ACMS MEETING – Out of session

8 September 2021

IVERMECTIN

Delegate-initiated scheduling proposal and reasons for the proposal

The Delegate is seeking advice from the Advisory Committee on Medicines Scheduling (ACMS) on a scheduling proposal to amend the current Poisons Standard with respect to oral ivermectin for human use.

Prescribing for human use

Concerns have been raised regarding the increase in off-label prescribing of oral ivermectin as a potential therapy for prophylaxis or treatment of COVID-19. Ivermectin is not currently approved in any OECD countries for COVID-19. However, there has been a noticeable increase in prescribing of oral ivermectin for this purpose.

There are numerous associated public health risks in relation to this practice. Persons who take ivermectin for COVID-19 believe themselves to be protected from the disease and decide not to get vaccinated as part of the national vaccination program. Similarly, persons who take ivermectin for COVID-19 decide not to get tested for COVID-19 or to seek appropriate medical care when they develop symptoms. As a result, use of oral ivermectin for unapproved COVID-19 indications has the potential to spread the risk of infection throughout the community.

Oral ivermectin also has the potential for severe adverse events when taken in the high doses described in social media and other sources for treatment of COVID-19 infection. While oral ivermectin is generally well-tolerated at the recommended dose for the approved indications, there is insufficient data to support higher dosages.

STROMECTOL ivermectin 3mg tablet blister pack (AUST R 181338) is the only oral ivermectin product registered on the Australian Register of Therapeutic Goods (ARTG). It has approved indications for the treatment of river blindness (onchocerciasis), threadworm involving the intestines (intestinal strongyloidiasis) and scabies.

The TGA has observed a significant increase in the volume of supply of STROMECTOL over the last 24 months (see Table 1 below). If this volume of supply is maintained, it has the potential to lead to material shortages for the treatment of approved indications in Australia. Any shortages of STROMECTOL would disproportionately impact those in vulnerable communities, in particular, the Aboriginal and Torres Strait Islander communities.

Table 1: Total supply (private & PBS prescriptions) August 2019 to July 2021 – packs of Stromectol tablets (ivermectin 3mg)

Month	8/19	9/19	10/19	11/19	12/19	1/20	2/20	3/20	4/20	5/20	6/20	7/20
Stromectol supply (number packs)	s47											

Month	8/20	9/20	10/20	11/20	12/20	1/21	2/21	3/21	4/21	5/21	6/21	7/21
Stromectol supply (number packs)	s47											

In mid-2021, a national medicines shortage of ivermectin 3 mg was reported to the TGA. While a national shortage has been resolved, local level shortages in southwestern and western Sydney have been advised to the TGA.

It is proposed that the specific health risks associated with off-label prescribing and potential local or national medicine shortages for the approved indications could be mitigated by restricting off-label prescribing to specialist medical practitioners.

In order to restrict prescribing of ivermectin for off-label indications, the Scheduling Delegate is proposing to make urgent amendments to the current Poisons Standard to create a new Appendix D entry for ivermectin (similar to the measures taken for hydroxychloroquine in March 2020). This is consistent with the scheduling factors for Appendix D outlined in the Australian Health Ministers' Advisory Council Scheduling Policy Framework for Medicines and Chemicals.

The purpose of the amendments would be to limit the use of oral ivermectin for approved indications only, except when prescribed by certain specialists. Patients suffering, or suspected to be suffering from, COVID-19 should seek appropriate medical care. It is also noted that prescribing of approved therapies for COVID-19, sotrovimab and remdesivir, is currently undertaken by hospital physicians and not general practitioners. There is also a critical need to ensure that general practitioners (in particular, those treating Aboriginal and Torres Strait Islander populations, but also more broadly) can continue prescribing ivermectin for approved indications.

Personal importation:

The personal importation scheme allows for the importation of a maximum of three months' supply of unregistered products (not included in the ARTG) at the maximum dose recommended by the manufacturer. If the goods contain Schedule 4 substances, then the importer must have a written authority issued by a medical practitioner registered under a law of a state or territory (in practice, a prescription).

The TGA works closely with the Australian Border Force to detect potentially unlawful importations of therapeutic goods for assessment by the TGA. As a result of this work, detections of ivermectin have increased significantly in recent months, more than 10-fold. An initial assessment of these importations by the TGA indicates:

- Imports referred to the TGA for assessment between July 2021 to early September 2021 include a total of s47 tablets of ivermectin:
    - in most instances, the quantity being imported exceeded the three months' supply; and
    - to date, no valid prescriptions, or other written authorities, have been provided to the TGA to support the release of the tablets under the personal importation scheme.
- In the matters assessed by the TGA to date, the tablets appear to have been manufactured in India and are presented in 6mg and 12mg dosages, usually in packs of 10. Note that the ARTG registered product is available in packs of 3 x 3mg tablets.
- The referrals received by the TGA from the ABF relate to ivermectin intended for human (not animal) use.
- The importers contacted to date have confirmed that the respective importation of ivermectin was intended for the prevention and/or treatment of COVID-19.

Agricultural and veterinary use

There are 185 veterinary products containing ivermectin included in PubCRIS. This includes oral and injectable products, as well as pour-on or jetting fluid products. It is considered that placing scheduling restrictions on the supply of veterinary ivermectin would be more difficult to achieve in terms of specifying evidence to establish appropriate need. Instead, communication and education activities may be necessary, as well as consultation with the Australian Veterinary Association and Veterinary Boards.

Current Scheduling

Schedule 4

IVERMECTIN:

for human use; or

for the treatment of mange in dogs

Schedule 5

IVERMECTIN for use in animals:

a. in preparations for the prophylaxis of heartworm in cats and dogs;

b. in the intraruminal implants containing 160mg or less of ivermectin;

c. in preparations containing 3.5 per cent or less of ivermectin when packed in child-resistant packaging or in packaging approved by the relevant registration authority; or

d. in other preparations containing 2 per cent or less of ivermectin.

Schedule 7

IVERMECTIN **except** when included in Schedule 4 or 5.

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IVERMECTIN

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Proposed scheduling

Proposal to amend Appendix D to include additional controls to restrict the availability of S4 ivermectin for human use as follows:

Preparations for oral administration of ivermectin may be prescribed for:

(a) an indication that is accepted in relation to the inclusion of ivermectin in tablet dosage form in the Australian Register of Therapeutic Goods for human therapeutic use (an ***accepted indication***); or

(b) an indication that is not an accepted 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 recognised specialties:

- emergency medicine;
- intensive care medicine; and
- infectious disease.

Note: Accepted 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.

Delegate questions

1. Is ivermectin used for any other parasitic conditions that would warrant genuine off-label prescribing by GPs?
2. Is there an alternative scheduling mechanism to restrict access?
3. If so, is the proposed wording appropriate?
4. Are there other specialists that should be reflected in the restrictions, for example, gastroenterology?

Attachment 1: Australian Register of Therapeutic Goods (ARTG)

As of 6 September 2021, there was one oral prescription medicine currently included in the Australian Register of Therapeutic Goods (ARTG) that contains ivermectin as an active ingredient. The other two products are topical creams (included for information only as no changes are proposed to the scheduling of these products).

STROMECTROL ivermectin 3mg tablet blister pack	Merck Sharp & Dohme (Australia) Pty Ltd	Onchocerciasis and intestinal strongyloidiasis (anguillulosis). Crusted scabies in conjunction with topical therapy. Human sarcoptic scabies when prior topical treatment has failed or is contraindicated. Treatment is only justified when the diagnosis of scabies has been established clinically and/or by parasitological examination. Without formal diagnosis, treatment is not justified in case of pruritis alone.	4
VASTREKA ivermectin 10mg/g cream	Galderma Australia Pty Ltd	Topical treatment of inflammatory lesions of rosacea (papulo-pustular) in adult patients 18 years and over.	4
SOOLANTRA ivermectin 10mg/g cream	Galderma Australia Pty Ltd	Topical treatment of inflammatory lesions of rosacea (papulo-pustular) in adult patients 18 years and over.	4

As of 6 September 2021, there were 185 products containing ivermectin on the Public Chemical Registration Information System Search (PubCRIS).

Attachment 2: Poisons Standard Appendix D Entries

The Australian Health Ministers' Advisory Council Scheduling Policy Framework for Medicines and Chemicals (Version 1.0 January 2018) relevantly provides the following factors in relation to Appendix D:

Inclusion of a substance in Appendix D may be considered by the Secretary for any human or veterinary medicine where the assessment of the proposal identifies:

- *a specific health risk that may be mitigated by restricting availability through **specialist medical practitioners**; or*
- *significant potential for illicit diversion and/or abuse which does not warrant inclusion in Schedule 8 but warrants particular control of possession; or*
- *a specific high potential for abuse, particular international treaty restrictions on availability or other matters of national public health policy which when weighed against the need for access to the substance, warrants, in addition to inclusion of the substance in Schedule 4 or 8, further restrictions on access, such as authorisation by the Secretary of the Department of Health or some other appropriate State/Territory or Commonwealth authority.*

Inclusion of a substance in Appendix D may be made following consultation with the appropriate advisory committee or a joint meeting, and must take into account the implications for professional practice by affected healthcare practitioners and regulatory control by the states and territories.

In practice, the controls may be specified in relation to formally recognised specialties.

Record of the 35th meeting (out of session) of the Advisory Committee on Medicines Scheduling

08 September 2021

TRIM Reference no. D21-3074411

Contents

1 Preliminary Matters

1.1 Opening of the Meeting

The 35th meeting of the Advisory Committee on Medicines Scheduling ([ACMS]) was held via videoconference on 08 September 2021.

The meeting was chaired by s22 , who opened the meeting at 10:32 am and welcomed attending members and observers.

Members were informed that the discussions and recommendations of the committee are confidential until the decisions are published.

A quorum was present. Those present at the meeting were:

Minister Appointments	**Jurisdictional Members**
s22	

Standing and invited observers:

Dr Tony GILL	Commonwealth Dept. of Health
Adj Prof John SKERRITT	Deputy Secretary, Health Products Regulation Group, Commonwealth Dept. of Health
Ms Gillian MITCHELL	First Assistant Secretary, Regulatory Practice and Support Division, Commonwealth Dept. of Health
Mr Benjamin NOYEN	Assistant Secretary, Regulatory Engagement & Planning Branch, Commonwealth Dept. of Health
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APVMA

Apologies

s22

1.2 Conflict of Interest

Conflict of interest declarations were received from all members. Declared conflicts froms22 s22 and s22 were discussed and it was agreed that they could be present and fully participate in the committee discussions.

s22

2 Proposed Changes to the Poisons Standard

2.1 Ivermectin

The TGA Delegate presented a discussion paper detailing concerns regarding increasing off-label prescribing of oral ivermectin for the prevention and treatment of COVID-19 and request for advice on the Delegate's proposal for an urgent scheduling amendment to place additional controls on supply of oral ivermectin.

The Committee noted that the TGA has observed a significant increase in the volume of supply of ivermectin tablets over the last 24 months (private and PBS prescriptions), particularly in July

and August 2021. Members were also aware of reports from pharmacies of increased prescribing ivermectin for COVID-19 and of some medical practices promoting the substance for this purpose, despite ivermectin not being approved for the prevention and treatment of COVID-19. The Committee noted that ivermectin is not currently registered or approved in any OECD countries for this purpose.

The Committee agreed that there were significant public health risks associated with the prescribing of ivermectin for COVID-19, including the likelihood that people who have been prescribed the substance for this purpose may believe themselves to be protected from the disease and not get vaccinated or tested and seek appropriate medical care if they developed symptoms. The Committee was concerned that the practice of prescribing ivermectin for COVID-19 presented a risk to the community through the spread of the disease as well as the risks to individuals using it for this purpose.

The Committee also noted that there is only one ARTG registered oral ivermectin product for human use; STROMECTOL ivermectin 3mg tablet blister pack (AUST R 181338), which has approved indications for the treatment of river blindness (onchocerciasis), threadworm involving the intestines (intestinal strongyloidiasis) and scabies. The Committee noted that the increased prescribing, if sustained, has the potential to lead to shortages, which would particularly impact Aboriginal and Torres Strait Islander communities who are at more risk of the conditions that require treatment with ivermectin. The Committee noted that there are topical ivermectin products registered on the ARTG, which are indicated for rosacea. Members noted that these products are not being used to treat COVID-19 and the proposed amendments would not impact topical ivermectin products.

The Committee unanimously agreed that there was a need to urgently restrict prescribing of oral ivermectin through amendments to the scheduling in the Poisons Standard. The Committee considered Appendix D entry proposed by the Delegate and discussed whether there were any other alternative approaches, including amending the Schedule 4 entry to restrict use, as this would allow for automatic adoption by the states and territories. One member queried whether Schedule 10 was an option. However, in response, the Committee agreed that ivermectin did not meet the Schedule 10 factors. The Committee noted that the purpose of Appendix D is to apply additional controls to Schedule 4 medicines and agreed that creating a new entry in Appendix D was the most appropriate mechanism for applying additional controls to oral ivermectin preparations. Some States and Territories noted that Appendix D is not automatically adopted and jurisdictional controls such as regulation amendment may be necessary.

The Committee noted that the Delegate's proposed scheduling amendments would not impact veterinary products. Members were aware of overseas reports of people suffering severe adverse effects after using ivermectin products intended for animals and raised the possibility of this practice increasing in Australia in the future. It was noted that placing scheduling restrictions on the supply of veterinary ivermectin would be more difficult and communication and education activities may be necessary.

Members considered the wording of the proposed Appendix D entry including whether there was merit in specifying indications that may or may not be prescribed or allowing for indications that had been registered or approved for general marketing overseas. Beyond allowing prescribing for the approved indications, the Committee agreed that it was not necessary to list specific indications and noted that it would be open to the specialists mentioned in paragraph (b) of the proposed new Appendix D entry to prescribe oral ivermectin for indications that had been registered or approved overseas, such as rosacea. The Committee noted that indications are not required to be documented on a prescription and considered the possibility of requiring the prescriber to declare on the script that it was being prescribed for an approved indication. Members noted that such an approach was outside of the scope of the Poisons Standard.

The Committee recommended the following regarding the proposed Appendix D entry:

- The entry should be limited to human therapeutic use.
- The word 'approved ARTG' indication was preferred to 'accepted' indication.
- The entry should allow for use in clinical trials that have been approved by the TGA.
- The wording should not imply any endorsement of prescribing for unapproved indications, particularly COVID-19.
- The relevant specialists listed in paragraph (b) should be confined to dermatologists, gastroenterologists, and infectious diseases specialists, as this would allow for prescribing for rare parasitic conditions that are not approved indications.
- The preamble 'an indication that is not an accepted indication' at the beginning of paragraph (b) was not entirely necessary.

The Committee requested that the Secretariat consult with relevant organisations to determine whether there is any use in other parasitic conditions that would warrant genuine off-label prescribing by GPs in Aboriginal and Torres Strait Islander communities.

The Committee also recommended that any communication about the changes be very clear about the intent of the restriction, particularly in relation to the risks of using ivermectin for the treatment and prevention of COVID-19 when it has not been registered or approved for this purpose.

3 Closure

The Chair closed the meeting at 12:32pm.

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s22

Date [08 September 2021]

Chair

35th Meeting of the Advisory Committee on Medicines Scheduling

National - Total vaccine doses administered	65,492,360
National - Weekly increase - Total vaccine doses recorded	191,868
National - Number of people 16 and over who have received at least 1 dose	20,139,881
National - Number of people 16 and over who have received at least 2 doses	19,845,963
National - Population 16 and over	20,629,070
ACT - Administration state - Total vaccine doses administered	2,010,213
NSW - Administration state - Total vaccine doses administered	20,308,679
NT - Administration state - Total vaccine doses administered	628,669
QLD - Administration state - Total vaccine doses administered	12,339,196
SA - Administration state - Total vaccine doses administered	4,580,754
TAS - Administration state - Total vaccine doses administered	1,493,937
VIC - Administration state - Total vaccine doses administered	17,031,913
WA - Administration state - Total vaccine doses administered	7,098,999
ACT - Administration state - Weekly increase doses recorded	9,407
NSW - Administration state - Weekly increase doses recorded	58,978
NT - Administration state - Weekly increase doses recorded	583
QLD - Administration state - Weekly increase doses recorded	33,981
SA - Administration state - Weekly increase doses recorded	18,085
TAS - Administration state - Weekly increase doses recorded	6,204
VIC - Administration state - Weekly increase doses recorded	51,132
WA - Administration state - Weekly increase doses recorded	13,498
National - Total doses administered in primary care	42,154,009
ACT - Population 16 and over	364,811
NSW - Population 16 and over	6,504,442
NT - Population 16 and over	193,211
QLD - Population 16 and over	4,161,009
SA - Population 16 and over	1,471,062
TAS - Population 16 and over	465,436
VIC - Population 16 and over	5,279,175
WA - Population 16 and over	2,185,967
ACT - Residence state - Number of people 16 and over who have received at least 1 dose	354,221
NSW - Residence state - Number of people 16 and over who have received at least 1 dose	6,329,413
NT - Residence state - Number of people 16 and over who have received at least 1 dose	171,185
QLD - Residence state - Number of people 16 and over who have received at least 1 dose	3,895,963
SA - Residence state - Number of people 16 and over who have received at least 1 dose	1,380,176
TAS - Residence state - Number of people 16 and over who have received at least 1 dose	444,040
VIC - Residence state - Number of people 16 and over who have received at least 1 dose	5,190,913
WA - Residence state - Number of people 16 and over who have received at least 1 dose	2,114,281
ACT - Residence state - Number of people 16 and over who have received at least 2 doses	349,038
NSW - Residence state - Number of people 16 and over who have received at least 2 doses	6,243,425
NT - Residence state - Number of people 16 and over who have received at least 2 doses	167,270
QLD - Residence state - Number of people 16 and over who have received at least 2 doses	3,837,846
SA - Residence state - Number of people 16 and over who have received at least 2 doses	1,354,224
TAS - Residence state - Number of people 16 and over who have received at least 2 doses	436,318
VIC - Residence state - Number of people 16 and over who have received at least 2 doses	5,126,036
WA - Residence state - Number of people 16 and over who have received at least 2 doses	2,087,324
Age group - 16-19 - Number of people who have received at least 1 dose	1,122,904
Age group - 20-24 - Number of people who have received at least 1 dose	1,521,903
Age group - 25-29 - Number of people who have received at least 1 dose	1,727,968

Age group - 30-34 - Number of people who have received at least 1 dose	1,821,666
Age group - 35-39 - Number of people who have received at least 1 dose	1,801,979
Age group - 40-44 - Number of people who have received at least 1 dose	1,663,089
Age group - 45-49 - Number of people who have received at least 1 dose	1,538,408
Age group - 50-54 - Number of people who have received at least 1 dose	1,605,343
Age group - 55-59 - Number of people who have received at least 1 dose	1,466,589
Age group - 60-64 - Number of people who have received at least 1 dose	1,456,597
Age group - 65-69 - Number of people who have received at least 1 dose	1,286,915
Age group - 70-74 - Number of people who have received at least 1 dose	1,123,626
Age group - 75-79 - Number of people who have received at least 1 dose	894,152
Age group - 80-84 - Number of people who have received at least 1 dose	563,565
Age group - 85-89 - Number of people who have received at least 1 dose	336,124
Age group - 90-94 - Number of people who have received at least 1 dose	158,043
Age group - 95+ - Number of people who have received at least 1 dose	51,010
Age group - 16-19 - Number of people who have received at least 2 doses	1,099,588
Age group - 20-24 - Number of people who have received at least 2 doses	1,487,471
Age group - 25-29 - Number of people who have received at least 2 doses	1,686,730
Age group - 30-34 - Number of people who have received at least 2 doses	1,783,050
Age group - 35-39 - Number of people who have received at least 2 doses	1,772,010
Age group - 40-44 - Number of people who have received at least 2 doses	1,640,444
Age group - 45-49 - Number of people who have received at least 2 doses	1,521,314
Age group - 50-54 - Number of people who have received at least 2 doses	1,589,695
Age group - 55-59 - Number of people who have received at least 2 doses	1,451,261
Age group - 60-64 - Number of people who have received at least 2 doses	1,440,565
Age group - 65-69 - Number of people who have received at least 2 doses	1,272,448
Age group - 70-74 - Number of people who have received at least 2 doses	1,113,382
Age group - 75-79 - Number of people who have received at least 2 doses	888,220
Age group - 80-84 - Number of people who have received at least 2 doses	559,985
Age group - 85-89 - Number of people who have received at least 2 doses	333,573
Age group - 90-94 - Number of people who have received at least 2 doses	156,331
Age group - 95+ - Number of people who have received at least 2 doses	49,896
Age group - 95+ - Population	49,975
Age group - 90-94 - Population	160,981
Age group - 85-89 - Population	323,304
Age group - 80-84 - Population	545,408
Age group - 75-79 - Population	807,195
Age group - 70-74 - Population	1,146,773
Age group - 65-69 - Population	1,280,143
Age group - 60-64 - Population	1,465,025
Age group - 55-59 - Population	1,550,507
Age group - 50-54 - Population	1,611,554
Age group - 45-49 - Population	1,650,035
Age group - 40-44 - Population	1,654,500
Age group - 35-39 - Population	1,867,387
Age group - 30-34 - Population	1,899,620
Age group - 25-29 - Population	1,822,031
Age group - 20-24 - Population	1,623,384
Age group - 16-19 - Population	1,171,248
Age group - 16-19 - F - Number of people who have received at least 1 dose	552,320
Age group - 16-19 - M - Number of people who have received at least 1 dose	569,519

Age group - 20-24 - F - Number of people who have received at least 1 dose	745,868
Age group - 20-24 - M - Number of people who have received at least 1 dose	768,928
Age group - 25-29 - F - Number of people who have received at least 1 dose	844,009
Age group - 25-29 - M - Number of people who have received at least 1 dose	872,922
Age group - 30-34 - F - Number of people who have received at least 1 dose	914,734
Age group - 30-34 - M - Number of people who have received at least 1 dose	897,689
Age group - 35-39 - F - Number of people who have received at least 1 dose	907,873
Age group - 35-39 - M - Number of people who have received at least 1 dose	888,514
Age group - 40-44 - F - Number of people who have received at least 1 dose	830,897
Age group - 40-44 - M - Number of people who have received at least 1 dose	828,922
Age group - 45-49 - F - Number of people who have received at least 1 dose	772,322
Age group - 45-49 - M - Number of people who have received at least 1 dose	763,975
Age group - 50-54 - F - Number of people who have received at least 1 dose	812,399
Age group - 50-54 - M - Number of people who have received at least 1 dose	790,933
Age group - 55-59 - F - Number of people who have received at least 1 dose	741,520
Age group - 55-59 - M - Number of people who have received at least 1 dose	722,648
Age group - 60-64 - F - Number of people who have received at least 1 dose	742,542
Age group - 60-64 - M - Number of people who have received at least 1 dose	710,977
Age group - 65-69 - F - Number of people who have received at least 1 dose	661,784
Age group - 65-69 - M - Number of people who have received at least 1 dose	622,074
Age group - 70-74 - F - Number of people who have received at least 1 dose	579,079
Age group - 70-74 - M - Number of people who have received at least 1 dose	542,459
Age group - 75-79 - F - Number of people who have received at least 1 dose	464,020
Age group - 75-79 - M - Number of people who have received at least 1 dose	429,013
Age group - 80-84 - F - Number of people who have received at least 1 dose	304,068
Age group - 80-84 - M - Number of people who have received at least 1 dose	258,917
Age group - 85-89 - F - Number of people who have received at least 1 dose	193,898
Age group - 85-89 - M - Number of people who have received at least 1 dose	141,909
Age group - 90-94 - F - Number of people who have received at least 1 dose	99,925
Age group - 90-94 - M - Number of people who have received at least 1 dose	57,923
Age group - 95+ - F - Number of people who have received at least 1 dose	36,568
Age group - 95+ - M - Number of people who have received at least 1 dose	14,325
Age group - 16-19 - F - Number of people who have received at least 2 doses	542,651
Age group - 16-19 - M - Number of people who have received at least 2 doses	556,514
Age group - 20-24 - F - Number of people who have received at least 2 doses	733,049
Age group - 20-24 - M - Number of people who have received at least 2 doses	750,244
Age group - 25-29 - F - Number of people who have received at least 2 doses	827,952
Age group - 25-29 - M - Number of people who have received at least 2 doses	851,426
Age group - 30-34 - F - Number of people who have received at least 2 doses	899,476
Age group - 30-34 - M - Number of people who have received at least 2 doses	877,438
Age group - 35-39 - F - Number of people who have received at least 2 doses	895,922
Age group - 35-39 - M - Number of people who have received at least 2 doses	872,511
Age group - 40-44 - F - Number of people who have received at least 2 doses	821,899
Age group - 40-44 - M - Number of people who have received at least 2 doses	816,522
Age group - 45-49 - F - Number of people who have received at least 2 doses	765,510
Age group - 45-49 - M - Number of people who have received at least 2 doses	754,600
Age group - 50-54 - F - Number of people who have received at least 2 doses	805,730
Age group - 50-54 - M - Number of people who have received at least 2 doses	782,886
Age group - 55-59 - F - Number of people who have received at least 2 doses	734,136
Age group - 55-59 - M - Number of people who have received at least 2 doses	716,098

