Using this therapeutic approach, COVID-19 was virtually eliminated in a population of 230 million people with a vaccination rate of less than 6% (compares to the US fully vaccinated rate at the same time of 54%). This result is in direct contrast to the comparable State of Kerala, a small state located in Southern India that is over-dependent on vaccines and restricted ivermectin use to more severe cases and late treatment if used at all.

Large scale observational studies such as this can provide valid and reliable real-world data and, in most cases, there is little evidence that the results of observational studies and RCTs systematically disagree (Reference 6).

https://www.researchgate.net/publication/261998443_Healthcare_outcomes_assessed_with_observational_study_designs_compared_with_those_assessed_in_randomized_trials

The regulatory agencies appear willing to provisionally release new drugs to treat COVID-19 on the basis of very limited safety and efficacy data (sometimes involving a relatively limited clinical trial data and/or no long-term safety data (eg. mRNA vaccines, molnupiravir and remdesivir). However, the NCCET appears to largely ignore the compelling body of evidence supporting the safe and effective use of ivermectin in more than 30 randomised clinical trials (RCTs) involving more than 20,000 patients and successful national ivermectin treatment programmes.

Literature Review and Meta-analyses

The NCCET continues to rely (and defends) an arbitrary selection of 18 published clinical trials upon which to base its current negative recommendation for ivermectin use. In contrast to the sophisticated meta-analysis methods employed in the published reviews on ivermectin (References 7 and 8), the NCCET has failed to detail or define its informal method of assessment which were used to arrive at the current recommendation.

Rather than relying on the results of any one clinical trial, properly conducted meta-analyses of a larger number of randomised controlled trials by highly trained and experienced staff are the most powerful tool in drawing reliable conclusions from pooled data. However, biases can be introduced in any meta-analysis. This is why it is important to publish the protocols and methods used in any meta-analysis so the work can be critically assessed for reliability.

A recent meta-analysis of ivermectin was conducted by the Cochrane group (Reference 9). However, according to a response to this meta-analysis by Fordham, Lawrie, MacGilchrist and Bryant (in pre-print, see attached Reference 10), the Cochrane report suffers from no less than 11 significant analytical and methodological defects rendering the conclusions unreliable – not the least of which, to give but one example, was the author's treatment of the important analysis of mortality.

Out of 24 available RCTs identified for the review, the authors chose only 4 to include in their mortality analysis, a small subset of those available. The Cochrane authors split this data up further into two separate analyses. This effectively dilutes their

findings to the extent that a meaningful result from meta-analysis was not possible. Instead of utilising all available evidence and presenting appropriate caveats around such wider evidence, as would normally be done according to accepted protocols, they present an empty review with considerable bulk but little useful analysis.

Conclusions

The reported diminishing efficacy of the COVID-19 vaccines to protect against the emergence of SARS-Co-2 variants demands an urgent review of the use of ivermectin.

I repeat my previous message (21 August Open Letter) to the NCCET and again request an urgent review of the recommendations regarding ivermectin:

"The current approach to symptomatic COVID-19 individuals is largely to do nothing and simply observe until they either get better or get worse, perhaps much worse, and need to go to hospital. The do-nothing approach places enormous strain on our health care system. Evidence for this 'do nothing, watch and observe' approach is lacking. Ivermectin offers a potentially effective, low cost, safe and rational approach to the management of such individuals with little or no disadvantage. The NCCET recommendation on ivermectin is considered to be misinformation by many experts and is viewed as contributing to needless hospitalisation – but for this recommendation, many Covid-19 infected individuals could be receiving early effective treatment."

Regards,

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