Age group - 60-64 - F - Number of people who have received at least 2 doses	734,563
Age group - 60-64 - M - Number of people who have received at least 2 doses	704,755
Age group - 65-69 - F - Number of people who have received at least 2 doses	655,025
Age group - 65-69 - M - Number of people who have received at least 2 doses	616,163
Age group - 70-74 - F - Number of people who have received at least 2 doses	574,537
Age group - 70-74 - M - Number of people who have received at least 2 doses	537,968
Age group - 75-79 - F - Number of people who have received at least 2 doses	461,361
Age group - 75-79 - M - Number of people who have received at least 2 doses	426,357
Age group - 80-84 - F - Number of people who have received at least 2 doses	302,264
Age group - 80-84 - M - Number of people who have received at least 2 doses	257,454
Age group - 85-89 - F - Number of people who have received at least 2 doses	192,469
Age group - 85-89 - M - Number of people who have received at least 2 doses	140,975
Age group - 90-94 - F - Number of people who have received at least 2 doses	98,862
Age group - 90-94 - M - Number of people who have received at least 2 doses	57,389
Age group - 95+ - F - Number of people who have received at least 2 doses	35,816
Age group - 95+ - M - Number of people who have received at least 2 doses	14,035
ACT - Population 12-15	20,888
NSW - Population 12-15	399,352
NT - Population 12-15	13,190
QLD - Population 12-15	278,225
SA - Population 12-15	85,541
TAS - Population 12-15	27,469
VIC - Population 12-15	313,711
WA - Population 12-15	140,783
National - Population 12-15	1,279,387
ACT - Residence state - Number of people 12-15 who have received at least 1 dose	19,999
NSW - Residence state - Number of people 12-15 who have received at least 1 dose	307,001
NT - Residence state - Number of people 12-15 who have received at least 1 dose	10,022
QLD - Residence state - Number of people 12-15 who have received at least 1 dose	194,427
SA - Residence state - Number of people 12-15 who have received at least 1 dose	65,625
TAS - Residence state - Number of people 12-15 who have received at least 1 dose	21,913
VIC - Residence state - Number of people 12-15 who have received at least 1 dose	261,620
WA - Residence state - Number of people 12-15 who have received at least 1 dose	111,505
ACT - Residence state - Number of people 12-15 who have received at least 2 doses	19,325
NSW - Residence state - Number of people 12-15 who have received at least 2 doses	289,504
NT - Residence state - Number of people 12-15 who have received at least 2 doses	8,850
QLD - Residence state - Number of people 12-15 who have received at least 2 doses	178,139
SA - Residence state - Number of people 12-15 who have received at least 2 doses	61,010
TAS - Residence state - Number of people 12-15 who have received at least 2 doses	20,488
VIC - Residence state - Number of people 12-15 who have received at least 2 doses	245,463
WA - Residence state - Number of people 12-15 who have received at least 2 doses	101,171
National - Number of people 16 and over who have received 3 doses	14,368,201
National - Weekly increase - 16 and over who have received 3 doses	3,911
ACT - Residence state - 16 and over who have received 3 doses	282,069
NSW - Residence state - 16 and over who have received 3 doses	4,404,000
NT - Residence state - 16 and over who have received 3 doses	132,934
QLD - Residence state - 16 and over who have received 3 doses	2,511,281
SA - Residence state - 16 and over who have received 3 doses	1,030,864
TAS - Residence state - 16 and over who have received 3 doses	325,755
VIC - Residence state - 16 and over who have received 3 doses	3,816,274

WA - Residence state - 16 and over who have received 3 doses	1,738,433
Unknown - Residence state - 16 and over who have received 3 doses	126,591
ACT - Residence state - Weekly increase 16 and over who have received 3 doses	63
NSW - Residence state - Weekly increase 16 and over who have received 3 doses	1,675
NT - Residence state - Weekly increase 16 and over who have received 3 doses	<10
QLD - Residence state - Weekly increase 16 and over who have received 3 doses	1,060
SA - Residence state - Weekly increase 16 and over who have received 3 doses	208
TAS - Residence state - Weekly increase 16 and over who have received 3 doses	82
VIC - Residence state - Weekly increase 16 and over who have received 3 doses	977
WA - Residence state - Weekly increase 16 and over who have received 3 doses	428
ACT - Population 5-11	40,719
NSW - Population 5-11	711,525
NT - Population 5-11	25,120
QLD - Population 5-11	476,567
SA - Population 5-11	149,048
TAS - Population 5-11	45,549
VIC - Population 5-11	568,488
WA - Population 5-11	252,235
National - Population 5-11	2,269,663
ACT - Residence state - Number of people 5-11 who have received at least 1 dose	29,519
NSW - Residence state - Number of people 5-11 who have received at least 1 dose	327,379
NT - Residence state - Number of people 5-11 who have received at least 1 dose	11,347
QLD - Residence state - Number of people 5-11 who have received at least 1 dose	187,537
SA - Residence state - Number of people 5-11 who have received at least 1 dose	76,144
TAS - Residence state - Number of people 5-11 who have received at least 1 dose	25,662
VIC - Residence state - Number of people 5-11 who have received at least 1 dose	297,105
WA - Residence state - Number of people 5-11 who have received at least 1 dose	126,703
National - Number of people 5-11 who have received at least 1 dose	1,090,140
ACT - Residence state - Number of people 5-11 who have received at least 2 doses	26,376
NSW - Residence state - Number of people 5-11 who have received at least 2 doses	270,346
NT - Residence state - Number of people 5-11 who have received at least 2 doses	8,158
QLD - Residence state - Number of people 5-11 who have received at least 2 doses	144,632
SA - Residence state - Number of people 5-11 who have received at least 2 doses	61,331
TAS - Residence state - Number of people 5-11 who have received at least 2 doses	21,468
VIC - Residence state - Number of people 5-11 who have received at least 2 doses	236,466
WA - Residence state - Number of people 5-11 who have received at least 2 doses	97,569
National - Number of people 5-11 who have received at least 2 doses	871,057
National - Number of people 12-15 who have received at least 1 dose	1,001,886
National - Number of people 12-15 who have received at least 2 doses	931,804
ACT - Residence state - Percentage of eligible population 16 and over who have received 3 doses	80.8%
NSW - Residence state - Percentage of eligible population 16 and over who have received 3 doses	70.6%
NT - Residence state - Percentage of eligible population 16 and over who have received 3 doses	79.5%
QLD - Residence state - Percentage of eligible population 16 and over who have received 3 doses	65.5%
SA - Residence state - Percentage of eligible population 16 and over who have received 3 doses	76.2%
TAS - Residence state - Percentage of eligible population 16 and over who have received 3 doses	74.7%
VIC - Residence state - Percentage of eligible population 16 and over who have received 3 doses	74.5%
WA - Residence state - Percentage of eligible population 16 and over who have received 3 doses	83.3%
National - Percentage of eligible population 16 and over who have received 3 doses	72.4%
National - Number of Indigenous people 16 and over who have received 3 doses	247,088
National - Percentage of eligible Indigenous population 16 and over who have received 3 doses	56.6%

National - Indigenous population 16 and over eligible for a third dose	436,776
National - Population 16 and over eligible for a third dose	19,840,500
National - Number of people 16 and over who have received 4 doses	5,552,682
National - Weekly increase - 16 and over who have received 4 doses	23,240
ACT - Residence state - 16 and over who have received 4 doses	124,230
NSW - Residence state - 16 and over who have received 4 doses	1,771,644
NT - Residence state - 16 and over who have received 4 doses	30,325
QLD - Residence state - 16 and over who have received 4 doses	1,050,893
SA - Residence state - 16 and over who have received 4 doses	433,275
TAS - Residence state - 16 and over who have received 4 doses	148,162
VIC - Residence state - 16 and over who have received 4 doses	1,390,718
WA - Residence state - 16 and over who have received 4 doses	572,689
Unknown - Residence state - 16 and over who have received 4 doses	30,746
ACT - Residence state - Weekly increase 16 and over who have received 4 doses	725
NSW - Residence state - Weekly increase 16 and over who have received 4 doses	7,636
NT - Residence state - Weekly increase 16 and over who have received 4 doses	129
QLD - Residence state - Weekly increase 16 and over who have received 4 doses	3,835
SA - Residence state - Weekly increase 16 and over who have received 4 doses	1,670
TAS - Residence state - Weekly increase 16 and over who have received 4 doses	764
VIC - Residence state - Weekly increase 16 and over who have received 4 doses	6,759
WA - Residence state - Weekly increase 16 and over who have received 4 doses	1,781
National - Percentage of eligible population 30 and over who have received 4 doses	45.2%
National - Percentage of eligible population 65 and over who have received 4 doses	76.9%
National - Population 30 and over eligible for a fourth dose	12,135,074
National - Population 65 and over eligible for a fourth dose	4,020,640
National - Number of people 65 and over who have received 4 doses	3,092,730
National - Number of people 30 and over who have received at least 1 dose	15,767,106
National - Number of people 30 and over who have received at least 2 doses	15,572,174
National - Number of people 30 and over who have received 3 doses	12,172,659
National - Number of people 30 and over who have received 4 doses	5,489,551
National - Population 30 and over	16,012,407
ACT - Population 30 and over	268,806
NSW - Population 30 and over	5,065,001
NT - Population 30 and over	140,954
QLD - Population 30 and over	3,219,394
SA - Population 30 and over	1,157,853
TAS - Population 30 and over	368,927
VIC - Population 30 and over	4,079,079
WA - Population 30 and over	1,709,089
ACT - Residence state - Number of people 30 and over who have received at least 1 dose	274,712
NSW - Residence state - Number of people 30 and over who have received at least 1 dose	4,981,249
NT - Residence state - Number of people 30 and over who have received at least 1 dose	127,140
QLD - Residence state - Number of people 30 and over who have received at least 1 dose	3,046,494
SA - Residence state - Number of people 30 and over who have received at least 1 dose	1,097,584
TAS - Residence state - Number of people 30 and over who have received at least 1 dose	353,397
VIC - Residence state - Number of people 30 and over who have received at least 1 dose	4,056,780
WA - Residence state - Number of people 30 and over who have received at least 1 dose	1,657,153
ACT - Residence state - Number of people 30 and over who have received at least 2 doses	271,166
NSW - Residence state - Number of people 30 and over who have received at least 2 doses	4,922,311
NT - Residence state - Number of people 30 and over who have received at least 2 doses	124,915

QLD - Residence state - Number of people 30 and over who have received at least 2 doses	3,009,838
SA - Residence state - Number of people 30 and over who have received at least 2 doses	1,081,723
TAS - Residence state - Number of people 30 and over who have received at least 2 doses	348,526
VIC - Residence state - Number of people 30 and over who have received at least 2 doses	4,011,657
WA - Residence state - Number of people 30 and over who have received at least 2 doses	1,639,730
ACT - Residence state - Number of people 30 and over who have received 3 doses	231,884
NSW - Residence state - Number of people 30 and over who have received 3 doses	3,760,492
NT - Residence state - Number of people 30 and over who have received 3 doses	105,159
QLD - Residence state - Number of people 30 and over who have received 3 doses	2,184,436
SA - Residence state - Number of people 30 and over who have received 3 doses	882,254
TAS - Residence state - Number of people 30 and over who have received 3 doses	282,277
VIC - Residence state - Number of people 30 and over who have received 3 doses	3,194,247
WA - Residence state - Number of people 30 and over who have received 3 doses	1,437,669
ACT - Residence state - Number of people 30 and over who have received 4 doses	121,827
NSW - Residence state - Number of people 30 and over who have received 4 doses	1,750,436
NT - Residence state - Number of people 30 and over who have received 4 doses	29,632
QLD - Residence state - Number of people 30 and over who have received 4 doses	1,041,638
SA - Residence state - Number of people 30 and over who have received 4 doses	429,666
TAS - Residence state - Number of people 30 and over who have received 4 doses	146,786
VIC - Residence state - Number of people 30 and over who have received 4 doses	1,372,302
WA - Residence state - Number of people 30 and over who have received 4 doses	567,203
National - Number of people 65 and over who have received at least 1 dose	4,413,435
National - Number of people 65 and over who have received at least 2 doses	4,373,835
National - Number of people 65 and over who have received 3 doses	4,024,861
National - Population 65 and over	4,313,779
ACT - Population 65 and over	60,463
NSW - Population 65 and over	1,393,416
NT - Population 65 and over	21,593
QLD - Population 65 and over	864,448
SA - Population 65 and over	352,458
TAS - Population 65 and over	116,037
VIC - Population 65 and over	1,072,562
WA - Population 65 and over	431,884
ACT - Residence state - Number of people 65 and over who have received at least 1 dose	65,066
NSW - Residence state - Number of people 65 and over who have received at least 1 dose	1,427,181
NT - Residence state - Number of people 65 and over who have received at least 1 dose	20,664
QLD - Residence state - Number of people 65 and over who have received at least 1 dose	858,935
SA - Residence state - Number of people 65 and over who have received at least 1 dose	351,893
TAS - Residence state - Number of people 65 and over who have received at least 1 dose	115,457
VIC - Residence state - Number of people 65 and over who have received at least 1 dose	1,102,237
WA - Residence state - Number of people 65 and over who have received at least 1 dose	434,651
ACT - Residence state - Number of people 65 and over who have received at least 2 doses	64,254
NSW - Residence state - Number of people 65 and over who have received at least 2 doses	1,414,368
NT - Residence state - Number of people 65 and over who have received at least 2 doses	20,402
QLD - Residence state - Number of people 65 and over who have received at least 2 doses	852,556
SA - Residence state - Number of people 65 and over who have received at least 2 doses	349,208
TAS - Residence state - Number of people 65 and over who have received at least 2 doses	114,758
VIC - Residence state - Number of people 65 and over who have received at least 2 doses	1,091,625
WA - Residence state - Number of people 65 and over who have received at least 2 doses	431,587
ACT - Residence state - Number of people 65 and over who have received 3 doses	60,976

NSW - Residence state - Number of people 65 and over who have received 3 doses	1,289,305
NT - Residence state - Number of people 65 and over who have received 3 doses	18,598
QLD - Residence state - Number of people 65 and over who have received 3 doses	783,712
SA - Residence state - Number of people 65 and over who have received 3 doses	327,625
TAS - Residence state - Number of people 65 and over who have received 3 doses	108,421
VIC - Residence state - Number of people 65 and over who have received 3 doses	996,885
WA - Residence state - Number of people 65 and over who have received 3 doses	409,975
ACT - Residence state - Number of people 65 and over who have received 4 doses	51,985
NSW - Residence state - Number of people 65 and over who have received 4 doses	985,709
NT - Residence state - Number of people 65 and over who have received 4 doses	12,232
QLD - Residence state - Number of people 65 and over who have received 4 doses	613,948
SA - Residence state - Number of people 65 and over who have received 4 doses	260,487
TAS - Residence state - Number of people 65 and over who have received 4 doses	88,197
VIC - Residence state - Number of people 65 and over who have received 4 doses	748,255
WA - Residence state - Number of people 65 and over who have received 4 doses	312,805
National - Number of Indigenous people 16 and over who have received at least 1 dose	454,438
National - Number of Indigenous people 16 and over who have received at least 2 doses	437,120
National - Percentage of Indigenous population 16 and over who have received at least 1 dose	85.5%
National - Percentage of Indigenous population 16 and over who have received at least 2 doses	82.3%
National - Number of Indigenous people 12-15 who have received at least 1 dose	44,399
National - Number of Indigenous people 12-15 who have received at least 2 doses	37,838
National - Percentage of Indigenous population 12-15 who have received at least 1 dose	63.3%
National - Percentage of Indigenous population 12-15 who have received at least 2 doses	54.0%
ACT - Medicare state - Percentage of Indigenous population 16 and over who have received at least 1 dose	92.3%
ACT - Medicare state - Percentage of Indigenous population 16 and over who have received at least 2 doses	90.2%
ACT - Medicare state - Percentage of eligible Indigenous population 16 and over who have received 3 doses	65.7%
ACT - Medicare state - Percentage of eligible Indigenous population 30 and over who have received 4 doses	43.9%
NSW - Medicare state - Percentage of Indigenous population 16 and over who have received at least 1 dose	87.8%
NSW - Medicare state - Percentage of Indigenous population 16 and over who have received at least 2 doses	86.0%
NSW - Medicare state - Percentage of eligible Indigenous population 16 and over who have received 3 doses	53.3%
NSW - Medicare state - Percentage of eligible Indigenous population 30 and over who have received 4 doses	38.5%
NT - Medicare state - Percentage of Indigenous population 16 and over who have received at least 1 dose	90.3%
NT - Medicare state - Percentage of Indigenous population 16 and over who have received at least 2 doses	86.3%
NT - Medicare state - Percentage of eligible Indigenous population 16 and over who have received 3 doses	70.1%
NT - Medicare state - Percentage of eligible Indigenous population 30 and over who have received 4 doses	26.7%
QLD - Medicare state - Percentage of Indigenous population 16 and over who have received at least 1 dose	82.4%
QLD - Medicare state - Percentage of Indigenous population 16 and over who have received at least 2 doses	78.8%
QLD - Medicare state - Percentage of eligible Indigenous population 16 and over who have received 3 doses	49.2%
QLD - Medicare state - Percentage of eligible Indigenous population 30 and over who have received 4 doses	38.0%
SA - Medicare state - Percentage of Indigenous population 16 and over who have received at least 1 dose	81.4%
SA - Medicare state - Percentage of Indigenous population 16 and over who have received at least 2 doses	76.3%
SA - Medicare state - Percentage of eligible Indigenous population 16 and over who have received 3 doses	61.1%
SA - Medicare state - Percentage of eligible Indigenous population 30 and over who have received 4 doses	39.1%
TAS - Medicare state - Percentage of Indigenous population 16 and over who have received at least 1 dose	89.2%
TAS - Medicare state - Percentage of Indigenous population 16 and over who have received at least 2 doses	86.8%
TAS - Medicare state - Percentage of eligible Indigenous population 16 and over who have received 3 doses	60.2%
TAS - Medicare state - Percentage of eligible Indigenous population 30 and over who have received 4 doses	42.8%
VIC - Medicare state - Percentage of Indigenous population 16 and over who have received at least 1 dose	90.9%
VIC - Medicare state - Percentage of Indigenous population 16 and over who have received at least 2 doses	89.0%
VIC - Medicare state - Percentage of eligible Indigenous population 16 and over who have received 3 doses	62.6%

VIC - Medicare state - Percentage of eligible Indigenous population 30 and over who have received 4 doses	37.0%
WA - Medicare state - Percentage of Indigenous population 16 and over who have received at least 1 dose	87.5%
WA - Medicare state - Percentage of Indigenous population 16 and over who have received at least 2 doses	82.2%
WA - Medicare state - Percentage of eligible Indigenous population 16 and over who have received 3 doses	66.2%
WA - Medicare state - Percentage of eligible Indigenous population 30 and over who have received 4 doses	30.4%
Unknown - Medicare state - Percentage of Indigenous population 16 and over who have received at least 1 dose	72.6%
Unknown - Medicare state - Percentage of Indigenous population 16 and over who have received at least 2 doses	67.7%
Unknown - Medicare state - Percentage of eligible Indigenous population 16 and over who have received 3 doses	51.5%
Unknown - Medicare state - Percentage of eligible Indigenous population 30 and over who have received 4 doses	25.0%
National - Percentage of eligible Indigenous population 30 and over who have received 4 doses	35.6%
National - Weekly increase - Total doses recorded in primary care	184,960
National - Total doses administered - General Practice (incl other Commonwealth)	32,492,328
National - Weekly increase - Total doses recorded - General Practice (incl other Commonwealth)	110,162
National - Total doses administered - Pharmacy	9,661,681
National - Weekly increase - Total doses recorded - Pharmacy	74,798
ACT - Medicare state - Total doses administered by jurisdictions - primary care	710,028
ACT - Medicare state - Weekly increase - Total doses recorded by jurisdictions - primary care	5,459
NSW - Medicare state - Total doses administered by jurisdictions - primary care	14,459,693
NSW - Medicare state - Weekly increase - Total doses recorded by jurisdictions - primary care	57,244
NT - Medicare state - Total doses administered by jurisdictions - primary care	242,090
NT - Medicare state - Weekly increase - Total doses recorded by jurisdictions - primary care	556
QLD - Medicare state - Total doses administered by jurisdictions - primary care	8,162,305
QLD - Medicare state - Weekly increase - Total doses recorded by jurisdictions - primary care	34,551
SA - Medicare state - Total doses administered by jurisdictions - primary care	2,604,225
SA - Medicare state - Weekly increase - Total doses recorded by jurisdictions - primary care	17,854
TAS - Medicare state - Total doses administered by jurisdictions - primary care	824,920
TAS - Medicare state - Weekly increase - Total doses recorded by jurisdictions - primary care	6,196
VIC - Medicare state - Total doses administered by jurisdictions - primary care	10,449,139
VIC - Medicare state - Weekly increase - Total doses recorded by jurisdictions - primary care	50,616
WA - Medicare state - Total doses administered by jurisdictions - primary care	4,342,951
WA - Medicare state - Weekly increase - Total doses recorded by jurisdictions - primary care	13,510
Unknown - Medicare state - Total doses administered by jurisdictions - primary care	358,658

Based on data from the Australia Immunisation Register as at 11:59pm 22-Mar-2023
Administration state indicates the state where a vaccine was administered.
Residential state may differ from the state where a vaccine was administered.
National population will not equal the sum of listed jurisdictions /age groups / sex due to a small number of people counted in national population residing in some 'other' territories, or due to incomplete or missing demographic information

ACMS MEETING #40

16 NOVEMBER 2022

AGENDA PAPER

Ivermectin

Referred scheduling proposal

The delegate[1] of the Secretary of the Department of Health and Aged Care that is responsible for medicines scheduling (the **Delegate**) is seeking advice from the Advisory Committee on Medicines Scheduling (the **Committee**) on a scheduling proposal with respect to ivermectin. The applicant has proposed deletion of the Appendix D entry relating to ivermectin. This will remove the restrictions on the prescription of ivermectin, which is currently limited to approved indications for general practitioners and specialists except for those in nominated fields. The restrictions were originally implemented due to concerns regarding the significant increase in off-label prescribing of ivermectin for the prevention and treatment of COVID-19.

Proposed scheduling

No changes are proposed for the entries for ivermectin in Schedules 4, 5 or 7. The applicant only proposes to remove the Appendix D entry for ivermectin, as depicted below:[2]

Index – Amend Entry

IVERMECTIN

Schedule 7
Schedule 5
Schedule 4
Appendix D, Item 10

Appendix D – Delete Entry

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 ***approved 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

[1] For the purposes of s 52D of the *Therapeutic Goods Act 1989* (Cth).
[2] Proposed additions are shown in green underlined font, proposed deletions are shown in red strikethrough font, and text without this formatting represents the current text in the Poisons Standard.

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;

(e) 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.

Summary of applicant's reasons for the proposal

- The listing of ivermectin in Appendix D of the Poisons Standard is irrational, irresponsible, reckless, negligent, and possibly criminal. It poses a serious threat to public safety and may have caused the unnecessary deaths of thousands of Australians by preventing general practitioners from effectively treating their patients.
- Ivermectin is a safe, cheap, and effective medication that may prevent 44 per cent of COVID-19 infections[3] and may prevent serious illness and death caused by COVID-19 infections. Ivermectin is well tolerated at doses well beyond those that are typically prescribed for approved indications, which is at odds with the reasoning provided for the Appendix D entry. The AusPAR for ivermectin[4] cites good tolerability and no safety concerns at doses ranging from 30 mg to 120 mg, which is up to 10 times the typical dose for the treatment of scabies.
- The Appendix D listing removes patient choice, and forces patients to access ivermectin on the black market or to use veterinary preparations of ivermectin. This unsupervised use of ivermectin is unsafe, caused by an undue change to the Poisons Standard which has the opposite effect to that which was intended.
- There is no evidence that general practitioners had been prescribing ivermectin unsafely or that this prescribing was undesirable prior to the inclusion of the Appendix D entry for ivermectin. Further, there is no evidence that ivermectin is unsafe when prescribed by doctors and dispensed by pharmacists.
- Vaccines against COVID-19 have not been completely effective and there is an unmet demand for an effective alternative treatment. Rising infection rates could also be ameliorated by the prophylactic use of ivermectin. The use of ivermectin in African countries and the corresponding relatively low rate of COVID-19 infection in these countries supports claims of the efficacy of ivermectin for this purpose and is supported by a considerable volume of published literature.

[3] Cureus | Ivermectin Prophylaxis Used for COVID-19: A Citywide, Prospective, Observational Study of 223,128 Subjects Using Propensity Score Matching
[4] Ivermectin AusPAR https://www.tga.gov.au/sites/default/files/auspar-ivermectin-131030.pdf

- The original decision to place ivermectin into Appendix D was based on research indicating that ivermectin is ineffective in preventing or treating COVID-19. There was a failure to consider if counterfeit ivermectin could explain some or all of the negative research upon which the decision was based.

Scheduling history

- Ivermectin was first recommended for scheduling by the National Drugs and Poisons Scheduling Committee (NDPSC) in November 1981. A Schedule 7 entry was created for ivermectin for approved research purposes only.
- In August 1983, the NDPSC recommended creation of a new Schedule 4 entry for preparations containing 2 per cent or less of ivermectin, for the treatment of internal parasites in horses. The NDPSC specified that the entry should includes the words "not for human consumption". This recommendation was later rejected due to the lack of available chronic toxicity data and the expected difficulty with ensuring the product is used in horses only.
- In May 1988, the Drugs and Poisons Scheduling Committee (DPSC) considered a scheduling proposal for ivermectin in dogs for the treatment of heartworm. Based on the data received, the DPSC recommended a new Schedule 4 entry for preparations of ivermectin in packs of 6 tablets or less for the treatment of heart worms in dogs. The limit on pack size was removed after the May 1989 meeting of the DPSC, and the entry was expanded to include the treatment of cats in February 1995.
- The Schedule 6 entry for ivermectin was expanded by the DPSC on multiple occasions to include various veterinary preparations until August 1994, when all such preparations containing 2 per cent or less of ivermectin were moved to Schedule 6 (except those already regarded as Schedule 4 medicines).
- In February 1996, the NDPSC recommended down-scheduling veterinary preparations for internal use containing 2 per cent or less of ivermectin from Schedule 6 to Schedule 5 (except when included in Schedule 4). The existing Schedule 6 entry was amended to capture veterinary ivermectin for external use. In August 1996, this distinction between internal and external preparations was removed by the deletion of the Schedule 6 entry.
- In November 2000, the Schedule 4 entry was amended to capture human use of ivermectin for the first time. Preparations of ivermectin previously classified as prescription-only medicines (those containing less than 2 per cent of ivermectin for the treatment of cats and dogs) were therefore moved to Schedule 5.
- In an out of session meeting of the Advisory Committee on Medicines Scheduling in September 2021, a new Appendix D entry for ivermectin was recommended in response to concerns of a considerable increase in off-label prescribing to treat and prevent COVID-19. The new entry meant that while the substance could still be prescribed by general practitioners for approved indications such as the treatment of parasitic infections, off-label prescription of ivermectin was restricted to certain specialists outlined in the Appendix D entry.

Australian regulations

- According to the TGA Ingredient Database,[5] ivermectin is:
  - available for use as an Active Ingredient in Biologicals, Export Only and Prescription Medicines;

[5] TGA Ingredient Database https://www.ebs.tga.gov.au/

  - available for use as an Excipient Ingredient in Biologicals, Devices and Prescription Medicines;
  - not available as an Equivalent Ingredient in any application.

- As of October 2022, there were 3 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[6] that contain ivermectin as an active ingredient, all available as prescription-only medicines. This includes one oral dosage form (STROMECTOL 3 mg tablets).
- Ivermectin is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[7] No.4 of 2022.
- The TGA prescribing medicines in pregnancy database[8] classifies ivermectin as:

Ivermectin	B3	Antimicrobials	Anthelmintics

Category B3 – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.

Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

- There are no warning statements pertaining to ivermectin in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019.[9]
- From January 2012 to October 2022, there were 15 reports of adverse events for products containing ivermectin as an active ingredient on the Database of Adverse Event Notifications (DAEN),[10] with 9 reports where ivermectin was the single suspected medicine. The recorded adverse events were widely varied in nature.
- As of October 2022, there were 186 products containing ivermectin as an active constituent listed on the Public Chemical Registration Information System Search (PubCRIS).[11]
- In 2015-2020 there were 15 adverse experiences recorded for ivermectin in the APVMA Adverse Experience Reporting Program database (AERP).[12] These included 11 incidents classified as related to animal health and one related to human health.

International regulations

- The Health Canada Drug Product Database[13] lists 20 marketed products containing ivermectin, including 2 prescription-only medicines for human use (one oral tablet and one topical cream).

[6] ARTG database https://www.tga.gov.au/artg
[7] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[8] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[9] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[10] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[11] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[12] APVMA Adverse Experience Reporting Program database (AERP) https://apvma.gov.au/node/10946
[13] Health Canada Drug Product Database https://health-products.canada.ca/dpd-bdpp/index-eng.jsp

- The Medsafe (New Zealand Medicines and Medical Devices Safety Authority) Medicines Classification Database[14] lists ivermectin as a prescription-only medicine.
- The United States Food and Drug Administration Orange Book[15] lists 8 products containing ivermectin, including two prescription-only oral dosage forms (tablets).
- The European Commission lists 95 products containing ivermectin in the Union Register of medicinal products.[16] All products listed are for veterinary use.
- The Health Products Regulatory Authority of Ireland[17] regulates two products containing ivermectin. Both are topical creams that are available by prescription-only.

International advice and recommendations

- The World Health Organization[18] recommends not to use ivermectin in patients with COVID-19 except in the context of a clinical trial.
- The United States National Institutes of Health[19] recommends against the use of ivermectin for the treatment of COVID-19, except in clinical trials.
- Ivermectin is not approved by the US Food and Drug Administration[20] for the treatment or prevention of COVID-19.
- The Journal of the American Medical Association (JAMA) published results of the ongoing ACTIV-6 trial into the effectiveness of ivermectin in treating mild to moderate COVID-19 on 21 October, 2022. The investigation detailed a randomised, double-blind, placebo-controlled study of 1800 participants. The study found that ivermectin did not significantly improve recovery time compared to placebo after 3 days treatment (see Attachment B).

[14] Medsafe Medicines Classification Database https://www.medsafe.govt.nz/profs/class/classintro.asp
[15] US FDA Orange Book https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm
[16] European Commission Union Register of medicinal products https://ec.europa.eu/health/documents/community-register/html/reg_index_inn.htm
[17] HPRA https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results/item?compare=PA22743/015/001,PPA23176/014/001
[18] WHO Therapeutic and COVID-19: living guideline https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.4
[19] NIH COVID-19 Treatment Guidelines https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ivermectin/?ACSTrackingID=USCDC_1052-DM74752&ACSTrackingLabel=Ivermectin%20Products%20are%20Not%20Approved%20by%20FDA%20to%20Prevent%20or%20Treat%20COVID-19&deliveryName=USCDC_1052-DM74752
[20] US FDA: Why you should not use ivermectin to treat or prevent COVID 19 https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19

Substance summary

Table 1: Chemical information for ivermectin

Chemical structure	
Molecular formula	$C_{47}H_{72}O_{14}$
CAS numbers	70288-86-7
IUPAC and/or common and/or other names	22,23-Dihydroabamectin; 22,23-dihydroavermectin B_1; 22,23-dihydro C-076B_1

Table 2: Acute toxicity end-points for ivermectin[21]

Acute oral toxicity	Rat	LD_{50}: 50 mg/kg	Schedule 7
Acute oral toxicity	Mouse	LD_{50}: 25 mg/kg	N/A
Acute oral toxicity	Monkey	LD_{50} >24 mg/kg	N/A
Acute inhalational toxicity	Rat	LC50 5.11 mg/L for 1 hr	Schedule 7
Eye irritation	Rabbit	Mild eye irritant	Schedule 5
Skin irritation	Rabbit	Non-irritant	Nil

Pre-meeting public submissions

A total of 17 public submissions were received through the consultation portal, with 12 supportive and 5 opposing the proposal (see Attachment C). All included a written component.

[21] Merck MSDS for ivermectin formulation https://www.merck.com/docs/product/safety-data-sheets/ah-sds/Ivermectin%20(3.5_pct)%20Formulation_AH_MX_EN.pdf
[22] See TGA website for SPF classification guideline AHMAC – Scheduling policy framework for medicines and chemicals

Main points in support:

- The proposal should be approved in consideration of the current spread of COVID-19 infection, despite high levels of immunisation. This will improve patient safety, alleviate pressures on the public and private health systems and move Australia's health policy for the treatment of COVID-19 toward a multi-therapy strategy. It will also allow access to effective alternatives for those patients who cannot tolerate existing treatments and prophylaxis.
- The primacy of the doctor/patient relationship within medicine stands firmly opposed to the placement of excessive constraint on the clinical judgement of doctors. Now that Australian vaccination rates have risen to such high levels, it is appropriate to re-evaluate the previous decision.
- There are a considerable number of studies purporting the use of ivermectin for the treatment and prevention of COVID-19, in addition to the apparent benefits when ivermectin is used for this purpose overseas. These include:
  - extensive toxicological and clinical safety data in relation to ivermectin
  - meta-analyses and reviews of the published medical literature concerning clinical trials of ivermectin
  - individual important clinical studies of ivermectin (several of these studies have become available subsequent to the imposition of restrictions on ivermectin prescribing)
  - accounts of the successful national ivermectin programs used by several countries in relation to COVID-19
  - specific rebuttals in response to key publications which purport to argue against the safe and effective use of ivermectin.

Main points in opposition:

- The recommendation against the use of ivermectin as a treatment against COVID-19 by the National COVID-19 Clinical Evidence Taskforce remains, and ivermectin is not listed as a recommended treatment on the National COVID-19 Clinical Evidence Guidelines. Measures other than the use of Appendix D to regulate off-label prescribing may need to be considered.
- The evidence base for ivermectin in the treatment of COVID-19 remains poor, with the Cochrane Review in 2021 concluding uncertainty in the limited evidence base and noting that most studies assessing ivermectin in the prevention and treatment of COVID-19 were small and of poor quality. With respect to public safety the current restrictions remain appropriate.
- Approved treatments for COVID-19 are readily available. Patients who are prescribed and dispensed ivermectin by their doctors and pharmacists are being treated with sub-optimal treatment that is not supported by National COVID-19 Clinical Evidence Guidelines.
- Since the Appendix D amendment was implemented in Sept 2021, there have been 35 calls to the Poisons Information Centre regarding exposures to ivermectin, which was being inappropriately used for COVID-19 treatment or prevention. Seventeen calls resulted from the use of veterinary products, 11 were products available on prescriptions in Australia, 3 were purchased from overseas and in 4 cases the source was unclear, demonstrating a continued demand from consumers for the unapproved use of ivermectin. If the restrictions on prescribing of ivermectin were removed, it is likely these numbers of inappropriate use would be much higher.

Internal consultation

The following sections at the TGA submitted feedback on the scheduling proposal:

- Regulatory Compliance Branch (RCB)
  - RCB notes that the advertisement of ivermectin to the public for any purpose continues to remain illegal. Additionally, there are currently no medicines containing ivermectin as an active ingredient that are approved to treat the indication of COVID-19 infection. As such, it remains an offence to promote ivermectin for this purpose to and by medical practitioners.
- Medicines Shortages Section provided the following data detailing wholesale supplies of Stromectol 3 mg tablets in Australia – the only oral dosage form of ivermectin on the ARTG – since January 2021, noting that the Appendix D entry for ivermectin was introduced into the Poisons Standard in September 2021:

Delegate's specific issues and questions to be considered by the Committee

The Medicines Scheduling Delegate seeks advice from the Committee on the following questions:

1. Is it appropriate to maintain the current Appendix D entry for ivermectin in the Poisons Standard?
2. If not, are there are other scheduling measures that should be undertaken to ensure the appropriate use of products containing ivermectin?

OPTIONS

OPTION 1

The Committee recommends that the current scheduling of ivermectin remains appropriate.

OPTION 2

The Committee recommends that the Appendix D entry for IVERMECTIN be amended as follows:

Appendix D – Delete Entry

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 ***approved 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;

(e) 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.

IMPLEMENTATION DATE

The Committee is asked to discuss and consider the resolutions with an implementation date of 1 June 2023/1 October 2023/1 February 2024.

RECOMMENDATION FOR OTHER ACTION BY THE DELEGATE

ATTACHMENTS

Attachment A: Application to amend the Poisons Standard with respect to ivermectin (D22-5816413)

Attachment B: Pre-meeting public submissions (D22-5952811)

Attachment C: JAMA Original Investigation: *Effect of Ivermectin vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19*. Published 21 October 2022. (D22-6018745)

ACMS #40

IVERMECTIN

APPLICATION TO AMEND THE POISONS STANDARD

Application to delete the Appendix D, Item 10 listing for Ivermectin

13 August 2022

Paragraphs 2 and 54 ("44% of" replacing "86% of") corrected and resubmitted 20th August 2022.

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South Wangaratta Medical Centre

47-51 Joyce Way Wangaratta Victoria 3677

This application contains no material claimed to be commercial-in-confidence

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PART 1 – SUMMARY OF THE APPLICATION

PART 2 – BODY OF THE APPLICATION

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APPLICANT'S DETAILS

1	**Applicant's name**	s22
2	**Applicant's Business Address**	South Wangaratta Medical Centre 47-51 Joyce Way Wangaratta Victoria 3677
3	**Business name (if applicable)**	n/a
4	**Date of submission**	14th August 2022
5	**Contact person**	s22
6	**E-mail Address of contact person**	s22
7	**Postal address of contact person**	s22
8	**Phone Number of contact person**	s22
9	**Fax Number of contact person**	s22

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DECLARATION

I, s22 :

- Declare that the information provided in this application is true and current; and
- s22 . I am well qualified to make this application because of my education, training and experience s22 and
- I declare that I have no competing interests or conflicts of interest in making this application; and
- I undertake not to publicly disclose the notices of interim decision or final decision in respect of this application, until (if relevant i.e. following referral to an expert advisory committee) these documents are published pursuant to subsections 42ZCZP and 42ZCZS of the Therapeutic Goods Regulations 1990, respectively.

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s22 Date: 13th August 2022

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PART 1 – SUMMARY OF THE APPLICATION

PROPOSED SCHEDULING / RESCHEDULING OR OTHER CHANGE TO THE POISONS STANDARD

1. I request the Appendix D, Item 10 listing (**listing**) for ivermectin in the Poisons Standard that was included on the 11th September 2021 be deleted in its entirety in order to allow general practitioners to prescribe ivermectin safely and effectively for patients who wish to use ivermectin off-label to prevent and treat Covid-19.

2. The basis for this request is that the Appendix D listing for ivermectin is clearly irrational, irresponsible, reckless, negligent and possibly criminal, because it poses a serious threat to public safety and may have caused the unnecessary deaths of thousands of Australians by preventing general practitioners from treating their patients with a safe and effective and cheap medication that may prevent 44% of Covid-19 infections and may prevent serious illness and death caused by Covid-19 infections

3. The listing forces patients to access ivermectin on the black market, or to use veterinarian ivermectin, and to use it without medical or pharmaceutical supervision, while simultaneously preventing the safe prescribing of ivermectin by doctors and the safe dispensing of ivermectin by pharmacists, for the prevention and treatment of Covid-19. The listing itself is unsafe and irrational and has the opposite effect to that which was intended.

4. There was never any rational basis for the Appendix D, Item 10 listing for ivermectin in the Poisons Standard. The listing provides for additional controls on possession and supply of poisons included in schedules 4 and 8. There was never, at any time, a specific health risk that could be mitigated by restricting off-label prescribing of ivermectin to dermatologists and gastroenterologists. There was never any evidence that specialist General Practitioners have been prescribing ivermectin unsafely or that the prescribing by General Practitioners was undesirable.

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5. The TGA has been aware that ivermectin is safe in the doses used in the prophylaxis and treatment of Covid-19 since 2013, when it undertook a rigorous analysis of the safety of ivermectin which was published in a 2013 AUSPAR.

6. There is no evidence that ivermectin is unsafe when prescribed by doctors and dispensed by pharmacists. There is evidence that ivermectin is an effective prophylactic and treatment for Covid-10. This application is based on a harm minimisation approach to patient care. The listing is causing harm separately to the question of the efficacy of ivermectin, in and of itself.

7. The use of ivermectin by Australians will be safer if the listing is deleted, because doctors and pharmacists can then be involved in the use of ivermectin by patients.

8. There is a strong possibility, based on published research, that ivermectin may help prevent and also treat Covid-19. It is unethical, immoral and possibly criminal to withhold a safe and effective prophylactic and/or treatment from the Australian publice when there is no rational basis for preventing Australians from accessing ivermectin safely.

9. The Appendix D, Item 10 listing appears to be a political act that is designed to support the government and public health authorities, rather than medicine or science or logic.

SUGGESTED SCHEDULING OR OTHER WORDING

10. I do not suggest re-scheduling of ivermectin. Ivermectin should remain in schedule 4. This schedule is appropriate and provides for ivermectin to be prescribed and dispensed safely, in contrast to the effect of the listing.

11. I do not suggest other wording. I request deletion of the Appendix D, Item 10 listing for ivermectin in its entirety.

Schedule N – Proposed New Entry/Amendment

12. The proposed amendment of the Poisons Standard is the deletion of the Appendix D, Item 10 listing for Ivermectin which was inserted on the 11th of September 2021.

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SUBSTANCE SUMMARY

13. The CAS ID of ivermectin is 70288-86-7.

14. The chemical structure, toxicity and pharmacology of ivermectin is well known to the department. Details can be found in the department's 2013 AUSPAR for ivermectin. Ivermectin has been registered and widely used in Australia since the 1980s. The AUSPAR for ivermectin can be found here: https://www.tga.gov.au/auspar/auspar-ivermectin

15. Relevantly, the most recent MSD safety data continues to confirm the wide therapeutic window of ivermectin treatment. The complete MSD Safety Data Sheet can be found here: MSD Safety Data for Ivermection 26/3/2022 https://www.merck.com/docs/product/safety-data-sheets/hh-sds/Ivermectin%20Solid%20Formulation_HH_IN_6N.pdf

16. MSD Safety Data Sheet 26 March 2022:

Acute oral toxicity : LD50 (Rat): 50 mg/kg

LD50 (Mouse): 25 mg/kg

LD50 (Monkey): > 24 mg/kg

Target Organs: Central nervous system
Symptoms: Vomiting, Dilatation of the pupil
Remarks: No mortality observed at this dose

OVERVIEW

17. Ivermectin is a safe and effective drug that has been used in humans since the 1980s. It is available in 3mg tablets in Australia, and is funded under the Pharmaceutical Benefits Scheme. There is no evidence that ivermectin is unsafe, or that it has a narrow therapeutic index, or any other significant safety concern when

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used as directed by general practitioners. Removing off-label prescribing of ivermectin from general practitioners was irrational and unnecessary.

18. Specialist qualifications and training are not required to prescribe ivermectin safely. There is no evidence or indication that other specialists prescribe ivermectin more safely than general practitioners. General practitioners have been safely and effectively prescribing ivermectin since the 1980s in Australia.

19. When it became apparent that ivermectin may be able to prevent and treat Covid-19 infections, some of the more enlightened doctors in Australia began treating Covid-19 patients with ivermectin. This was in accordance with the ethical principles for medical research formulated by the World Medical Association and published as the Declaration of Helsinki in 1964, 58 years ago, which states [at 37]:

> ***Unproven Interventions in Clinical Practice***
>
> *37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.*

20. On the 11th of September 2021, a delegate of the Secretary of the Department of Health amended the Poisons Standard to include an Appendix D to prevent general practitioners from treating Covid-19 with ivermectin, or using ivermectin as prophylaxis against Covid-19 infections.

21. There was no proper basis for this amendment. It was irrational and irresponsible and was not supported by fact or reason. The delegate appears to be hysterical. The reasons provided are dramatic imaginings, exaggerated risks and minimise the possible benefits. The fabrications by the delegate about safety concerns are particularly concerning.

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22. The amendment may have caused the unnecessary deaths of thousands of Australians, and may cause the unnecessary deaths of thousands more Australians in the future, by preventing the use of ivermectin in the prophylaxis and treatment of Covid-19.

23. The other public health impact of the amendment has been to cause patients to access black market ivermectin of uncertain quality and quantity, and to use it without the advice or prescription of a doctor, or the checking and safety function of the dispensing pharmacist. Alternatively, some patients are using veterinarian preparations of ivermectin designed for animal use.

24. The public health impact of the amendment may continue, and contribute to an ongoing and worsening health catastrophe through the mechanisms above.

25. It is clear from Australia's historical use of ivermectin that it is very safe and is extremely unlikely to cause serious adverse drug reactions. Contrary to the reasons provided for the listing, there is no vitiating risk to public health from ivermectin. The only risks the delegate identified were caused by a lack of medical and pharmaceutical supervision of the use of ivermectin, *which the listing exacerbates.*

26. In contrast to the justification offered for the Appendix D listing for ivermectin, it is clear from the TGA's own 2013 AUSPAR for ivermectin that ivermectin is generally safe and well tolerated. The TGA's evaluator concluded (at 4.3) that:

> *No indication of CNS toxicity associated with oral ivermectin was observed for any of the doses administered in this study. This was most strongly supported by the absence of a mydriatic effect documented with pupillometry. The standard used was the difference in pupil size between baseline and the approximate time of Cmax after the Study Day 7 dose. A conservative measure of a 1 mm difference between the ivermectin and placebo groups was considered significant. Comparison of pupil size to baseline was made after the third dose when maximum drug concentration was likely to be present if any accumulation occurred. Considering this criterion, the mydriatic effect following 30 mg ivermectin administration was equal to that observed with placebo. Escalation to a single dose of 120 mg (up to 2 mg/kg), 10 times*

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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.

27. The overall conclusion and risk/benefit assessment of ivermectin also contradicts the reason provided the delegate that *"Oral ivermectin also has the potential to cause severe adverse events in persons"* . The TGA's own assessment of ivermectin in nearly one and half million patients in its own AUSPAR report reaches the opposite conclusion, stating [at VI] that (bold emphasis added):

> ## *Safety*
>
> *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***

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28. Australia's historical use of ivermectin confirms the above. There is only a very small risk to public health from ivermectin prescribed by doctors and checked by pharmacists. Ivermectin is certainly much safer than many other medications commonly in use today.

29. The effect of the new Appendix D listing for ivermectin is to force patients who want to use ivermectin to do so without the advice of the medical practitioners or the safety check and counselling by pharmacists.

30. Clearly, the Appendix D listing was reckless and negligent and had the opposite effect of that intended. Patients now source and use ivermectin on the black market.

31. Ivermectin is extremely cheap, especially compared to the current vaccines and treatments for Covid-19. It would remain cheap and accessible for vulnerable patients if the listing is removed. Patients will still be protected by the Australian Scheduling Policy Framework (**SPF**) and other medical and pharmaceutical safety regulations if the listing is deleted.

32. There are now many research articles of reasonable quality that provide reasonable evidence that ivermectin may help prevent Covid-19 infections and may prevent Covid deaths.

33. Vaccines have not been as helpful as the public health authorities trumpeted. There has been a large increase in the number of Covid-19 infections and deaths despite good vaccination rates in Australia.

34. Antivirals for treating Covid-19 are subject to age and other restrictions. They are extremely expensive and subject to authority prescription rules which exclude most patients. In contrast, ivermectin has a proven safety profile in school-aged children.

35. There is currently a large increase in the number of infections and deaths from Covid, which ivermectin may ameliorate immediately and may prevent future surges in the infection rate, lessening the strain on public health facilities like hospitals.

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36. The possible benefits of ivermectin in the prevention and treatment of Covid-19 have become clearer. Ivermectin is very safe when taken as properly prescribed by a medical practitioner. There is little to no risk of adverse effects from using ivermectin in the prevention and treatment of Covid-19 if it is taken as prescribed, even in children.

37. The listing does not prevent patients from obtaining and using ivermection, but it does remove the safety provided by involvement of the patients' doctors and pharmacists. The delegate demonstrated that they were aware that the listing would not prevent patients from obtaining ivermectin when they wrote "*there has been significant increase in personal importation of ivermectin"* (sic).

38. There may be significant public health benefits to Australia from making ivermectin available as prophylaxis and treatment of Covid-19. The risk/benefit assessment is clearly in favour of the approach the World Medical Association suggests because ivermectin is safe and may be effective in preventing and treating Covid-19. Ivermectin should be available for doctors to prescribe for prophylaxis and treatment of Covid-19, even though there is still debate about the efficacy of ivermectin in preventing and treating Covid-19.

39. The published evidence supporting the use of ivermectin in the prophylaxis and treatment of ivermectin is available to the TGA. The failure to act on the data held by the TGA, and the voluminous published evidence that suggests ivermectin is more accessible, cheaper, safer, and more stable than vaccination and anti-viral treatment is inexplicable.

40. In addition, removing the listing will provide an alternative treatment for those patients who do not tolerate other Covid-19 prophylactics and treatment.

41. The listing appears to be improperly based on the public health narrative and political considerations, not on therapeutic and safety concerns, because there are no vitiating therapeutic or safety concerns that could reasonably lead to this effective ban on using ivermectin for the prophylaxis and treatment of Covid-19.

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PART 2 – BODY OF THE APPLICATION

BACKGROUND

42. Ivermectin is well known to the department. It has been widely used all over the world and in Australia. Ivermectin's use and safety was confirmed by the department in 2013, when it reviewed nearly one and a half million patients who had taken ivermectin orally. There is more than enough data available to the TGA about ivermectin to confirm its safety, contrary to the reasoning of the delegate who made the amendment to the Poisons Standard.

43. For further detail on the background of ivermectin, please see your own AUSPAR documentation from 2012 and 2013.

44. The only change, and the basis for this application, is that it appears ivermectin may prevent and treat Covid-19 cheaply and effectively, and that it may be safer than the alternatives the TGA has forced on medical practitioners and the public.

45. Ivermectin is very cheap and very stable. This means that ivermectin is more accessible to rural and remote Australia than current vaccinations and anti-viral medication. In contrast to the reasoning of the delegate that *"Such a shortage may disproportionately impact vulnerable communities, including Aboriginal and Torres Strait Islander communities".* In fact, ivermectin may be far more effective than the delicate vaccines because ivermectin can be administered by enrolled nurses and Aboriginal Health Workers who may not be qualified to administer vaccinations, or lack the specialised storage facilities required by some vaccinations.

46. The concern of the delegate that *"it is possible that oral ivermectin will be in shortage in Australia for the treatment of the conditions for which it has been properly evaluated and approved in accordance with scientific data. Such a shortage may disproportionately impact vulnerable communities, including Aboriginal and Torres Strait Islander communities"* is irrational and

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has basis in fact. There is no shortage of ivermectin in Australia, and it is unlikely that there would be such a shortage.

47. If this was a real concern, rather than a fabrication to justify the listing, then it could be managed easily, simply and cheaply by stockpiling the usual quantity of ivermectin used in a six month period and setting that stockpile aside for the approved treatments. This data is available easily from the PBS.

48. There was no medical, scientific or rational basis for the Appendix D, Item 10 listing for ivermectin.

DETAILED CLAIMS AGAINST THE REQUIREMENTS OF THE SCHEDULING POLICY FRAMEWORK

PART 2.1 CRITERIA WHICH MUST BE ADDRESSED – PROPOSALS TO CHANGE PART 4 OF THE POISONS STANDARD – SCHEDULING OR RESCHEDULING OF SUBSTANCES

(A) Risks and Benefits Associated with the Use of a Substance

49. The risks of using ivermectin have been identified and addressed by the TGA previously, including the major risk factors, in the TGA's own 2013 AUSPAR for ivermectin. There is little to no risk in using ivermectin in the recommended doses for treating or preventing Covid-19. Again, this is a fabrication by the TGA.

50. The benefits of ivermectin may now include the prevention and treatment of Covid-19. There is debate about how effective ivermectin is in regard to Covid-19, but there is no debate about the safety of ivermectin.

51. The risks of ivermectin use remain low, while the research indicates there may be significant benefits from ivermectin, including prevention of hospitalisation and death from Covid-19 in a significant proportion of treated patients.

52. Ivermectin, is, of course, used by millions of people in Africa, regularly, for the prevention of parasitic infections. Relevantly, those populations have been protected from Covid-19 infection to a significant extent.

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(B) the purposes for which a substance is to be used and the extent of use of that substance

53. Ivermectin is not currently used officially for the prevention and treatment of Covid-19 in Australia because of the Appendix D, Item 10 listed by the delegate to the Secretary on 10th September 2021.

54. Overseas use of ivermectin in the prevention and treatment of Covid-19 has been extensive (see reference to ivermectin use in Africa, above) and has provided contemporary and convincing evidence that ivermectin may help prevent Covid-19 in up to 44% of patients, and may help reduce the severity of Covid-19 infections in a significant proportion of patients.

55. This is important because of the current pressures on Australian hospitals. Ivermectin may help reduce Covid-19 infections and hospitalisations.

(C) Toxicity and Safety of the Substance

56. I refer the reader to the TGA's own assessment of ivermectin, which is contained in the 2013 AUSPAR and attachments 1 and 2. This AUSPAR confirms the safety of ivermectin in much higher doses than would be used to treat or prevent Covid-19.

57. The AUSPAR address the factors set out in Chapter 3 of the SPF for the deletion of the Appendix D, Item 10 listing for ivermectin proposed in this application.

(D) Dosage, Formulation, labelling, packaging and presentation of a Substance

58. These factors have been considered by the TGA in the 2013 AUSPAR for ivermectin.

59. No changes are requested or required to the presentation of ivermectin. The 3mg tablet is sufficiently versatile for use in adult patients and older children.

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(E) Potential for Misuse/Abuse of the Substance

60. The potential for accidental misuse of ivermectin has been increased by the Appendix D, Item 10 listing for ivermectin because patients who want to use ivermectin can no longer have it safely prescribed by the doctor and safely dispensed by a pharmacist.

61. The listing has forced patients who are intent on using ivermectin for the prophylaxis and treatment of Covid-19 to use the black market or use a veterinarian product to obtain supplies of ivermectin. This is clearly unsafe.

62. The listing has the opposite effect of the intended effect.

(F) Any Other Matter that May be Relevant to the Scheduling of a Substance

63. **Harm Minimisation** is a recognised policy approach that the Appendix D, Item 10 listing for ivermectin has removed from public health. It is clearly much safer to have a doctor prescribe, and a pharmacist check the prescription and dispense ivermectin than forcing patients to source and dose themselves with black market ivermectin. Harm Minimisation policy is 40 years old, and the situation with ivermectin is directly comparable to Opioid Substitution Therapy, where Australia substitutes prescribed opioids for black market opioids to increase patient safety.

64. The delegate has based their listing on speculation and hypothetical fabrications for which there is no basis or evidence and which is simply scare-mongering, including:

> *… the likelihood that people who have been prescribed ivermectin for this purpose may believe themselves to be protected from the disease and not get vaccinated or tested and seek appropriate medical care if they developed symptoms. This also poses the potential risk to the community through the spread of the disease as well as the risks to individuals using it for this purpose.*

65. There is research that does not find ivermectin to be helpful in preventing or treating Covid-19. The delegate did not consider if counterfeit ivermectin could explain some, or all, of the negative research upon which the delegate based their decision.

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66. And in any event patients in Australia have the right to access safe alternatives for Covid-19 prevention and treatment. The listing removes choice from Australians.

67. There will be some Australians who do not tolerate the current prophylactics and treatments for Covid-19, and those Australians should have alternatives made available to them.

68. There is now evidence in the form of substantial research that ivermectin is cheap, safe and effective in the prevention and treatment of Covid-19.

PART 2.2 CRITERIA WHICH MUST BE ADDRESSED – PROPOSALS TO CHANGE PARTS 1-3 OR PART 5 OF THE POISONS STANDARD

69. The risk of using ivermectin when properly prescribed and dispensed remains unchanged. These risks are very low. They are well known to the TGA.

70. Contrary to the magical thinking, speculation and hypothetical, imaginary problems concocted by the delegate to the Secretary, there is no rationale for stopping general practitioners from prescribing ivermectin. There is no basis for the listing.

71. In contrast, the Appendix D, Item 10 listing for ivermectin must cause unsupervised and possibly hazardous use of ivermectin by excluding the doctor and the pharmacist from patient care. Some patients are, quite reasonably, convinced that ivermectin may help them and may be safer than the alternatives forced upon them by the public health authorities. These patients will use the black market, or veterinarian ivermectin and will calculate their does themselves.

CONCLUSION

72. There was no medical, scientific or rational basis for the Appendix D, Item 10 listing for ivermectin by the delegate. This listing is bizarre and has the opposite effect to that intended. It makes the use of ivermectin less safe by excluding medical and pharmaceutical supervision. The listing cannot prevent patients from accessing and using ivermectin from unregulated sources.

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73. The listing does not comply with the harm minimisation policy that Australia has implemented, because it removes medical and pharmaceutical supervision of ivermectin prophylaxis and treatment.

74. There were no problems with the safety of ivermectin prescribed by general practitioners. The listing does not actually address any real issue.

75. The listing has created the hazard of patients sourcing and dosing themselves with black-market ivermectin, or veterinarian ivermectin, by preventing doctors from prescribing ivermectin and preventing pharmacists from checking the safety of ivermectin prescriptions and counselling patients about the safe use of ivermectin.

76. The current evidence is that ivermectin may help prevent infection by Covid-19, which would obviously decrease death rates and hospital overcrowding in Australia from Covid-19.

77. The current evidence is that ivermectin may help reduce the length of hospital stays caused by infection with Covid-19, which would obviously decrease hospital overcrowding in Australia from Covid-19.

78. The current evidence is that ivermectin may help prevent deaths caused by Covid-19.

79. The TGA's prevention of the use of ivermectin by general practitioners is bizarre and irrational. The delegate's listing of the Appendix D, Item 10 for ivermectin may be a crime, under section 54 of the Crimes Act 1900 (NSW) because the delegate of the Secretary of the Department of Health may be responsible for a reckless and negligent act that may have caused grievous bodily harm and thousands of unnecessary deaths.

80. I request the Appendix D, Item listing for ivermectin be removed immediately in order to improve patient safety and access to Covid-19 prophylaxis and treatment and to provide a safe and possibly effective alternative for those patients who do not tolerate existing treatments and prophylaxis.

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PART 3 – SUPPORTING DATA

SUPPORTING DATA SUMMARY

81. The 2013 TGA AUSPAR for ivermectin and its attachments provide all of the historical, safety and product data required for this application.

82. The following recently published papers present a compelling case for the use of ivermectin in the prophylaxis and treatment of Covid-19. The results or conclusions of the supporting evidence are reproduced. URLs are provided to allow access to the contemporaneous copies of the research.

83. There are five groups of supporting research presented. They are -

    83.1. The safety of ivermectin.I have included a few papers to prove ivermectin remains safe. The supporting data presented is clinical research that is relevant to Australian patients;

    83.2. Effectiveness of ivermectin in preventing Covid-19. The supporting data presented is clinical research that is relevant to Australian patients;

    83.3. Effectiveness of ivermectin in treating Covid-19. The supporting data presented is clinical research that is relevant to Australian patients;

    83.4. Molecular mechanisms of action and pathway reviews that explain how ivermectin could be active *in vivo* against Covid-19. These papers are not clinical; and

    83.5. Systematic reviews and meta-analyses of the use of ivermectin in preventing and treating Covid-19. These papers are clinically focused.

84. The supporting data presented was selected on the basis of relevance and recency, because of concerns about early studies with ivermectin and Covid-19.

85. I have restricted the number of supporting articles for each of the five groups for the sake of brevity and to prevent repetition. The articles are relevant to Australia.

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SUPPORTING DATA DETAILS

The Safety of Ivermectin

86. Ozer M, Goksu SY, Conception R, Ulker E, Balderas RM, Mahdi M, Manning Z, To K, Effendi M, Anandakrishnan R, Whitman M. Effectiveness and safety of Ivermectin in COVID-19 patients: A prospective study at a safety-net hospital. Journal of Medical Virology. 2022 Apr;94(4):1473-80. https://onlinelibrary.wiley.com/doi/full/10.1002/jmv.27469

> *Our study used two doses regimen of 200 µg/kg, with no ivermectin-related adverse events observed. Recent studies have evaluated ivermectin doses up to 800 µg/kg, given in a single dose or three consecutive days, and reported good safety profiles.[15-17] A meta-analysis of the safety profile of higher doses of ivermectin showed no increased risk of adverse events with higher ivermectin doses compared to 200 or 400 µg/kg.[1] To date, the most optimal dose of ivermectin that balances efficacy with tolerability remains unknown.*

87. Wimmersberger D, Coulibaly JT, Schulz JD, Puchkow M, Huwyler J, N'Gbesso Y, Hattendorf J, Keiser J. Efficacy and safety of ivermectin against Trichuris trichiura in preschool-aged and school-aged children: a randomized controlled dose-finding trial. Clinical Infectious Diseases. 2018 Sep 28;67(8):1247-55. https://pubmed.ncbi.nlm.nih.gov/29617737/

> ***Results:*** *A total of 126 PSAC and 166 SAC were included in an available case analysis. In PSAC, efficacy against T. trichiura did not differ between 200 µg/kg ivermectin and placebo treatment arm, as expressed in CRs (20.9% [95% confidence interval {CI}, 11.9%-52.8%] vs 19.5% [10.4%-49.9%]) and geometric mean ERRs (78.6% [60.1%-89.5%] vs 68.2% [40.5%-84.8%]). In SAC, the highest administered ivermectin dose of 600 µg/kg had a low CRs (12.2% [95% CI, 4.8%-32.3%]) and moderate*

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ERRs (66.3% [43.8%-80.2%]). Only mild adverse events and no organ toxicity, based on serum biomarkers, was observed.

88. Tavul L, Laman M, Howard C, Kotty B, Samuel A, Bjerum C, O'Brian K, Kumai S, Amuga M, Lorry L, Kerry Z. Safety and efficacy of mass drug administration with a single-dose triple-drug regimen of albendazole+ diethylcarbamazine+ ivermectin for lymphatic filariasis in Papua New Guinea: An open-label, cluster-randomised trial. PLoS neglected tropical diseases. 2022 Feb 9;16(2):e0010096. https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0010096

Principal findings

Of the 4,563 participants enrolled, 96% were assessed for AEs within 2 days after treatment. The overall frequency of AEs were similar after either DA (18%) or IDA (20%) treatment. For those individuals with AEs, 87% were mild (Grade 1), 13% were moderate (Grade 2) and there were no Grade 3, Grade 4, or serious AEs (SAEs). The frequency of AEs was greater in Mf-positive than Mf-negative individuals receiving IDA (39% vs 20% p<0.001) and in Mf-positive participants treated with IDA (39%), compared to those treated with DA (24%, p = 0.023). One year after treatment, 64% (645/1013) of participants who were antigen-positive at baseline were re-screened and 74% of these participants (475/645) remained antigen positive. Clearance of Mf was achieved in 96% (52/54) of infected individuals in the IDA arm versus 84% (56/67) of infected individuals in the DA arm (relative risk (RR) 1.15; 95% CI, 1.02 to 1.30; p = 0.019). Participants receiving DA treatment had a 4-fold higher likelihood of failing to clear Mf (RR 4.67 (95% CI: 1.05 to 20.67; p = 0.043). In the DA arm, a significant predictor of failure to clear was baseline Mf density (RR 1.54; 95% CI, 1.09 to 2.88; p = 0.007).

89. Buonfrate D, Chesini F, Martini D, Roncaglioni MC, Fernandez ML, Alvisi MF, De Simone I, Rulli E, Nobili A, Casalini G, Antinori S. High-dose ivermectin for early treatment of COVID-19 (COVER study): a randomised, double-blind, multicentre, phase II, dose-finding, proof-of-concept clinical trial. International journal of antimicrobial agents. 2022 Feb 1;59(2):106516. https://www.sciencedirect.com/science/article/pii/S0924857921013571

High-dose ivermectin was safe but did not show efficacy to reduce viral load.

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90. Hazan S, Dave S, Gunaratne AW, Dolai S, Clancy RL, McCullough PA, Borody TJ. Effectiveness of ivermectin-based multidrug therapy in severely hypoxic, ambulatory COVID-19 patients. Future microbiology. 2022 Mar;17(5):339-50. https://www.futuremedicine.com/doi/full/10.2217/fmb-2022-0014

conclusions: *All subjects resolved symptoms (in 11 days on average), and oxygen saturation improved in 24 h (87.4% to 93.1%; p = 0.001). There were no hospitalizations or deaths, less than (p < 0.002 or 0.05, respectively) background-matched CDC database controls. Triple combination therapy is safe and effective even when used in outpatients with moderate to severe symptoms.*

91. Guzzo CA, Furtek CI, Porras AG, Chen C, Tipping R, Clineschmidt CM, Sciberras DG, Hsieh JY, Lasseter KC. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. The Journal of Clinical Pharmacology. 2002 Oct;42(10):1122-33. https://pubmed.ncbi.nlm.nih.gov/12362927/

Ivermectin was generally well tolerated, with no indication of associated CNS toxicity for doses up to 10 times the highest FDA-approved dose of 200 microg/kg. All dose regimens had a mydriatic effect similar to placebo. Adverse experiences were similar between ivermectin and placebo and did not increase with dose. Following single doses of 30 to 120 mg, AUC and Cmax were generally dose proportional, with t(max) approximately 4 hours and t1/2 approximately 18 hours. The geometric mean AUC of 30 mg ivermectin was 2.6 times higher when administered with food. Geometric mean AUC ratios (day 7/day 1) were 1.24 and 1.40 for the 30 and 60 mg doses, respectively, indicating that the accumulation of ivermectin given every fourth day is minimal. This study demonstrated that ivermectin is generally well tolerated at these higher doses and more frequent regimens.

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Effectiveness of Ivermectin in Preventing Covid-19

92. Umar M, Shahid R, Khan MM, Hayat U, Nadar A, Afzal S. Effectiveness of Ivermectin among COVID-19 patients: A Randomized Controlled Trial. Journal of Rawalpindi Medical College. 2022 Jun 30;26(2). http://www.journalrmc.com/index.php/JRMC/article/view/1802

> *Results: Males constituted the majority (56.7%) of our study participants. Statistically insignificant difference in mean age (P = 0.42) and mean length of hospital stay (P= 0.32) between experimental and control group subjects was observed. Mean time to PCR negativity was reported to be significantly less (P= 0.002) in experimental group. Significant improvement was seen in PCR negativity (P<0.05), mean Clinical Severity Score (CSS) (P0.02), mean hemoglobin level (P=0.03) and mean platelet count (P=0.03). Difference in health outcome of both groups was determined to be statistically insignificant (P<0.2, 95% CI (-0.20 – 0.12)). Relative Risk of 0.8 proved the protective effect of Ivermectin in COVID.*
>
> *Conclusion: Ivermectin was quite effective in reducing mortality and improving the health outcome in COVID-19 patients.*

93.

94. Kerr L, Cadegiani FA, Baldi F, Lobo RB, Assagra WL, Proença FC, Kory P, Hibberd JA, Chamie-Quintero JJ. Ivermectin Prophylaxis Used for COVID-19: A Citywide, Prospective, Observational Study of 223,128 Subjects Using Propensity Score Matching. Cureus. 2022 Jan 15;14(1).https://www.cureus.com/articles/82162

> *Of the 223,128 citizens of Itajaí considered for the study, a total of 159,561 subjects were included in the analysis: 113,845 (71.3%) regular ivermectin users and 45,716 (23.3%) non-users. Of these, 4,311 ivermectin users were infected, among which 4,197 were from the city of Itajaí (3.7% infection rate), and 3,034 non-users (from Itajaí) were infected (6.6% infection rate), with a 44% reduction in*

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COVID-19 infection rate (risk ratio [RR], 0.56; 95% confidence interval (95% CI), 0.53-0.58; p < 0.0001).

95. Tanioka H, Tanioka S, Kaga K. Comparative epidemiology of ivermectin and vaccines against Delta variant based on real-world data and hypothesized mechanisms of ivermectin immunological action. https://assets.researchsquare.com/files/rs-1631602/v1/f1c92a52-4993-4522-aefb-6a8ba33a01ee.pdf?c=1652836834

Efficacy of ivermectin against vaccines

The mortality efficacy rate of the non-inactivated vaccines against the ivermectin group is 35% (95% CI = 19–52%). An efficacy rate of 35% means that a person is 35% less likely to become dead than someone who was not vaccinated. The results indicate that ivermectin is effective, although less effective than the non-inactivated vaccines. The mortality effective rate of the inactivated vaccine-approved group against ivermectin is 18% (95% CI, 4–34%). This value shows almost the same effect as the ivermectin group. Thus, ivermectin is more effective than the inactivated vaccines alone.

Conclusions

Ivermectin may have both chemical actions and immune response mechanisms against SARS-CoV-2. And its activity is similar to a vaccine and is more effective than the inactivated vaccines against Delta variant. Ivermectin is less effective but not as pronounced as non-inactivated vaccines. Ivermectin is superior effective than inactivated vaccines. When used in combination with a non-activated vaccine, it may further reduce morbidity. It is supposed that the vaccine effect of ivermectin may last approximately 5 months. A possible immune mechanism is that ivermectin activates the RIG-I pathway to produce innate immunity, antibodies against SARS-CoV-2, and autophagy.

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96. Sardana K, Mathachan SR. Is there any prophylactic role for ivermectin in COVID-19—A literature summary. Journal of Cosmetic Dermatology. 2022 Jan;21(1):24-6. https://onlinelibrary.wiley.com/doi/full/10.1111/jocd.14633

> *Also, the studies on prophylactic use need further enunciation to determine its role in possible prevention of COVID-19, and data listed in Table 1 suggest that a prophylactic dose may be useful as is practiced in certain countries, including Africa, India, and Southeast Asia.11 A classic example is the prophylactic use of ivermectin against parasitic infections, which is most common in Africa11 and has been done under the aegis of the WHO. It has been shown that the incidence, mortality rates and the number of cases were significantly lower among these countries.12 In our country, such a prophylactic dose may possibly have played a role in mitigating the mortality and morbidity of COVID-19. Ivermectin is a cheap and effective drug, that in a prophylactic warrants more research in prevention of the disabling complications of COVID 19.*

Effectiveness of Ivermectin in Treating Covid-19

97. Niaee MS, Namdar P, Allami A, Zolghadr L, Javadi A, Karampour A, Varnaseri M, Bijani B, Cheraghi F, Naderi Y, Amini F. Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial. Asian Pacific Journal of Tropical Medicine. 2021 Jun 1;14(6):266. https://www.apjtm.org/article.asp?issn=1995-7645;year=2021;volume=14;issue=6;spage=266;epage=273;aulast=Shakhsi;utm_source=fbia

> ***Results:*** *A total of 16.7% (5/30) and 20.0% (6/30) patients died in arms treated with hydroxychloroquine 200 mg twice per day and placebo plus hydroxychloroquine 200 mg twice per day, respectively, and a reduction in*

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mortality rate in patients receiving ivermectin treatment to 0%, 10%, 0% and 3.3% for arms 1-4 were observed. Risk of mortality was also decreased about 15% in the ivermectin treated arms.

Conclusions: *Ivermectin as an adjunct reduces the rate of mortality, time of low O_2 saturation, and duration of hospitalization in adult COVID-19 patients. The improvement of other clinical parameters shows that ivermectin, with a wide margin of safety, had a high therapeutic effect on COVID-19.*

98. Chahla, R.E., Ruiz, L.M., Mena, T., Brepe, Y., Terranova, P., Ortega, E.S., Barrenechea, G.G. and Goroso, D.G., 2022. Randomized trials-Ivermectin repurposing for COVID-19 treatment of outpatients with mild disease in primary health care centers. *Research, Society and Development*, *11*(8), pp.e35511830844-e35511830844. https://rsdjournal.org/index.php/rsd/article/view/30844

Conclusion: This work supports the potential efficacy of Ivermectin in outpatient care with mild COVID-19 as a potentially useful intervention of public health consideration.

99. OE B, Adesuyi A, O O. A comparison of Ivermectin and Non Ivermectin based regimen for covid 19 in Abuja: effects on virus clearance, Days-to-Discharge and Mortality. https://assets.researchsquare.com/files/rs-1373673/v1/7d50cfad-d6b7-4f78-8b09-544f508c4a0e.pdf?c=1646065300

Conclusions: The IVM-based regimen caused earlier discharge from treatment and reduced mortality, in addition to clinical and laboratory improvements. Vaccination did not protect some patients from SARS-CoV-2 breakthrough infection and mortality.

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100. Shimizu K, Hirata H, Kabata D, Tokuhira N, Koide M, Ueda A, Tachino J, Shintani A, Uchiyama A, Fujino Y, Ogura H. Ivermectin administration is associated with lower gastrointestinal complications and greater ventilator-free days in ventilated patients with COVID-19: A propensity score analysis. Journal of Infection and Chemotherapy. 2022 Apr 1;28(4):548-53. https://www.sciencedirect.com/science/article/pii/S1341321X21003603

> ***Conclusions***
>
> *Ivermectin improved gastrointestinal complications and the number of ventilator-free days in severe COVID-19 patients undergoing mechanical ventilation. Prevention of gastrointestinal symptoms by SARS-Cov-2 might be associated with COVID-19 outcome.*

101. Vergeire-Dalmacion GR. The Use of Oral Human Grade Ivermectin with Supplements Known As Immunomodulators for Treating Patients with COVID-19 Infections At Home. J Clin Immunol Microbiol. 2022;3(2):1-6. https://athenaeumpub.com/wp-content/uploads/The-Use-of-Oral-Human-Grade-Ivermectin-with-Supplements-Known-as-Immunomodulators-for-Treating-Patients-with-COVID-19-Infections-at-Home.pdf

> *Conclusion*
>
> *The results of our study revealed the effectiveness of IVM for treating COVID-19 infection provided it is given early and the dose is adjusted based on severity and co-morbidities of cases. Patients' Bill of Rights to information and informed consent must be upheld notwithstanding a pandemic. Our results also suggest that government would fare better in controlling the pandemic by implementing focused protection based on age, gender and co-morbidities. The government should adopt a less myopic and terrified approach to managing the pandemic which includes long term lockdowns in various permutations with artificial effects. Opportunities for use and access to IVM and other drugs with preclinical or clinical evidence of antiviral properties should be allowed for the treatment of COVID infections by competent and licensed physicians. Finally, until a sterilizing vaccine is*

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available, the most promising and cost effective treatment to control the pandemic may be a combination drug therapy with or without vaccines

Mechanisms of Action of Ivermectin

102. Aminpour M, Cannariato M, Preto J, Safaeeardebili ME, Moracchiato A, Doria D, Donato F, Zizzi EA, Deriu MA, Scheim DE, Santin AD. In Silico Analysis of the Multi-Targeted Mode of Action of Ivermectin and Related Compounds. Computation. 2022 Apr;10(4):51. https://www.mdpi.com/2079-3197/10/4/51

This in silico investigation explores potential modes of action of ivermectin and 14 related compounds, by which the infectivity and morbidity of the SARS-CoV-2 virus may be limited. Binding affinity computations were performed for these agents on several docking sites each for models of (1) the spike glycoprotein of the virus, (2) the CD147 receptor, which has been identified as a secondary attachment point for the virus, and (3) the alpha-7 nicotinic acetylcholine receptor (α7nAChr), an indicated point of viral penetration of neuronal tissue as well as an activation site for the cholinergic anti-inflammatory pathway controlled by the vagus nerve. Binding affinities were calculated for these multiple docking sites and binding modes of each compound. Our results indicate the high affinity of ivermectin, and even higher affinities for some of the other compounds evaluated, for all three of these molecular targets. These results suggest biological mechanisms by which ivermectin may limit the infectivity and morbidity of the SARS-CoV-2 virus and stimulate an α7nAChr-mediated anti-inflammatory pathway that could limit cytokine production by immune cells.

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103. Patil VM, Verma S, Masand N. Prospective mode of action of Ivermectin: SARS-CoV-2. European Journal of Medicinal Chemistry Reports. 2022 Apr 1;4:100018. https://www.sciencedirect.com/science/article/pii/S2772417421000182

> *Present manuscript attempts to provide an overview of the detailed mechanism of action based on experimental and computational studies. The knowledge of binding interaction of IVM and SARS-CoV-2 targets will give the direction to developed new and potential anti-COVID agents.*

104. Low ZY, Yip AJ, Lal SK. Repositioning Ivermectin for Covid-19 treatment: Molecular mechanisms of action against SARS-CoV-2 replication. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2022 Feb 1;1868(2):166294. https://www.sciencedirect.com/science/article/pii/S0925443921002271#s0065

> *This review compiles all the molecular evidence to date, in review of the antiviral characteristics exhibited by IVM. Thereafter, we discuss IVM's mechanism and highlight the clinical advantages that could potentially contribute towards disabling the viral replication of SARS-CoV-2. In summary, the collective review of recent efforts suggests that IVM has a prophylactic effect and would be a strong candidate for clinical trials to treat SARS-CoV-2.*

Systematic Reviews and Meta-analyses of Ivermectin in Covid-19

105. Kory P, Meduri GU, Varon J, Iglesias J, Marik PE. Review of the emerging evidence demonstrating the efficacy of ivermectin in the prophylaxis and treatment of COVID-19. American journal of therapeutics. 2021 May;28(3):e299. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8088823/

> *Conclusions:*

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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.

106. Bryant A, Lawrie TA, Dowswell T, Fordham EJ, Mitchell S, Hill SR, Tham TC. Ivermectin for prevention and treatment of COVID-19 infection: a systematic review, meta-analysis, and trial sequential analysis to inform clinical guidelines. American journal of therapeutics. 2021 Jul;28(4):e434. https://journals.lww.com/americantherapeutics/fulltext/2021/08000/ivermectin_for_prevention_and_treatment_of.7.aspx

Conclusions:

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.

107. Ivermectin and outcomes from Covid-19 pneumonia: A systematic review and meta-analysis of randomized clinical trial studies. Reviews in Medical Virology. First published: 06 June 2021 https://doi.org/10.1002/rmv.2265 https://onlinelibrary.wiley.com/doi/10.1002/rmv.2265

This meta-analysis showed that ivermectin was associated with reduction in severity of Covid-19 (RR 0.43 [95% CI 0.23–0.81], p = 0.008), reduction of mortality (RR 0.31 [95% CI 0.15–0.62], p = 0.001), higher negative RT-PCR test results rate (RR 1.23 [95% CI 1.01–1.51], p = 0.04), shorter time to

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negative RT-PCR test results (mean difference [MD] −3.29 [95% CI −5.69, −0.89], p = 0.007), higher symptoms alleviations rate (RR 1.23 [95% CI 1.03−1.46], p = 0.02), shorter time to symptoms alleviations (MD −0.68 [95% CI −1.07, −0.29], p = 0.0007) and shorter time to hospital discharge (MD −2.66 [95% CI −4.49, −0.82], p = 0.004). Our study suggests that ivermectin may offer beneficial effects towards Covid-19 outcomes.

108. The effect of ivermectin on the viral load and culture viability in early treatment of nonhospitalized patients with mild COVID-19 – a double-blind, randomized placebo-controlled trial. **International Journal of Infectious Diseases** Volume 122, September 2022, Pages 733-740. https://ecommons.aku.edu/pakistan_fhs_mc_med_pulm_critcare/178/

Conclusion

There were lower viral loads and less viable cultures in the ivermectin group, which shows its anti-SARS-CoV-2 activity. It could reduce transmission in these patients and encourage further studies with this drug.

109. Is Ivermectin Effective in Treating COVID-19? Front Pharmacol. 2022; 13: 858693. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9253511/

Our systematic review indicated that ivermectin may be effective for mildly to moderately ill patients. There is no clear evidence or guidelines to recommend ivermectin as a therapeutic agent for COVID-19, so physicians should use it with caution in the absence of better alternatives in the clinical setting, and ***self-medication is not recommended for patients.***

110. Sethi P, Sharma A. Ivermectin-the Trinity of Efficacy, Safety and Tolerability in the Global Crusade against the Deadly Pandemic of Covid-19. Int. Jr. Infect Dis & Epidemlgy. 2022;3(1):32-3. https://skeenapublishers.com/journal/ijide/IJIDE-03-00016.pdf

There is emerging data that Ivermectin may also be useful in the prevention of the disease in high risk populations especially healthcare workers which strongly emphasizes the role of this drug in prophylaxis [8].

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To conclude, Ivermectin is an oral drug which has shown efficacy in the treatment of Covid-19 patients and prophylaxis to high risk populations which is evident by the results of number of randomized Control Trials. Keeping in mind its efficacy, safety, tolerability and compliance, it may be utilized more by Clinicians in their management protocol of Covid-19 infections.

COPIES OF PAPERS REFERENCED

111. I have used URLs instead of paper or otherwise static copies of the papers so the reader can be assured they are reading the current version of the paper. This is necessary because of corrections to, and withdrawals of, research that may occur after this application has been submitted.

112. The URLs are inserted below the citation of each research paper.

PART 4 – BIBLIOGRAPHY

113. I have included citations in the body of Part 3 of this application under the heading SUPPORTING DATA DETAILS. The citations are provided above the relevant excerpts from the article.

114. The citations are in the Vancouver format, as requested.

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ACMS #40

IVERMECTIN

CONSOLIDATED PRE-MEETING PUBLIC SUBMISSIONS

Document for TGA and ACMS Reconsideration of making ivermectin available for covid

To: medicines.scheduling@health.gov.au
Subject: Reconsideration of making ivermectin available for covid

This is what we wish to be considered by the ACMS in its November review of the use of ivermectin, alone or in combination, for covid.
The numbers are as taken from the ivmmeta.com website, and the table further down is constructed from that website (first 7 entries), while the entries that follow that are as summarised by us, grouped according to Prophylaxis studies [including ecological studies], early treatment studies and late treatment studies.

There is Bernigaud's work:
30. **Bernigaud** et al., Annals of Dermatology and Venereology, doi:10.1016/j.annder.2020.09.231, *Ivermectin benefit: from scabies to COVID-19, an example of serendipity*, https://www.sciencedirect.com/science/article/pii/S015196382030627X.

And Berhera's initial study and follow-up study:

26. **Behera** et al., PLoS ONE, doi:10.1371/journal.pone.0247163 (preprint 11/3), *Role of ivermectin in the prevention of SARS-CoV-2 infection among healthcare workers in India: A matched case-control study*, https://journals.plos.org/plosone/..le?id=10.1371/journal.pone.0247163.

27. **Behera (B)** et al., Cureus 13:8, doi:10.7759/cureus.16897 (preprint 2/15/21), *Prophylactic Role of Ivermectin in Severe Acute Respiratory Syndrome Coronavirus 2 Infection Among Healthcare Workers*, https://www.cureus.com/articles/64..infection-among-healthcare-workers.

And Hellwig et al's retrospective comparison of susceptibility to Covid in those African states for many years regularly using Ivermectin as a prophylaxis against locally endemic parasitic infections and neighbouring states that had not instituted such a program (ecological study):

167.**Hellwig** et al., International Journal of Antimicrobial Agents, doi:10.1016/j.ijantimicag.2020.106248, *A COVID-19 Prophylaxis? Lower incidence associated with prophylactic administration of Ivermectin*, https://www.sciencedirect.com/science/article/pii/S0924857920304684.

And a similar type of retrospective (ecological) comparison by Tanioka et al:
322.**Tanioka** et al., medRxiv, doi:10.1101/2021.03.26.21254377, *Why COVID-19 is not so spread in Africa: How does Ivermectin affect it?*, https://www.medrxiv.org/content/10.1101/2021.03.26.21254377v1

Then the effect of early treatment of Covid infection with Ivermectin is demonstrated, beginning with the (Australian) Borody et al study, which was planned to have 2000 patients, but was terminated early) when particularly tight restrictions were placed on the prescription of Ivermectin, but showed a 92% reduction in death rate.

39.**Borody** et al., TrialSite News, *Combination Therapy For COVID-19 Based on Ivermectin in an Australian Population*, https://covidmedicalnetwork.com/me..lSite-media-release-19.10.2021.pdf

And the study by Biber and colleagues, showing a 70% reduction in hospitalisation:

32.**Biber** et al., International Journal of Infectious Diseases, doi:10.1016/j.ijid.2022.07.003 (results 2/12/21), *The effect of ivermectin on the viral load and culture viability in early treatment of non-hospitalized patients with mild COVID-19 – A double-blind, randomized placebo-controlled trial*, https://www.sciencedirect.com/science/article/pii/S120197122200399X.

And the study by Chowdhury and colleagues, showing an 81% reduction in hospitalisation:

78.**Chowdhury** et al., Eurasian Journal of Medicine and Oncology, doi:10.14744/ejmo.2021.16263, *A Comparative Study on Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin Therapy on COVID-19 Patients*, https://ejmo.org/10.14744/ejmo.2021.16263/.

And the study by Bukhari and colleagues, showing an 82% reduction in risk of no viral clearance:

45.**Bukhari** et al., medRxiv, doi:10.1101/2021.02.02.21250840 (results 1/16), *Efficacy of Ivermectin in COVID-19 Patients with Mild to Moderate Disease*, https://www.medrxiv.org/content/10.1101/2021.02.02.21250840v1

And then there is the study of Okumus and colleagues, examining the effectiveness of late treatment for established Covid infection in Turkey. Six of the 30 patients treated died, resulting in a case fatality rate of 20%, which was one third less than the 9 who died of 30 controls, and risk of no improvement at day 5 was 16% lower (and 43% lower at day 10), while risk of NO viral clearance was 80% lower:

251.**Okumuş** et al., BMC Infectious Diseases, doi:10.1186/s12879-021-06104-9 (preprint 1/12), *Evaluation of the Effectiveness and Safety of Adding Ivermectin to Treatment in Severe COVID-19 patients* https://bmcinfectdis.biomedcentral..rticles/10.1186/s12879-021-06104-9.

The ivmmeta.com website is carefully written and is an essential reading in its entirety for a review as important as this one. I note that it discusses the following well ventilated subjects:

The WHO, Merck, FDA, NIH Analyses, and,

The Popp and Roman Meta-analyses, and,

The TLDR (Too long, didn't read), BBC, GMK, Scott Alexander and AT Responses.

And as well, it provides study notes regarding:

Together trial, ACTIV-6 trial, COVID-OUT and PRINCIPLE trials, as well as,

Lopez-Medina et al, Vallejos et al, Beltrah-Gonzales et al

Safety
Ivermectin has an enviable record of safety over a large dosage range, with a very favourable therapeutic ratio. Indeed, none of the mRNA vaccines or antivirals has been able to show a safety record to compare.

Further
We are unable to locate the claim appearing some time ago that if Ivermectin had been used from the beginning of the pandemic then more than 2 million lives would have been saved around the world; but such a claim is fully consistent with the results that are presented and discussed in the ivmmeta.com composition. And, of course, great physical, psychological and social suffering and economic harm could also have been modified.

Indeed, it is sad that the drug Ivermectin has not been readily available in Australia and to perhaps 80% of the world's population. The guiding principle which we followed in our clinical lives was to first do no harm. The safety profile of Ivermectin is such that it is one of the most unlikely drugs to be associated with causing harm. But the prohibition placed on its prescribing has been the cause of possible harm from two different directions. A miniscule number of people have been at risk of harm from self-dosing with dosages used for large animals (e.g., horses and cows); but a much greater potential cause for harm has been the denial of the drug as prophylaxis and treatment.

Thus, we are lead to the conclusion that, with a good safety profile and 90 supportive studies, including observational studies, controlled trials, random controlled trials, meta-analyses in over 134,000 patients and careful consideration and discussion of published responses to the various publications, unless the review committee has a greater reasonable doubt about the effectiveness of Ivermectin than they now have about the mRNA vaccines, we would ask that they show the same mercy to the Australian people as was shown when the mRNA vaccines were provisionally registered.

In short, we respectfully express the hope that delegates to the committee act as representatives of the Australian people and that they endeavour to read at least half of the 90 papers referenced on the website ivmmeta.com before voting against removing the restrictions placed in late 2021 on the prescribing of this drug in Australia

So that the whole Australian community can be fully confident in the committee's judgement, we would request that each member of the committee declares any conflict of interest, and that the other committee members, after hearing those declarations, express their view on whether those so-declaring should pass judgement on the removal of restrictions from this drug.

Studies	Number of studies	Number of patients	Reduced case risk%	Reduction in death	Improvement
All	91	134,052			62%
Death	47	120,648		51%	51%
RCTs	41	11,141			52%
Peer reviewed	71	121,147			62%
Prophylaxis	16	19,365			83%
Early treatments	37	57,715			62%
Late treatment	38	56,972			41%
Prophylaxis					
Berniguad	1	3,131		99%	55%
Behera “A”	1	372	54%		
Behera “B”	1	3,346	83%		
Helwig	1	22 countries Ecological study	78%		
Tanioka	1	53 countries, possibly 40-50 million people	88%	~88%	
Early Treatment					
Borody.	1	600 treated plus synthetic control		92%	92%
Chowdhury	1	116 Reduced hospitalisation			81%
Biber	1	89 Reduced hospitalisation			70%
Bukari	1	86 Viral clearance studied			82%
Late treatment					
Okomus	1	60 Reduction in deaths		33%	33%

Thank you,

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Subsequent Document for TGA and ACMS Reconsideration of making ivermectin available for covid

To: medicines.scheduling@health.gov.au
Subject: Reconsideration of making ivermectin available for covid

This is what we wish to be considered by the ACMS in its November review of the use of ivermectin, alone or in combination, for covid.

Since preparing our submission for consideration by the ACMS in November [submitted 25th September 2022 at 1.30PM], we have become aware of an Australian Review article "COVID-19 vaccines - An Australian Review", by Conny Turni of the University of Queensland and Astrid Lefringhausen, published last week in the Journal of Clinical & Experimental Immunology, and which we want to bring to the attention of the ACMS. A pdf copy of the article is attached.

These authors, inter alia say :

" Treatments

It is truly disturbing that treatments recommended by doctors in America, some of them having successfully treated COVID-19 patients, including very sick patients, have not been investigated in Australia. These treatments are mainly based on vitamins, zinc and zinc ionophores, such as ivermectin or hydroxychloroquine. The recommendation is to treat as early as possible. Scientific papers support the use of ivermectin according to Bryant et al. [62]. They found moderate to strong evidence that ivermectin can reduce COVID-19 deaths while being safe and inexpensive.

(Reference 62. Bryant, A., Lawrie, T. A., Dowswell, T., Fordham, E. J., Mitchell, S., Hill, S. R., & Tham, T. C. (2021). Ivermectin for prevention and treatment of COVID-19 infection: a systematic review, meta-analysis, and trial sequential analysis to inform clinical guidelines. American journal of therapeutics, 28(4), e434)

Yet here in Australia the recommendation is to isolate and monitor yourself. Only if you have difficulty breathing, experience loss of speech or mobility, confusion or chest pain should you contact the health care provider. Additionally, the government strongly advises not to use the following treatment for COVID-19 off label: Ivermectin, doxycycline, zinc and hydroxychloroquine (https:// www.health.gov.au/health-alerts/covid-19/treatments). The TGA provisionally approved the first oral treatments in January 2022 for Australia, Lagevrio® (molnupiravir) and Paxlovid® (nirmatrelvir + ritonavir) and recommend that both treatments should be started as soon as possible after diagnosis of COVID-19 (https://www.health.gov.au/health-alerts/covid-19/treatments/ oral). The TGA also accepted - similar to the agreement for the provisionally approved vaccines - rolling data for COVID-19 treatments, to enable early evaluation of data as it comes to hand (https://www.tga.gov.au/apm-summary/lagevrio). In other words, both drugs have been provisionally approved on the basis of shortterm efficacy and safety data and

permanent approval depends on the efficacy and safety data from ongoing clinical trials and postmarketing assessment. (https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2022-PI-01049-1)

Therefore, these treatments are still in trial phase and all patients treated with them are trial participants. Paxlovid has listed numerous potential complex and serious drug-drug interactions against its registration which could result in severe or life-threatening side effects(https://www1.racgp.org.au/newsgp/clinical/what-gpsneed-to-know-about-the-new-covid-antivira) ”

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Review Article

COVID-19 vaccines – An Australian Review

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Abstract

After millions of people have been vaccinated as often as four times within a year, the effects of these vaccinations are slowly becoming apparent. This review has been written from an Australian perspective with the main focus on the COVID-19 mRNA vaccines. We will look at the promises/predictions originally made and the actual facts. We will evaluate the safety and efficacy by looking at the literature and the data from government agencies. The literature review will be summed up in a table listing the so far reported side effects of which many are very serious including death, with this data coming from 1011 case reports. Long term side effects will also be covered and the risk benefit ratio will be explored. The review is ending with some very critical question that need further discussion.

Introduction

This review is written from an Australian perspective and will concentrate on the COVID-19 mRNA vaccines. In Australia the COVID vaccination is still heavily promoted. Until April 2022 only the mRNA vaccines Comirnaty (Pfizer) and Spikevax (Moderna), as well as the vector vaccines Vaxzevria (AstraZeneca) and COVID-19 Vaccine Janssen (Janssen) were preliminarily registered for use. Every one of these vaccines forces the vaccinees body to produce the spike protein for which the genetic code is delivered into the cells as mRNA via a nanoparticle or as double stranded DNA via a viral vector. (https://www.tga.gov.au/international-covid-19-vaccines-recognised-australia).

In April 2022 yet another vaccine, Nuvaxovid (Biocelect on behalf of Novavax, based on a new concept) received preliminary approval in Australian. Nuvaxoid contains a modified spike derived from moth cells cultured after transfection using Baculovirus, which express the spike protein on their cell membrane. This spike protein is harvested and assembled onto a synthetic lipid nanoparticle, which displays 14 spike proteins each. (https://www.precisionvaccinations.com/vaccines/novavax-covid-19-vaccine). The vaccine is registered for 18 years of age and older.

The government continues to push particularly the mRNA vaccinations by encouraging a fourth vaccination and recommending the vaccine for pregnant women as well as children 5 to 11 years old. The official public message is that the mRNA vaccines are safe. However, the Therapeutic Goods Administration (TGA), the medicine and therapeutic regulatory agency of the Australian Government, states quite clearly on their website that the large-scale trials are still progressing and no full data package has been received from any company. The TGA is currently getting rolling data and safety and effectiveness are still being assessed (https://www.tga.gov.au/covid-19-vaccines-undergoing-evaluation).

Initial information

The mRNA vaccines were supposed to remain at the injection site and be taken up by the lymphatic system. This assumption proved to be wrong. During an autopsy of a vaccinated person that had died after mRNA vaccination it was found that the vaccine disperses rapidly from the injection site and can be found in nearly all parts of the body [1]. The mRNA is enveloped in liquid nano particles (LNP) containing a mixture of phospholipids, cholesterol, PEGylated lipids and cationic or ionizable lipids [2]. Research has shown that such nanoparticles can cross the blood-brain barrier [3] and the blood-placenta barrier [4], so it came as no surprise that the European Medicines Agency assessment report for the Moderna vaccine on page 47 (https://www.ema.europa.eu/en/documents/assessment-report/spikevax-previously-covid-19-vaccine-moderna-epar-public-assessment-report_en.pdf) also noted that mRNA could be detected in the brain following intramuscular administration at about 2% of the level found in plasma. In 2021 researchers from Japan reported a disproportionately high mortality due to cerebral venous sinus thrombosis and intracranial haemorrhage. Despite not being able to prove a causal link with vaccines, as no autopsies were performed, they still believed that a link with vaccination is possible and further analysis is warranted [5].

It was furthermore stated that the mRNA will degrade quickly. Normally, mRNA breaks down within a few minutes to hours, however, the mRNA in these vaccines is nucleoside-modified to reduce potential innate immune recognition [6, 7] and it has been shown that production of the spike protein in some vaccines is kept up for an extraordinarily long time. A study by Röltgen et al. [8] found that the vaccine mRNA persists in the body up to 60 days, with 60 days being the end point of their study. It is thus unknown and impossible to define how much of the spike protein is actually produced in the vaccinated. It is a standard requirement for vaccine producers to define the amount of antigen in each injection. For a "so called "vaccine that is using the human body as the production facility there is no possible quantification of antigen. This is highly variable and dependant on the amount and stability of nanoparticles in the injection, age and fitness of the vaccinee, their immune status and the injection technique – if a blood vessel is directly injected, the nanoparticles will travel in minutes to all major organs including the brain. It is therefore impossible to assess how much spike protein any individual vaccinee produces following an inoculation. In summary, it is unknown where exactly the vaccine travels once it is injected, and how much spike protein is produced in which (and how many) cells.

Prominent cardiologist Dr Peter McCullough stated that the spike protein - a cytotoxin solely responsible for the severity of the respiratory infection - makes the use of it as immunizing agent dangerous. The spike protein in itself can produce COVID- 19 symptoms as shown in animal experiments. The S1 subunit of the SARS-CoV-2 spike protein when injected into transgenic mice overexpressing human ACE-2 caused a COVID-19 like response (a decline in body weight, dramatically increased white blood cells and protein concentrations in bronchoalveolar lavage fluid (BALF), upregulation of multiple inflammatory cytokines in BALF and serum, histological evidence of lung injury, and activation of signal transducer and activator of transcription 3 (STAT3) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathways in the lung [9].

It was further shown that the spike protein S1 subunit, when added to red blood cells in vitro, could induce clotting by binding fibrinogen and ACE2 on platelets, thus triggering their aggregation [10]. The S protein also increases human cell syncytium formation, removes lipids from model membranes and interferes with the capacity of high-density lipoprotein to exchange lipids [11, 12]. Another in silico study showed that the spike protein S2 subunit specifically interacts with BRCA-1/2 and 53BP1 [13]. BRCA-1 is frequently mutated in breast cancer in women and prostate cancer in men, while 53BP1 is a well-established tumor suppressor protein.

A paper published by Liu et al. conducted single-cell mRNA sequencing of peripheral blood mononuclear cells (PBMCs) harvested from patients before and 28 days after the first injection of a COVID-19 vaccine [14]. While this vaccine was based on an attenuated virus and not a mRNA vaccine, it also is injected directly into the deltoid muscle, bypassing the mucosal and vascular barriers.

The authors found consistent alteration of gene expression following vaccination in many different immune cell types. One housekeeping gene of high importance is RNA polymerase I (POL I) which transcribes ribosomal DNA into RNA and monitors rDNA integrity in the process. Many of the downregulated genes identified by Liu et al. (2021) were linked to the cell cycle, telomere maintenance, and both promoter opening and transcription of POL I, indicative of impaired DNA repair processes [14].

Seneff et al (2022) describe another mechanism by which the mRNA vaccines could interfere with DNA repair [15]. The microRNA miR-148 has been shown to downregulate homologous recombination in the G1 phase of the cell cycle. MiR-148 is one of two microRNAs found in exosomes released by human cells following SARS-CoV-2 spike protein synthesis in the experiments by Mishra and Banerjea [16].

Natural immunity ignored

It is an amazing fact that natural immunity is completely disregarded by health authorities around the world. We know from SARS-CoV-1 that natural immunity is durable and persists for at least 12-17 years [17]. Immunologists have suggested that immunity to SARS-Cov-2 is no different. The human population has encountered and co-existed with a great number of coronaviruses throughout evolution. Most of us have cross-reacting T-cells, B cells and antibodies derived from encounters with common cold coronaviruses that can recognise SARS-CoV-2 [18-20]. A survey of more than 100 immunologists, infectious-disease researchers and virologists working on the coronavirus, who were asked whether the virus could be eradicated, showed that almost 90% of respondents believe that the coronavirus will become endemic [21]. The four human coronaviruses that cause common colds are also endemic, without there ever having been a vaccine for any of them. The existence of related viruses might explain that approximately 40% to 45% of COVID infected people are asymptomatic and about 80% of COVID cases are mild infections. In some cohorts, the asymptomatic infection figure jumps as high as 96% depending on the age and cross-immunity imparted by other viruses such as beta coronaviruses HCoV-OC43 and HCoV-HKU1, which have been proposed as a mitigating factor in the spread of SARS-CoV-2 [22-23].

The Brownstone institute has established the most updated and comprehensive library list of 150 of the highest-quality, complete, and robust scientific studies and evidence reports/position statements on natural immunity as compared to the COVID-19 vaccine-induced immunity. The consensus of these studies is that immunity induced by COVID infection is robust and long lasting (https://brownstone.org/articles/79-research-studies-affirm-naturally-acquired-immunity-to-covid-19-documented-linked-and-quoted/).

When comparing the immune response to vaccination and natural infection, differences in the responses were detected. For example, a strong upregulation of genes associated with type I interferon production, cytotoxicity and an increase in circulating plasmablasts were only observed after natural infections [24]. In contrast, mRNA vaccines seem to suppress interferon responses [25]. A literature review by Cardozo and Veazev [26] concluded that COVID-19 vaccines could potentially worsen COVID-19 disease through antibody-dependent enhancement when natural infection occurs after vaccination, regardless of the delivery mechanism - vector or LNP containing RNA – of the nucleic acid coding for the spike protein.

A retrospective cohort study from Sweden revealed that individuals who survived and recovered from a previous infection had a lower risk of COVID-19 re-infection and hospitalisation for up to 20 months. The authors concluded that both previous infection and vaccination should be sufficient proof of immunity to COVID-19 [27, 28].

When comparing 2,653 fully vaccinated individuals with 4,361 individuals recovered from COVID-19, initial levels of antibodies were higher in the vaccinated but decreased exponentially and much faster than in individuals recovered from COVID-19 [29].

There have been discussions about risk and value of vaccination in the previously infected part of the population. Study results have shown that the second dose in people already exposed to the virus leads to a reduction of cellular immunity, inferring those individuals previously infected with COVID-19 should not get a second injection [30].

All of these facts should have led to the standard operating procedure of establishing antibody titres in patients before vaccination for SARS CoV-2, similar to other vaccinations. However, this did not happen and natural immunity is still not accepted as proof of immunity in Australia.

Protection

The vaccine was never meant to prevent the spread of the virus, but to decrease disease severity. A study at the University of California followed up on infections in the workforce after 76% had been fully vaccinated with mRNA vaccines by March 2021 and 86.7% by July 2021. In July 2021 75.2% of the fully vaccinated workforce had symptomatic COVID [31].

Paul Elias Alexander pointed out this troubling situation in an article published by the Brownstone Organisation by citing three studies where we see this emerging situation of the vaccinated increasingly being infected and transmitting the virus. The study by Chau et al. reported a seminal nosocomial outbreak occurring in fully vaccinated Hospital Care workers (HCW) in Vietnam in 2021 [32]. The second study described an outbreak in a Finnish hospital where the virus spread among HCWs and patients [33]. In this study the Delta variant of the virus was introduced by an inpatient. Both symptomatic and asymptomatic infections occurred among vaccinated HCWs. Secondary transmissions were observed from those with symptomatic infections despite the use of personal protective equipment. The third publication detailed an outbreak in an Israeli hospital, where the virus spread among vaccinated HCWs and vaccinated patients [34]. (https://brownstone.org/articles/79-research-studies-affirm-naturally-acquired-immunity-to-covid-19-documented-linked-and-quoted/).

Acharya et al. (2021) and Riemersma et al. (2021) both showed that the vaccinated have very high viral loads similar to the unvaccinated and are therefore as infectious [35, 36]. Brown et al. (2021) and Servelitta et al (2021) suggested that vaccinated people with symptomatic infection by variants, such as Delta, are as infectious as symptomatic unvaccinated cases and will contribute to the spread of COVID even in highly vaccinated communities [37-38].

A study from the US found that increases in COVID 19 cases are unrelated to levels of COVID-19 vaccination across 68 countries and 2,947 counties in the United States. On the contrary, it seems that countries with higher vaccination rates have also higher caseloads. It was shown that the median of new COVID-19 cases per 100,000 people was largely similar to the percent of the fully vaccinated population [39].

Multiple recent studies have indicated that the vaccinated are more likely to be infected with Omicron than the unvaccinated. A study by Kirsch (2021) from Denmark suggests that people who received the mRNA vaccines are up to eight times more likely to develop Omicron than those who did not [40]. This and a later study by Kirsch (2022a) conclude that the more one vaccinates, the more one becomes susceptible to COVID-19 infection [41].

This has to be seen in context with the small risk of dying from COVID-19. A recent peer-reviewed review paper by one of the world's most cited and respected scientist, Professor John Ioannidis of Stanford University notes an infection fatality rate (IFR) for Covid of 0.00-0.57% (0.05% for under 70s), far lower than originally feared and no different to severe influenza [42]. The chances of someone under 50 years old with symptoms dying from COVID-19 is 0.05%. The chances of someone under 18 years old dying from COVID is near 0%. Those that die usually have severe underlying medical conditions. It is estimated that children are seven times more at risk to die from influenza than from COVID-19.

A worldwide Bayesian causal Impact analysis suggests that COVID-19 gene therapy (mRNA vaccine) causes more COVID-19 cases per million and more non-Covid deaths per million than are associated with COVID-19 [43]. An abundance of studies has shown that the mRNA vaccines are neither safe nor effective, but outright dangerous. Never in vaccine history have we seen 1011 case studies showing side effects of a vaccine (https://www.saveusnow.org.uk/covid-vaccine-scientific-proof-lethal).The

Covid-19 Vaccine Monitor, an interim study report for cohort event monitoring of vaccinated persons in the EU, published on June 9, 2022 concludes that across all sites 0.2-0.3% of participants reported at least one serious adverse reaction after receiving the first and/or second dose, and similar numbers are reported after the first booster. (https://zenodo.org/record/6629551)

We are now hearing that the EU issued a warning that taking the boosters may cause adverse effects to the immune system and may not be warranted [44]. A top Israeli immunologist has called on the leaders at the Israeli Ministry of Health to admit that the mass vaccination campaign has failed in Israel [45]. The vaccine is in trial phase and has been linked to not only instant side effects but also short to medium-term side effects [44]. Thorp et al. (2022) highlighted just a few of these side effects, such as miscarriage, foetal death and malformation, chronic autoimmune disease, permanent immune deficiency syndrome, chronic permanent CNS diseases and chronic cognitive disorders, seizure disorders and neonatal/infant cancers; and this only refers to foetuses and infants [46]. Not enough time has passed since administration of the first injections to know what the long-term effects might be.

Pfizer's documents show lipid nanoparticles with their mRNA cargo being distributed throughout the entire body and passing through the blood brain, placental and foetal blood brain barriers and concentrate in the ovaries. From US life insurance reports we know that the all-cause death rates were up 40% in ages 18-64 years by the end of Q3 2021, and according to life insurance companies there are 100,000 excess deaths per month in the US in all age groups, which cannot be attributed to COVID-19 alone [46].

In a recently published study by Doshi et al from August [47], the authors looked for serious adverse events (SAE) and adverse events of special interest (AESI) in the randomized phase III trials of both Pfizer and Moderna. Because both companies began unblinding study participants and offering them the vaccines only weeks after the emergency use authorization was granted by the FDA, the interim datasets from the time point of the EUA was used. By looking in depth at the total number of SAE instead of only the number of participants reporting one or more SAE, they found that the Pfizer injection was associated with a 36% higher risk of SAE in the vaccine versus the placebo group, while the Moderna vaccine was associated with a 6% increase of SAE in the vaccine group. They concluded after a simple risk-benefit analysis using the companies' own data, that for both Pfizer and Moderna excess risk of serious AESI exceeded the benefit of reduction in Covid-19 hospitalizations. They finish with a request for full transparency of the Covid-19 vaccine clinical trial data which to this day are inaccessible.

In a study by Shimabukuro et al. [48] following 3,958 pregnant participants in the v-safe pregnancy registry only 827 (20.89%) women enrolled in the study completed pregnancy. In the v-safe table the number of pregnant women registered as pregnant was 30,887 and the number registered as pregnant after vaccination with either Moderna or Pfizer vaccine was 4,804, which suggests loss of pregnancy and stillbirths in 84.45% of the pregnant women [48].

In a study concentrating on the second booster dose by Regev-Yochay et al. (2022) breakthrough infections were shown to be common, mostly very mild, but with high viral loads [49]. The vaccine efficacy against infection was as low as 30% for BNT162b2 (Pfizer) and 11% for mRNA1273 (Moderna) with local and systemic adverse reactions reported for 80% of BNT162b2 recipients and 40% of mRNA1273 [50].

Children under 18 are 51 times more likely to die from the mRNA vaccines than from COVID-19 if unvaccinated. Young adults in the age range of 18 to 29 are eight times more likely to die from vaccination than from COVID-19. Adults from 30 to 39 are 7 times more likely to die from vaccination and those aged 40 to 49 are 5 times more likely to die after vaccination. People in the group aged 50 to 59 are still twice as likely to die after vaccination than after COVID-19. Only when over 60 years of age is the chance of death equal for both causes. Even when over 80 years old the likelihood of dying from Covid inoculation is just 0.13% lower than the risk of dying from the infection. The authors concluded that the protection from COVID-19 death falls far short of the risk of dying from the vaccine for people below 50 years old [51].

According to Kostoff [52] the number of deaths attributable to each inoculation is five times higher in the most vulnerable 65+ demographic than deaths attributable to COVID–19. With decreasing age, the risk of death from COVID-19 decreases drastically. Combined with the longer-term effects of the inoculations, most of which are still unknown, this increases the risk-benefit ratio, perhaps substantially, in the lower age groups.

A study looking at the length of protection over time indicated that immunity against the delta variant of SARS-CoV-2 waned in all age groups a few months after receiving the second dose of the vaccine [53]. Another study found that antibody titres increased significantly at five weeks after the first vaccination but decreased rapidly at four months after the second injection. This significant decrease was independent of gender or age [54]. The fact that immunity after vaccinations seems to wane over time has been reported by other researchers who also found that antibody titres are decreasing by up to 40% each months [55] with no detectable antibody levels recorded in 16.1% of the subjects in one study within six months. Therefore, booster vaccinations were recommended [56]. Another study found that decrease in neutralising antibody titres to alpha, beta, gamma and delta variants was not significantly different between the different vaccines. They used modelling and predicted below 50% protection against symptomatic infection within the first year, also urgently recommending booster shots [57]. Scientists agree though, that introducing a booster too early

and too frequently carries increased risks especially for vaccines that have immune-mediated side-effects, such as myocarditis, Guillaine-Barre syndrome and thrombosis [58].

Lui et al. [59] specifically looked at protection against Omicron and concluded that the Omicron variant of COVID-19 was remarkedly resistant to neutralization by serum from individuals vaccinated with one of the four widely used COVID-19 vaccines. Serum from persons vaccinated and boosted with mRNA-based vaccine was also showing substantially diminished neutralization of Omicron.

A study investigated the neutralizing antibody titres against the reference strain WA1/2020 and omicron subvariants BA.1, BA.2, BA.2.12.1 and BA.4 or BA.5. in participants that had been double vaccinated and boosted with the Pfizer mRNA vaccine versus participants that had been vaccinated (bar one) and infected with the BA.1 or BA.2 variant of omicron on average 29 days prior. Their conclusion was that compared to the reference strain neutralising antibody titres to the Omicron variants were substantially decreased in both groups (6.4, 7.0 and 14.1 times (vaccinated) and 6.4, 5.8 and 9.6 times (infected) lower against BA.1, BA.2, BA.2.12.1 respectively and 21.0 (vaccinate) and 18.7 (infected) times lower against BA.4 or BA.5), suggesting that the later variants increasingly escape neutralizing antibodies [60].

Even a fourth shot of a Covid-19 vaccine is “not good enough” to prevent Omicron, according to a preliminary study in Israel. Sheba Hospital tested a fourth shot given to more than 270 medical workers, with 154 getting the Pfizer jab and 120 receiving Moderna. The researchers found that both groups showed a “slight” increase in antibodies - but not sufficient to prevent Omicron. Disturbingly, the vaccinated infected health care workers had relatively high viral loads, which suggests that they were infectious [49].

In a letter to the editor Yamamoto (2022) sums up the literature pointing to the fact that 8 months after being vaccinated twice the immune functions are less than those of an unvaccinated person according to a study by Nordstroem et al (2022) [61]. Booster shots can impair immunity due to a variety of factors leading to the recommendation to discontinue further booster shoots.

A paper by John Gibson from the University of Waikato looked at the excess death rate in New Zealand and found that rising excess mortality was closely related to the booster rollout. The author calculated 16 excess deaths for each 100,000 booster doses (https://repec.its.waikato.ac.nz/wai/econwp/2211.pdf).

According to the Health NSW government site the data obtained in 14 days until 16th of July 2022 continues to show the trend of worsening effects after the booster shots. Figure 1 shows the hospitalisation, the ICU admission and deaths sorted by vaccination status with a total of 806, 77 and 142 respectively. Comparing data of people infected with COVID the figures provided by the NSW Health Department (Fig 1) seem to confirm this trend.

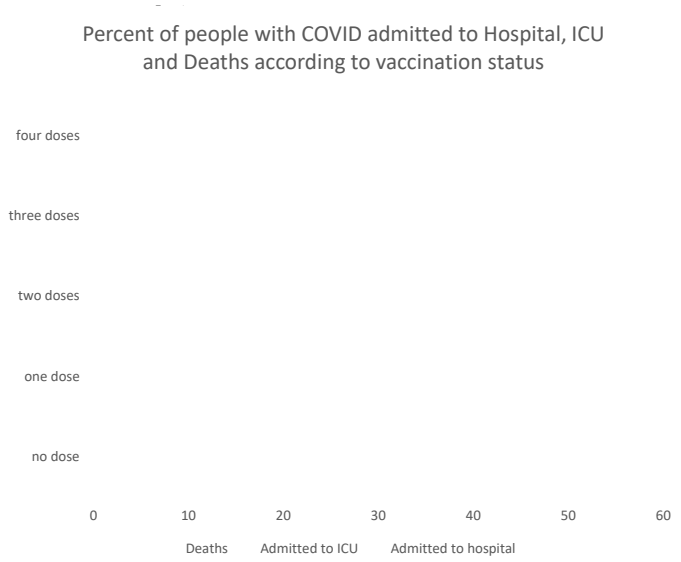

Figure 1: People diagnosed in 14 days up to the 16th of July 2022 who were submitted to hospital, ICU and died in New South Wales, Australia. Numbers represented as percentage of the total (https://www.health.nsw.gov.au/Infectious/covid-19/Documents/weekly-covid-overview-2-22-716.pdf)

Treatments

It is truly disturbing that treatments recommended by doctors in America, some of them having successfully treated COVID-19 patients, including very sick patients, have not been investigated in Australia. These treatments are mainly based on vitamins, zinc and zinc ionophores, such as ivermectin or hydroxychloroquine. The recommendation is to treat as early as possible. Scientific papers support the use of ivermectin according to Bryant et al. [62]. They found moderate to strong evidence that ivermectin can reduce COVID-19 deaths while being safe and inexpensive. The same was found for hydroxychloroquine in a review by McCullough et al, which also stated that a reduction of mortality strongly depends on an early start of the treatment. Hydroxychloroquine has been registered in the US since 1955 and has a well-characterized safety profile [63].

Yet here in Australia the recommendation is to isolate and monitor yourself. Only if you have difficulty breathing, experience loss of speech or mobility, confusion or chest pain should you contact the health care provider. Additionally, the government strongly advises not to use the following treatment for COVID-19 off label: Ivermectin, doxycycline, zinc and hydroxychloroquine (https://www.health.gov.au/health-alerts/covid-19/treatments).

The TGA provisionally approved the first oral treatments in January 2022 for Australia, Lagevrio® (molnupiravir) and Paxlovid® (nirmatrelvir + ritonavir) and recommend that both treatments should be started as soon as possible after diagnosis of COVID-19 (https://www.health.gov.au/health-alerts/covid-19/treatments/oral). The TGA also accepted - similar to the agreement for the

provisionally approved vaccines - rolling data for COVID-19 treatments, to enable early evaluation of data as it comes to hand (https://www.tga.gov.au/apm-summary/lagevrio). In other words, both drugs have been provisionally approved on the basis of short-term efficacy and safety data and permanent approval depends on the efficacy and safety data from ongoing clinical trials and post-marketing assessment. (https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2022-PI-01049-1)

Therefore, these treatments are still in trial phase and all patients treated with them are trial participants. Paxlovid has listed numerous potential complex and serious drug-drug interactions against its registration which could result in severe or life-threatening side effects(https://www1.racgp.org.au/newsgp/clinical/what-gps-need-to-know-about-the-new-covid-antivira).

Short Term Side Effects

Just to name a few short-term side effects: Death, Cardiac disorders such as Myocarditis, Blood and lymphatic system disorders, such as blood clots, thrombocytopenia, low platelet count, cerebral venous sinus thrombosis, capillary leakage syndrome, Congenital and genetic disorders, Eye disorders, Immune disorders, Muscular, skeletal and connective tissue disorders, Cancerous tumours, Nervous system disorders, Pregnancy and perinatal conditions, Guillain-Barre syndrome and the list goes on.

Pfizer's documents demonstrate lipid nanoparticles with their mRNA cargo being distributed to the entire body and pass through the blood brain, placental and foetal blood brain barriers and concentrate in the ovaries. The vaccine is in trial phase and has been linked to not only instant but also long-term side effects.

Thorp et al. [46] highlighted just a few of the side effects, such as miscarriage, foetal death and malformation, chronic autoimmune disease, permanent immune deficiency syndrome, chronic permanent CNS diseases and chronic cognitive disorders, seizures and neonatal/infant cancers; and this is only with regard to foetuses and infants.

The data from NSW (Figure 1) showed clearly that COVID injections were correlated with increases in hospitalization and ICU admissions and indicate a relation to death with COVID injections. The increase in hospitalisation, ICU admissions and deaths is very pronounced after the third injection although only 69% of the population took the booster shot versus 95% taking the initial series.

The Australian Bureau of statistics has just released the national death rate for March 20, 2021 up until 31 March 2022 (registered by 31 May 2022) as 44,331, which according to their own statement lies 6,609 (17.5%) above the historical average. These extra deaths cannot be explained by COVID alone (Fig 2) which is responsible for less than half of the excess deaths in the first 4 months of 2022 in Australia. Cancer, diabetes and neurodegenerative diseases are all above the baseline in this time frame (https://www.abs.gov.au/statistics/health/causes-death/provisional-mortality-statistics/latest-release?fbclid=IwAR3fpywSvxWCXTRUaZx99M6s_w_kBRdMa3b_13msQ3bNPRanFjGHi-wWTZQ).

Figure 2: Death rate for Australia from 20th of March 2021 to 27 March 2022 according to the Australian Bureau of Statistics (https://www.abs.gov.au/statistics/health/causes-death/provisional-mortality-statistics/latest-release?fbclid=IwAR3fpywSvxWCXTRUaZx99M6s_w_kBRdMa3b_13msQ3bNPRanFjGHi-wWTZQ)

We get an insight into what is really going on in England where the government released COVID related death data (if the death certificate mentioned COVID) and all other death data sorted by vaccination status (Figure 3). The overall death rate for the unvaccinated was 17% while for the vaccinated it was 83%. The trend seems to be an ever increasing all causes death rate with added vaccinations without getting any protection from additional injections.

Figure 3: The cause of death according to vaccine status in the UK from the 1 January 2021 to the 31 May 2022 https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsbyvaccinationstatusengland

Unexplained deaths in Germany have been shown to be the consequence of mRNA vaccines causing an autoimmune response of CD8 T killer lymphocytes in all organ systems throughout the body. Dr Sucharit and Dr Burkhardt stated that the mRNA vaccine is killing the young and the old (https://doctors4covidethics.org/on-covid-vaccines-why-they-cannot-work-and-irrefutable-evidence-of-their-causative-role-in-deaths-after-vaccination/).

According to the VAERS database over 22,000 deaths have been associated with the COVID-19 vaccine. This is particularly alarming as according to the VAERS website adverse events including deaths are underreported by an unknown factor which could be between 10 and 100, so the actual number of deaths is likely much higher and could be over a million.

From large insurance companies in the US we know that the all-cause death rates are up 40% in ages 18-64 years and there are 100,000 excess deaths per month in the US across all age groups, which cannot be attributed to COVID-19 alone. However, caution has to be taken in interpreting these data as deaths due to suicides and delayed hospital treatment are not taken into consideration. Nevertheless, the trend seems to be the same and should raise alarm.

A study by Gat et al. on semen of male semen donors revealed a transient decrease in semen concentration and a reduction in the total motile count (TMC) after COVID-19 vaccination [64].

In January 2022 the "Save us now" organisation put together a list of 1011 case studies reporting side effects after vaccination (Table 1) (https://www.saveusnow.org.uk/covid-vaccine-scientific-proof-lethal/). Most of these side effects have not been listed in any of the vaccine brochures or on the Australian Government websites. Knowing that the mRNA vaccine can be found in nearly all organs including the brain the involvement of so many organs and tissues is not surprising. The explanation for multiple disorders and multiple affected organs post-vaccination is the toxicity of the S1 subunit of the spike protein which creates similar symptoms as the viral disease. Additionally, the lipid nanoparticles alone cause inflammation and vascular damage [65].

Table 1 A and B: All symptoms reported from the 1011 case studies listed by the "Save us now organisation" and some additional case studies by Di Mauro et al. [66]; Erro et al. [67]; Garreffa et al. [68]; Jabagi et al. [69] and Jee-Eun et al. [70] https://www.saveusnow.org.uk/covid-vaccine-scientifc-proof-lethal/

A

System organ class	Vaccine-induced SE	Pfizer/ BioNTech	Moderna	Oxford/ Astra Zeneca	Johnson & Johnson
Auditory and balance disorders	Acute vertigo [71]	x			
	Sudden sensorineural hearing loss			x	
Autoimmune disease	Autoimmune encephalitis			x	
	Autoimmune hepatitis	x	x	x	
	Graves' disease	x			
	Limbic encephalitis	x			
	Multiple sclerosis	x	x	x	
	Myasthenia gravis	x			
	Psoriasis	x		x	

	Severe autoimmune hemolytic anemia		x		
	Systemic lupus erythematosus	x			
	Vogt-Koyanagi-Harada Syndrome	x		x	
Cardiac disorders	Arrhythmia		x		
	Cardiac tamponade	x			
	Cardiomyopathy	x			
	Endocarditis		x		
	Kounis hypersensitivity-associated acute myocardial infarction	x			
	Myocardial infarction	x	x	x	
	Myocarditis *	x	x	x	x
	Myocarditis-induced Sudden Death	x			
	Myopericarditis	x	x		
	Pericarditis	x	x	x	x
	Takotsubo cardiomyopathy	x	x	x	
	Transient Cardiac Injury	x			
Death		x	x	x	x
Dermal disorders	Chilblains	x	x		
	Delayed adverse skin reactions *2	x	x	x	
	Dermal hypersensitivity (Covid arm)	x	x	x	
	Exacerbated Hailey-Hailey	x	x		
	Petechiae and peeling of fingers	x	x		
	Purpuric rash *1	x	x	x	
	Reactivation of alopecia areata	x		x	
	Reactivation of Bacille Calmette-Guérin scar	x	x		
	Sweet's syndrome	x		x	x
	Toxic epidermal necrolysis			x	
Endocrine disorders	Menstrual disorders, heavy menstrual bleeding	x	x	x	x

Gastrointestinal disorder	Appendicitis	x				
	Gastroparesis	x				
	Oral aphthous ulcers	x				
Immune and Lymphatic disorders	Allergy to PEG-ASNase	x		x		
	Anaphylaxis *4	x		x	x	
	Antibody-dependent cell cytotoxicity				x	x
	Arthritis	x				
	Complement-dependent cytotoxicity				x	x
	Hemophagocytic lymphohistiocytosis				x	
	Immune-mediated disease outbreaks	x		x	x	
	Lymphadenopathies *3	x		x	x	
	Multisystemic inflammatory syndrome	x			x	
	Rapid Progression of Angioimmunoblastic T Cell Lymphoma	x				
	Seronegative Polyarthritis	x			x	
	Splenic infarction				x	
	Thymic hyperplasia			x		
Infections	Covid-19	x		x	x	x
	Herpes Simplex	x		x	x	
	Herpes Zoster (Shingles)	x		x	x	
	Hepatitis C reactivation	x				
	Non-disseminated herpes zoster	x				
Liver and gallbladder disorders	Acute liver injury			x		
	ANCA glomerulonephritis			x		
Musculosceletal disorders	Amyotrophic neuralgia				x	
	Fasciitis			x		
	Myositis (inflammatory)	x			(x)	
	Polyarthralgia and Myalgia Syndrome				x	
	Polymyalgia rheumatica	x			x	

Rhabdomyolysis	x	x		
Still's disease			x	
Synovitis	x			

*Acute Fulminant Myocarditis and Cardiogenic Shock, lymphocytic, eosinophilic, infarct-like and autoimmune myocarditis, acute haemorrhagic encephalomytitis [72].

*1 Haemorrhagic rash, Cutaneous thrombosis
*2 Eczematous, Shingles-like skin lesion, Pityriasis rosea-like reaction, Urticaria, Lichen planus-like dermatitis, Bullous drug eruption, Pruritus, Spongiotic dermatitis, Morbiliform rash, Papulovesicular reaction, Purpura annularis telangiectodes
*3 Cervical lymphadenopathy, Axillary lymphadenopathy (Garreffa et al, 2021), [68]
*4 Prolonged anaphylaxis, biphasic anaphylaxis, Anaphylactoid reaction and coronary thrombosis

B

System organ class	Vaccine-induced SE	Pfizer/ BioNTech	Moderna	Oxford/ Astra Zeneca	Johnson & Johnson
Neurological disorders	Acute inflammatory neuropathies	x	x	x	
	Abducens Nerve Palsy	x			
	Adrenomyeloneuropathy	x			
	Bell's palsy	x	x	x	
	Cerebral hemorrhage *8	x	x	x	x
	Cerebral venous sinus thrombosis	x	x	x	x
	Cerebral venous sinus thrombosis (CVST) with thrombocytopenia				x
	CNS demyelination	x	x	x	x
	CNS inflammation	x	x		
	Distal small fiber neuropathy			x	
	Encephalomyelitis *5	x		x	
	Encephalopathy (acute)	x	x		
	Guillain-Barré syndrome (Jee-Eun, 2022)	x	x	x	x
	Miller-Fisher syndrome	x		x	
	Myelitis *9	x	x	x	
	Neuro-ophthalmic complications with VITT			x	
	Optic neuritis	x			
	Parsonage-Turner Syndrome	x	x		
	Stroke (Jabag et al, 2021) *6	x	x	x	x
	Status epilepticus, seizures*7	x	x	x	
Olfactory disorders	Phantosmia	x			

Optical disorders	Acute corneal endothelial graft rejection	x				
	Bilateral choroiditis				x	
	Central Serous Chorioretinopathy	x				
	Diplopia				x	
	Immune mediated keratolysis				x	
	Macular Neuroretinopathy				x	
	Oculomotor palsy				x	
	Retinal necrosis due to varicella zoster reactivation	x				
	Transient visual field loss	x				
	Tolosa-Hunt syndrome	x				
	Uveitis, Panuveitis	x				
Other disorder	Pancreas allograft rejection				x	
	Pancreatitis	x				
Pregnancy outcomes	Miscarriage (Pfizer's own data)	x				
Psychiatric disorder	Depression				x	
Pulmonary disorder	Acute eosinophilic pneumonia				x	
	Squamous cell carcinoma of the lung with hemoptysis	x				
Renal and urinary disorders	Acute renal failure		x			
	Crescentic Pauci-Inmune glomerulonephritis	x	x			
	Genital necrosis with cutaneous thrombosis	x				
	IgA nephropathy	x	x			
	Lipschuetz ulcer				x	
	Nephrotic syndrome				x	x
	Macroscopic hematuria	x	x			
	Minimal change disease and acute kidney injury	x			x	
Respiratory and thoratic disorders	Asthma exacerbation	x				
	Pulmonary embolism	x	x		x	x
	Semi Occluded Vocal Tract				x	
	Vaccine-induced interstitial lung disease	x				
Tissue disorders	Hemophagocytic lymphohistiocytosis				x	

Vascular disorders	Accelerated hypertension							
	Diffuse prothrombotic syndrome					x		
	Fatal systemic capillary leak syndrome					x		
	Giant cell arteritis	x						
	Haemolysis	x				x		
	Haemorrhage *10	x		x		x		
	Inflammation and platelet activation					x		x
	Limb ischemia					x		
	Microscopic polyangiitis	x						
	Symptomatic carotid occlusion							x
	Thrombocytopenia *11	x		x		x		x
	Thromboembolic events *12	x		x		x		
	Thrombotic events *13	x		x		x		x
	Vasculitis *14	x		x		x		x

*5 Acute disseminated Encephalomyelitis, acute demyelinating Encephalomyelitis, acute haemorrhagic encephalomyelitis (Ancau et al, 2022) [72]
*6 Ischemic stroke, acute ischemic stroke and hemorrhage, haemorrhagic stroke
*7 Acute hemichorea-hemiballismus, Dyskinesia (Erro et al, 2021) [67]
*8 Intracerebral hemorrhage and thrombocytopenia, Intracerebral hemorrhage associated with vaccine-induced thrombotic thrombocytopenia
*9 Extensive longitudinal transverse myelitis, Transverse myelitis, acute transverse myelitis, partial transverse myelitis, Myelitis, Acute bilateral optic neuritis/chiasm with longitudinal extensive transverse myelitis, Neuromyelitis optica (Devic's disease)
*10 Acral hemorrhage, Pulmonary hemorrhage, Retinal haemorrhage, Lobar hemorrhage with ventricular rupture
*11 Thrombotic thrombocytopenia, Thrombocytopenia and splanchnic thrombosis, Thrombotic thrombocytopenic purpura, Immune thrombocytopenic purpura
*12 Venous thromboembolism and mild thrombocytopenia
*13 Arterial thrombosis, Cerebral venous sinus thrombosis, Both transverse sinuses thrombosis, Left sigmoid sinus thrombosis, Portal vein thrombosis, Bilateral superior ophthalmic vein thrombosis, Major artery thrombosis, Idiopathic external jugular vein thrombophlebitis, Disseminated intravascular coagulation, Ophthalmic vein thrombosis, Central retinal vein occlusion
*14 Cutaneous vasculitis, Leukocytoclastic vasculitis, Small-vessel vasculitis, Granulomatous vasculitis, Vasculitis and bursitis, ANCA-associated vasculitis, Urticarial vasculitis, Neutrophil anti-cytoplasmic antibody-associated vasculitis, Cutaneous leukocytoclastic vasculitis

Side Effects (SE) are listed by organ class in alphabetical order, not by severity. To keep these tables manageable, we sorted subclasses of specific side effects under one heading and the foot notes below explain which subclasses can be found under the listed SE. Note that not all subclasses of SE have been demonstrated for all 4 vaccines.

COVID-19 vaccines cause more side effects than any other vaccine, a fact that is attributed to its interactions with the immune system. Not only does spike protein produces unwanted side effects, but mRNA and nanoparticles do as well. Seneff et al [15] enumerated Covid-19 vaccine effects on the innate immune system, importantly a decrease of type I interferon signalling, as well as disturbances in the regulation of protein synthesis affecting the formation of immune cells and the apoptosis of tumor cells. These are major disturbances that in turn can lead to a multitude of disorders such as those listed in Table 1. The suppression of the interferon response by the mRNA vaccines alone can lead to a wide variety of disorders, such as reactivation of viral infections and reduce the immune system's ability to not only fight disease but to keep tumors and autoimmune reactions suppressed [73]. A case report by Glas et al from [74] illustrates the effects of a disseminated viral infection on an immune-suppressed patient: In this instance fatal multiorgan failure associated with disseminated Herpes simplex virus-1 infection. Considering that reactivation and spread of dormant viral infections including Herpes simplex and Herpes zoster are listed as side effects from both mRNA injections as well as the Astra Zeneca vaccine, it is maybe not surprising that pathology reports by Dr Sucharit and Dr Burkhardt (2021) show multiorgan failure as cause of death in several cases of post-vaccine deaths.

Spike proteins enter the circulation when the cell they were attached to is destroyed by the immune system. The freely circulating spike proteins attach to any cell that expresses ACE2 receptors, explaining the multitude of sites where disorders occur [75]. Another method of viral spread that escapes the immune system is the formation of syncytia which can be induced by the spike protein itself. Heterotypic cell-in-cell structures with lymphocytes inside multinucleate syncytia are prevalent in the lung tissues of coronavirus disease 2019 (COVID-19) patients. This membrane fusion is dictated by a bi-arginine motif within the polybasic S1/S2 cleavage site leading to the formation of multinucleate syncytia. Host metalloproteases (ADAM-17 and ADAM-10) promote such spike protein-mediated lung cell fusion [76, 77]. Pepe et al (2022) [77] showed furthermore that the formation of tunneling nanotubes can be induced by Covid-19 in a so far undisclosed way and used to transport viral particles or indeed viral components like S and N proteins from infected to ordinarily non-permissive cells, e.g. neuronal cells. There are multiple ways in which the virus and the spike protein can spread throughout the body and from cell to cell without attracting too much attention from the immune system. Further weakening of the immune system through rashly promoted genetic intervention can only lead to more severe disease.

What needs to be further emphasised is that the majority of deaths with and from COVID- 19 occur in the elderly with multiple co-morbidities and generally weaker immune systems. Yet they are vaccinated with an injection that amplifies underlying disorders (Fig 4) and is dependent on a strong immune response. Ironically, the survival of many of those patients is probably due to their immune system not being able to mount a significant response to the induced spike protein production.

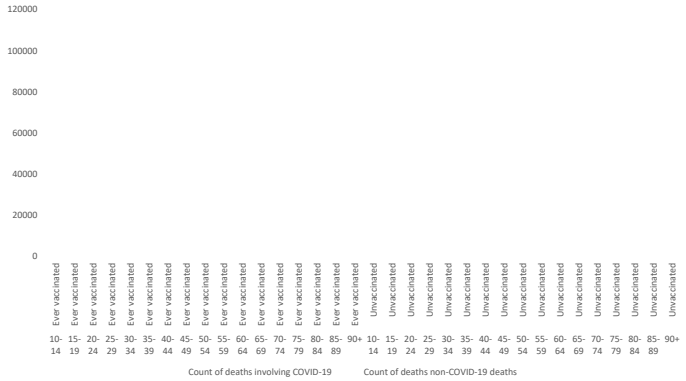

Figure 4: Death rate due to COVID and other causes comparing the vaccinated (at least one vaccination) and unvaccinated in each age group. The data of deaths occurring was for the period of the 1st of January 2021 to 31st of May 2022 in England (https://www.ons.gov.uk/)

Long Term Side Effects

Long-term risks of vaccination as predicted by scientists, many already validated by scientists and doctors:
Vaccine-induced autoimmunity, pathogenic priming, multisystem inflammatory disease and autoimmunity, antibody dependent enhancement (ADE), activation of latent viral infections, neurodegeneration and prion disease, increased thrombosis, cardiomyopathy and other vascular events following vaccination, babies suffering enduring adverse consequences, mRNA reverse transcribing intracellularly into the DNA and death due to autoimmune disease long after vaccination [78-84].

Some More Details

Autoimmune Disease

A study by Lyons-Weiler [79] revealed that over 1/3 of SARS CoV-2 proteins, including the spike protein show problematic homology to key proteins in the human adaptive immune system which might lead to autoimmune reactions against these proteins. Kelleni [78] reports on the potential risk of the vaccine to induce auto-immune diseases such as thrombocytopenia, myocarditis and immune induced thrombosis and thromboembolism which can have fatal outcomes and might be behind some of the post vaccination reports on sudden deaths.

Antibody Dependent Enhancement (ADE)

Hasan et al. [80] analysed data from the National Health Service published by Public Health England and showed that the death rate due to the Delta variant infection was eight times higher in fully vaccinated than in unvaccinated infected people. The authors suggest that in a subset of individuals the pre-existing anti-S-IgG titre induced by vaccination may be sub-neutralizing and leading to accelerated infectivity via ADE, which is displayed as higher death rates.

Prion Disease

The potential risk factors of the mRNA or vector DNA vaccine are protein sequences that can induce TDP-43 and FUS to aggregate into prion configuration, which might lead to neurodegenerative diseases, such as Alzheimers [85]. The spike protein encoded by the mRNA binds to the ACE2 receptor which releases zinc molecules. Zinc also causes TDP-43 to transform into a pathological prion [81]. The link with neurodegenerative disease is the ability of the spike protein to interact with the heparin binding amyloid forming proteins. A study indicated that the S1 protein forms a stable bond with the aggregation-prone proteins, which might initiate aggregation of brain proteins and thereby accelerate neurodegeneration [82]. Finisterer and Scorza [86] further stated that SARS-CoV-2 vaccines trigger neurological adverse reactions and both mild and severe neurological side effects have been occasionally reported. Studies support the theory that the onset and progression of neurodegenerative diseases such as Alzheimer and Parkinson disease, including TDP-43 proteinopathy, are associated with propagation of protein aggregates between neuronal cells. These speculations are supported by a case report of prion disease due to vaccination from Turkey [87, 88].

Thrombosis, Capillary Leakage Syndrome and Myocarditis

Scientific studies have raised serious concerns about the safety of AstraZeneca after reports of cerebral venous sinus thrombosis and a variety of other thrombotic events the AstraZeneca vaccination with studies reporting such events in medical journals. Kircheis [22] reported that other serious conditions have been reported for COVID vaccines such as capillary leakage syndrome

(AstraZeneca) and coronary myocarditis (Pfizer).

Pregnancy and Vaccination

Some concerns about vaccinating pregnant women were voiced by Anand and Stahel [83]. Walsh et al. [89]. reported that the results of the Pfizer vaccine demonstrate a broad immune response to vaccination with stimulation of neutralizing antibody responses, stimulation of CD4+ cells and growth of effector memory CD8+T cells in men and women. Anand and Stahel [83] hypothesised that one could assume this would also happen in pregnant women. This would not be favourable for a perinatal outcome and might lead to preterm birth and fetal loss, as a good outcome relies on amplifcation of helper T cell type 2 and regulatory T cell activity coupled with decreased Th1 response [90]. Evidence has suggested that mothers with variant CD4+ T cell responses give birth to babies that may suffer enduring adverse consequences [91].

Side Effects Acknowledged but Played Down as Extremely Small Risk

The TGA report in Australia on a weekly basis and the report of the 2nd of September 2021 mentioned nine more blood clots and low platelet counts, confirmed as probably Thrombocytopenia syndrome linked to the AstraZeneca vaccine with two connected deaths during that week, one from Queensland and one from NSW. An assessment of the 125 cases of thrombosis with thrombocytopenia syndrome (TTS) showed that women in the younger age groups were slightly more likely to develop TTS in more unusual places such as brain and abdomen with more serious outcomes projected (TGA).

Another rare side effect is Guillian-Barre syndrome (GBS), which affects the nerves. Up to the 29 August 99 reports of GBS after vaccination have been received. Further 61 reports of immune thrombocytopenia were lodged after AstraZeneca vaccination. For the Pfzer vaccine the TGA reports 293 instances of suspected myocarditis and/or pericarditis following vaccination to the 29 August 2021. Nine of these reports were from children 16 to 17 years of age. A study concluded that observations of increased thrombosis, cardiomyopathy and other vascular events following vaccination might be caused by the mRNA vaccines dramatically increasing inflammation of the endothelium and T cell infiltration of cardiac muscle [92].

Whistleblowers

At a parliament enquiry by US senator Ron Johnson lawyer Thomas Renz presented three US military doctors, Drs. Samuel Sigoloff, Peter Chambers, and Theresa Long, whose declarations he planned to use in federal court under penalty of perjury. These doctors revealed a 300% increase in miscarriages in the military above the five-year average in 2021 with the five-year average being 1,499 miscarriages per year while in the first 10 months of 2021 the registered miscarriages were 4,182. Other diseases went up in a similar fashion such as an almost 300% increase in cancer diagnoses (from a five-year average of 38,700 per year to 114,645 in the first 11 months of 2021). Neurological issues increased by 1000% from a baseline average of 82,000 to 863,000 in 2021. Some other increased conditions were:

- 269% increase of myocardial infarction
- 291% increase of Bell's palsy
- 156% increase of children's congenital malformations of military personnel
- 471% increase of female infertility
- 467% increase of pulmonary embolisms

https://newlifenarrabri.wordpress.com/2022/02/01/jo-nova-huge-spike-in-us-military-injuries-from-covid-vaccinations/ and https://www.ronjohnson.senate.gov/2022/2/sen-johnson-to-secretary-austin-has-dod-seen-an-increase-in-medical-diagnoses-among-military-personnel

According to an interview in February 2022 with Julian Gillespie, who is currently fighting in court against the vaccine mandates, an evaluation of the TGA reports revealed that Australia's average of adverse events after vaccination since 1971 up to 2020 is recorded as 2.4 death per year and up to 3,500 adverse events per annum. Since the rollout of the COVID vaccines there have been 755 deaths and 105,000 adverse events in a year with these figures likely to be underreported. https://rumble.com/vtv5pe-julian-gillespie-update-on-avn-judicial-review-to-stop-vaccines-in-australi.html?fbclid=IwAR34RTAAYX_nf9eTe1LOJSxuZ0-TbUFasXPQ37qhPEqrQI9wNe8Yig4ZwQ8

The question is how many deaths and side effects are we accepting as normal for vaccines and where do we draw the line to say more investigations need to be done before any further vaccines are distributed?

Conclusion

Never in Vaccine history have 57 leading scientists and policy experts released a report questioning the safety and efficacy of a vaccine [93]. They not only questioned the safety of the current Covid-19 injections, but were calling for an immediate end to all vaccination. Many doctors and scientists around the world have voiced similar misgivings and warned of consequences due to long-term side effects. Yet there is no discussion or even mention of studies that do not follow the narrative on safety and efficacy of Covid-19 vaccination.

In the USA, as Blaylock [94] states it very nicely, federal bureaucrats have forced the acceptance of special forms of care and prevention, which includes experimental mRNA vaccines [93]. Medical experts that have questioned the safety of these vaccines have been attacked and demonised, called conspiracy theorists and have been threatened to be de-registered if they go against the narrative. Alternative treatments were prohibited and people who never practised medicine are telling experienced doctors how to do their job. AHPRA is doing the same here in Australia to the detriment and in ignorance of science. When Adjunct Professor John Skerritt, who is currently the Deputy Secretary and directly responsibility for both the Therapeutic Goods Administration and the Office of Drug Control, was asked why the registration process for vaccines was shortened he wrote: "It is nonsense to assert that vaccines typically take 10 years to licence. The standard regulatory process for vaccines is about 10-12 calendar

months and in the case of COVID-19 vaccines this period was shortened by accepting data on a rolling basis, teams reviewing different parts of the dossier in parallel, working collaboratively with international regulators, and by many members of the teams working long hours" (personal e-mail communication). One has to wonder how they propose to assess long-term side effects. Can we really trust any pharmaceutical drug approval by the TGA after this statement?

Pfizer never planned to reveal its clinical trial data and had to be ordered by a judge in the USA to release the data to the public. Even then they and the CDC tried to limit the number of pages published per month which would have made the full study data public knowledge sometime in the 2070ies. The reason given was that some proprietary information had to be blacked out before release to the public. Again, it is inconceivable why it would be impossible to go through the study data in a few months, when it took the CDC less than 4 weeks to give the injections emergency use authorization - unless you want to entertain the idea that the study data were never actually read and scrutinised, a frightening perspective.

As scientists we put up hypotheses and test them using experiments. If a hypothesis is proven to be true according to current knowledge it might still change over time when new evidence comes to light. Hence, sharing and accumulating knowledge is the most important part of science. The question arises when and why this process of science has been changed. No discussion of new knowledge disputing the safety of the COVID-19 vaccines is allowed. Who gave bureaucrats the means to destroy the fundaments of science and tell scientists not to argue the science?

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NSW poisons Information Centre
the children's hospital at Westmead

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Sept 19, 2022

Advisory Committee on Medicines Scheduling
Therapeutic Goods Administration
136 Narrabundah Lane
Symonston ACT 2609

Re: Proposed amendments referred for scheduling advice to ACMS meeting #40, November 2022

The NSW Poisons Information Centre (NSW PIC) provides a phone-based advice service on suspected poisonings to the public and health professionals calling from NSW, TAS and ACT on a near full-time basis and a shared after-hours service to the remainder of Australia. This results in approximately half of Australia's poisons-related calls being received by our Centre.

Ivermectin

The NSW Poisons Centre opposes the proposed change to the regulations which would remove restrictions currently in place for the prescribing of ivermectin.

Since the change in regulations which requires restrictions in prescribing of ivermectin was implemented in Sept 2021, the NSW PIC has received 35 calls regarding exposures to ivermectin which was being inappropriately used for Covid treatment or prevention. Of these 17 were vet products, 11 were products available on prescriptions in Australia, 3 were purchased from overseas and in 4 cases the source was unclear. This demonstrates a continued demand from consumers for the inappropriate use of ivermectin. The use of vet products would indicate the restrictions in prescribing is working, to a degree, in reducing the availability of prescribed ivermectin to those who would use it inappropriately. If the restrictions on prescribing of ivermectin were removed, it is likely the numbers of inappropriate use would be much higher.

s22 [redacted]

s22

s22

s22

Regards

s22

s22

APPLICATION IN SUPPORT OF IVERMECTIN REGISTRATION

s22 [redacted]

s22 [redacted]

Note Fig 6, which must speak for itself as overwhelming evidence of IVM benefit, not found with any other early treatment.

In this article, I summarise benefits of IVM, not available elsewhere:

(i) Broad therapeutic window re time for effective therapy including prophylaxis and later disease.

(ii) Infectious viral production is shortened
(iii) Solid safety record – not age restricted.
(iv) Objective reversal of hypoxia. Dramatic effect on disease course.
(v) Evidence of reduced Long Covid.
(vi) Multiple loci of therapeutic effect, means less chance of mutant escape.
(vii) Cheap and available
(viii) Numerous examples of regional/national use changing the course of disease outcomes (most recent in Brazil – an outstanding study, attracting “Fact Check” response of ludicrous proportions, indicating the “narrative lore of unprecedented fashion”. The reality is that IVM made widely available has the capacity to change the outcome quickly of the Pandemic. Working with a science-based use of vaccines.
(ix) Dramatic reversal of reduced oxygen saturation, within 24 hours.

I would like to finish with four comments:

(i) The reasons given by the TGA for its earlier decision to not make IVM freely available no longer exist (with the TGA decisions re Molnupiravir and Paxlovid).

(ii) Any decision to preclude IVM – a safe and effective drug for the treatment of Covid-19 in the experience and knowledge of senior doctors around the world, including Australia, is now untenable. It crosses the line of interfering with the - doctor patient relationship, in ways without precedent in Australia.

(iii) Extensive data supports the premise that widespread availability of IVM could change the pace of the pandemic, its economic impact, and the pressure on health facilities, in short time.

(iv) IVM has been subject to unprecedented misinformation, some fraudulent, to comply with a narrative that protects vaccination at all costs. Critiques have focussed on selected RCT's, cherry picked to avoid the bulk of data strongly supporting value of IVM therapy.

OPEN LETTER

21 August 2021

s22 [redacted]
National Covid Clinical Evidence Taskforce
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email: s22 [redacted]@monash.edu
email: s22 [redacted]@covid19evidence.net.au

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,

s22 [redacted]

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OPEN LETTER

14 October 2021

s22 [redacted]r
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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,

s22 [redacted]

REFERENCES

1. Open Letter to NCCET dated 21 August 2021

2. TGA "New restrictions on prescribing ivermectin for COVID-19" - 10 Sept. 2021

3. The TGA Australian Public Assessment Report for Ivermectin (October 2013)

4. Huge: Uttar Pradesh, India Announces State is COVID-19 Free Proving ghe Effectiveness of "Deworming Drug" IVERMECTIN
Jim Hoft, Sept 15 2021, Gateway Pundit
https://www.thegatewaypundit.com/2021/09/huge-uttar-pradesh-india-announces-state-covid-19-free-proving-effectiveness-deworming-drug-ivermectin/

5. The Desert Review: Justus R Hope - TheDesertReview.com

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10. Fordham, EJ, Lawrie, TA, MacGilchrist, K and Bryant A. The uses and abuses of systematic reviews: the case of ivermectin in Covid-19. EbMCsquared CIC, Northgate House, Upper Borough Walls, Bath BA1 1RG, UK

Australian Medical Network

Submission - Appendix D, Item 10

Listing For Ivermectin

Title	Submission and support for the application under section 52EAA of the Therapeutic Goods Act 1989 (the Act) to delete the Appendix D, item 10, listing for Ivermectin Application
Committees	Advisory Committee on Medicines Scheduling (ACMS) Advisory Committee on Chemicals Scheduling (ACCS)
Regulatory Authority & Leadership	Therapeutic Goods Administration (TGA) Professor John Skerritt
Minister	The Hon. Mark Butler MP Federal Minister for Health and Aged Care Disability
Date of Submission	26 September 2022
Organisation Details	Australian Medical Network (AMN) PO Box Essendon North, Victoria, 3041 admin@australianmedicalnetwork.com
Contact	s22 [redacted] [redacted] Australian Medical Network (AMN) s22 [redacted]@australianmedicalnetwork.com

SUBMISSION CONTENTS

DECLARATION

The Australian Medical Network (AMN) uses the power of the network and wider community to overcome Australia's health challenges and supports medical doctors and clinicians to discover new health therapies that provide safe and effective solutions to all Australians. Along with advancing health, we offer medical legal support, medical research, the latest health-related news, networking and educational events.

Across Australia, AMN has over 10,000 health professionals and private citizens in its network. They include medical practitioners, surgeons, virologists, epidemiologists, critical care specialists, pharmacologists, lawyers, health economists, academics, other health professionals and health management executives. Because of our combined education, training, and experience, this makes us highly competent to provide further insights in support of the application to delete the Appendix D, Item 10 listing for Ivermectin, and allow general practitioners to prescribe ivermectin and pharmacists to dispense it.

In making this application, we certify that the information is accurate, and we do not have any conflicts of interest or competing interests.

We agree to keep the notifications of intermediate and final decisions in relation to this consultation and submission confidential until they are published in accordance with subsections 42ZCZP and 42ZCZS of the Therapeutic Goods Regulations of 1990, as applicable (i.e., after referral to an expert advisory committee).

s22 [redacted]

PART 1 - REASONS FOR SUPPORTING THE APPLICATION

We agree with the initiating applicant's request that the entire Appendix D, Item 10 listing (listing) for ivermectin in the Poisons Standard, which was added on September 11, 2021, be removed, for all the reasons given by the Applicant. This will enable general practitioners to safely and effectively prescribe ivermectin, including where they judge appropriate to treat and prevent COVID-19. We also agree and emphasize the following;

1. The listing has prevented pharmacists and doctors from safely providing and supervising ivermectin usage for the prevention and treatment of COVID-19. Instead, the listing is forcing patients to obtain ivermectin illegally or to use ivermectin manufactured for animals. The prohibition has produced the opposite desired impact.

2. If the listing is removed, Australians' usage of ivermectin will be safer since doctors and pharmacists can then supervise patient use of the medication. In addition, no evidence was provided that ivermectin was being prescribed by general practitioners in an unsafe and unfavourable way.

3. In 2013, the TGA published a report titled, 'Australian Public Assessment Report for Ivermectin' (AUSPAR)[1]. The report highlighted the safety characteristics of ivermectin especially when recommended by doctors and given by pharmacists. If the listing is removed, Australians' usage of ivermectin will be safer because doctors and pharmacists can then monitor the patients progress and suggest other complimentary treatment suggestions.

4. *In terms of the risks and benefits of the use of a substance*, AUSPAR outlined the major risks and found ivermectin was safe as long as the recommended dose was observed. Used regularly by millions of people in Africa for the prevention of parasitic infections, it has also helped them with COVID-19 infections.

5. Upon investigating the *purposes for which a substance is to be used and the extent of use of a substance*, Ivermectin may help reduce COVID-19 infections, hospitalisations and reduce current pressures on Australian hospitals and the health ecosystem. While ivermectin is not officially used for the prevention and treatment of COVID-19 in Australia at this time, the applicant provided positive evidence that ivermectin may help prevent COVID-19 in up to 44% of patients. This in turn may help reduce the severity of COVID-19 infections in a sizable portion of patients.

6. *The toxicity of a substance* is also covered in AUSPAR, where safety levels of ivermectin is in considerably higher dosages than would be required to treat or prevent COVID-19. Compared to Paracetamol which is widely available despite overdoses being a regular feature in EDs across the country, ivermectin's toxicity and safety profile is far less toxic.

[1] https://www.tga.gov.au/sites/default/files/auspar-ivermectin-131030.pdf

7. When considering the *dosage, formulation, labelling, packaging and presentation of a substance*, ivermectin's presentation requires no additional modifications. Both adult patients and older children can utilise ivermectin with success.

8. The *potential for abuse of a substance if left unsupervised in this case is high*. This is because patients who desire to use ivermectin can no longer have it securely prescribed by a doctor and properly distributed by a pharmacist, the possibility for accidental abuse of ivermectin has grown as a result of its placement in Appendix D, Item 10. The listing's results are the exact reverse of what the TGA intended.

9. *Any other matters necessary to protect public health* - relate to Australian patients having the right to use secure substitutes for COVID-19 prevention and treatment. The listing limits Australians' options. There will be certain Australians who cannot handle the present COVID-19 preventatives and treatments, and those Australians should be provided with alternatives.

ADDITIONAL SUBMISSIONS

1. Infections with COVID-19 still affects Australian states and territories. Although the Omicron variant is less threatening, it is contagious and eluding vaccine protection and transmissibility. The current approach is placing strain on hospital resources, hospital staff, medical institutions, mental health across all demographics and damaging the economy. Removing the listing will be a positive step to resolving these problems.

2. To date, close to fifteen thousand Australians have died from or with COVID and over ten million have had the COVID virus. The applicant argues ivermectin treatment may prevent 44% of infections, this suggests that ivermectin may have a positive impact on the SARS-CoV-2 virus if used in conjunction with other approved and safe therapies.

3. Removing this restriction will help the government, the public and private health systems and patients, whether they are vaccinated or unvaccinated. The Appendix D listing for ivermectin was made during a period of uncertainty. Moving to a multi-therapy approach strategy, would potentially help decrease infections and deaths, boost public health confidence and move Australia forward to deal with emerging economic, geo-political, mental health and societal issues.

PART 2 – THE REASONS GIVEN FOR RESTRICTING IVERMECTIN NO LONGER APPLY

On September 11, 2022, the TGA restricted the prescribing of oral ivermectin on the advice of the ACMS. It was decided that ivermectin could only be prescribed by general practitioners for TGA-approved conditions. Ivermectin prescriptions for further unapproved conditions were also allowed by some experts, including infectious disease doctors, dermatologists, gastroenterologists, and hepatologists.

This section will demonstrate that the concerns[2] held by the TGA and ACMS are no longer applicable.

IVERMECTIN IS NOT APPROVED FOR THE TREATMENT OR PREVENTION OF COVID-19

Firstly, there are a number of significant public health risks associated with taking ivermectin in an attempt to prevent COVID-19 infection rather than getting vaccinated. Individuals who believe that they are protected from infection by taking ivermectin may choose not to get tested or to seek medical care if they experience symptoms. Doing so has the potential to spread the risk of COVID-19 infection throughout the community.

AMN RESPONSE

While ACMS and the TGA were dealing with intense political and public pressure at the time, the data and experience since the vaccination rollout began in early 2021, indicates;

1. National vaccination rates are over 90%, and the data is showing Australians are still transmitting and getting infected with COVID-19[3]. Patients have been returning with recurring COVID infections and Long COVID complications.

2. Health care workers in both the public and private hospital systems are working under difficult conditions due to high levels of staff sick leave, stress leave and worker shortages[4].

3. Other than COVID-19 vaccination and the introduction of Paxlovid and Molnupiravir, Australians have access to no other treatments when symptoms arise. Both Paxlovid and Molnupiravir have not shown statistically significant reductions on hospitalisation and mortality[5].

[2] https://www.tga.gov.au/news/media-releases/new-restrictions-prescribing-ivermectin-covid-19
[3] https://www.health.gov.au/health-alerts/covid-19/case-numbers-and-statistics
[4] https://www.afr.com/policy/health-and-education/new-data-shows-the-state-hospital-systems-under-most-covid-stress-20220721-p5b3db
[5] https://www1.racgp.org.au/newsgp/clinical/trial-shows-muted-impact-of-paxlovid-on-healthier

IVERMECTIN DOSES ARE BEING ADVOCATED FOR USE BY SOCIAL MEDIA AND ARE TOO HIGH

Secondly, the doses of ivermectin that are being advocated for use in unreliable social media posts and other sources for COVID-19 are significantly higher than those approved and found safe for scabies or parasite treatment. These higher doses can be associated with serious adverse effects, including severe nausea, vomiting, dizziness, neurological effects such as dizziness, seizures and coma.

AMN RESPONSE

Currently in Australia there are nationally approved ivermectin trials underway for COVID-19. The dosage levels in these trials are lower than what is recommended in AUSPAR. Before Ivermectin was prohibited the same dosages as the approved trials were being prescribed in 2020/2021 by medical practitioners. Dosages are more likely to be inappropriate when patients procure ivermectin independently from untrusted sources and then consume them unsupervised rather than have it dispensed by a pharmacist in consultation with their doctor.

The TGA, ACMS and ACCS are invited to meet with frontline critical care specialists to discuss how in fact ivermectin was legally prescribed in safe dosages. In addition to dosage safety, the patient was closely monitored on a daily basis. Extensive data has been collected, and the factors of success are attributed to safe dosages being administered, national peer collaboration and high standards of care, communication, and reporting.

THERE IS A SHORTAGE OF IVERMECTIN

Finally, there has been a 3-4-fold increased dispensing of ivermectin prescriptions in recent months, leading to national and local shortages for those who need the medicine for scabies and parasite infections. It is believed that this is due to recent prescribing and dispensing for unapproved uses, such as COVID-19. Such shortages can disproportionately impact vulnerable people, including those in Aboriginal and Torres Strait Islander communities.

AMN RESPONSE

There are multiple and reputable global producers and suppliers of ivermectin who assert there is no shortage[6]. While the market is fragmented, ivermectin is not difficult to produce and could be produced here in Australia, which would not only help all Australians and also provide Australia with a lucrative export opportunity. Finally, the tens of thousands of Australians suffering from COVID-19 and Long COVID are themselves vulnerable members of Australian society in need of treatment options.

[6] https://www.pipelinepharma.com/marketplace/ivermectin-manufacturers

PART 3 – CONCLUSION

Considering the current spread of COVID-19 infection and despite high levels of immunization, we request that Appendix D, Item 10 listing for ivermectin be removed. The major reasons for this removal are to improve patient safety, alleviate pressures on the public and private health systems and move Australia's health policy toward a multi-therapy strategy. Plus, it will allow access to effective alternatives for those patients who do not tolerate existing treatments and prophylaxis.

Australian governments (federal, state and territory) must encourage supervised use of ivermectin by general practitioners. We thank you for your consideration and welcome broader discussions because we are all working toward the same goal.

Ivermectin Statement

Introduction

This statement provides the justification for our request for the drug ivermectin to be used for the prevention and treatment of Covid-19 infections. We are a group of senior physicians, academics and researchers who have joined together to advocate for the medically supervised use of ivermectin-based combinations for the prophylaxis and treatment of Covid-19. Our names, experience and affiliations are listed at the end of this statement.

There is a current crisis affecting Australian states and territories with Covid-19 infections. While the omicron variant appears less dangerous, it is highly infectious and is stressing health facilities and harming the economy in an unprecedented fashion. Although hospital admission rates and mortality rates are possibly lower than the previous variants of the virus, omicron remains a significant health challenge because of its enormous transmissibility and its ability to evade vaccine protection, leading to huge numbers of the population becoming infected.

Vaccines have been the basis of strategic management, and have effectively shifted the spectrum of disease from severe to mild, moderate and asymptomatic disease, while reducing the load on health facilities. However, it is clear that current vaccine strategy alone is inadequately controlling infections within the community (ref 1). Booster vaccination is now required to improve protection, but the duration of effectiveness is limited and booster timing is critical to prevent recurrent vaccination causing increased vulnerability to infection (ref 2). Current vaccines do not prevent COVID-19 infection or virus transmission from infected individuals to others (ref 3), and there is no specific treatment modality recommended by Australian authorities to reduce disease severity or transmission in the primary care setting, which in turn can reduce the need for hospital admission.

It is highly likely that ongoing medical management with re-purposed and new antiviral agents will be required for the foreseeable future. It is now clear that medical authorities have recognized that drug therapies are needed for controlling Covid-19. The Therapeutic Goods Administration in Australia has recently approved a number of new antiviral agents for this purpose despite limited efficacy data. In this context, it is now time to seriously consider use of the safe and effective re-purposed drug, ivermectin, to prevent infection, to reduce the severity of Covid-19 disease, to reduce the load on health care services, and to facilitate the strategic spacing of booster vaccines.

The approach used in this statement is based on the principles of Evidence Based Medicine (EBM). The essence of EBM is the convergence of (i) science-based evidence; (ii) clinical experience; and (iii) patient contribution and views. The arguments presented in this statement meet these essential requirements. They do not rely on ideological positions and or personal prejudices.

The statement is set out as follows. The history of ivermectin and its conventional use and safety record are described. The unique properties of this drug relevant to its use in Covid-19 are outlined. The evidence-base for the effectiveness and safety of ivermectin and ivermectin-containing combinations (eg. ivermectin triple therapy [ivermectin, doxycycline and zinc] – ITT) in preventing and treating Covid-19 is critically examined; first the published controlled trials, then the systematic reviews and meta-analyses, and finally its wide application in various countries and states and regions. The Australian experience with ITT as a treatment is described with reference to a large prospective observational trial recently completed. Finally, the medically supervised use of ivermectin-based therapy for Australian patients is recommended.

Ivermectin – history and conventional use and safety

Discovery

Ivermectin was discovered in 1975 and first marketed as a veterinary medicine in 1981. Ivermectin belongs to a group of avermectins, which is a group of 16 membered macrocyclic lactone compounds. Human applications followed in the late 1980s. William Campbell and Satoshi Ōmura won the 2015 Nobel Prize in

Physiology or Medicine for its discovery and applications. The medication is on the World Health Organization's List of Essential Medicines, and is approved by the U.S. Food and Drug Administration as an antiparasitic agent. In 2018, ivermectin was the 420th most commonly prescribed medication in the United States, with more than one hundred thousand prescriptions. Its safety profile is benign. It is available as a generic medicine.

Use in parasitic and other infections

In humans it is used for treatment of parasitic infections like river blindness (onchocerciasis) and lymphatic filariasis. It is the treatment of choice for strongyloidiasis. Ivermectin is used to treat scabies and head and pubic lice. It can be given in mass distributions to whole communities to treat these conditions or used in sequential doses over days to weeks for individuals.

Safety record

The usual dose range of ivermectin in humans is 0.150 – 0.300 mg per kilo of body weight (ie. 21 mg for a 70 kg person if given at 0.300 mg/kg). Ivermectin is contraindicated in children under age five and in individuals who weigh less than 15 kg and in persons with liver and kidney disease. It is excreted in breast milk and its safety in pregnancy has not been determined.

Ivermectin has had billions of doses taken worldwide. It has an enviable safety record. When used in the recommended dose ranges it is relatively free of toxicity. Uncommon adverse events include fever, itching, and skin rash when taken by mouth. Serious side effects are rare in individuals not heavily infected with parasites.

There are relatively few studies on the pharmacokinetics of ivermectin in humans. Ivermectin has rapid oral absorption, high liposolubility, is widely distributed in the body, metabolized in the liver (cytochrome P450 system), and excreted almost exclusively in feces (ref 4). Following a standard oral dose in healthy humans, it reaches peak plasma levels at 3.4–5 h, and plasma half-life has been reported to be 12–66 h. It is strongly bound to plasma proteins.

Ivermectin overdose may cause neurotoxicity due to potentiation of inhibitory chloride channels. This may present with central nervous system depression, ataxia, coma and even death. Ivermectin inhibits the enzyme CYP3A4 and it may have adverse interactions with other drugs metabolised via the CYP3A4 system like statins, HIV protease inhibitors, calcium channel blockers, lidocaine, benzodiazepines, glucocorticoids, and dexamethasone. It can interact with warfarin and alter blood clotting. During treatment ivermectin can cause transient elevations of liver enzymes. It should be used with care in possible Loiasis exposure.

Ivermectin dose

The lethal dose 50 (LD50 range) for ivermectin is in the range of 2.02-43.24 mg/kg (between 141 mg to 3,026 mg for a 70 kg person). In suicidal overdose attempts using 4.2-67mg/kg [294-4,690 mg in a 70kg person], 1/14 died from the overdose. These doses far exceed the standard upper recommended anti-parasitic dose of 0.300 mg/kg.

An early concern about the use of ivermectin was the dose presumed to be needed to inhibit the virus in vivo based on in vitro experiments (ref 5) which would be up to 35 times the recommended antiparasitic dose for humans, but these concerns failed to consider the contribution to the immune response from the zinc level in tissues, so that in vivo a much lower and hence non-toxic ivermectin dose would be required.

Nonetheless, warnings about adverse effects of ivermectin need to be mentioned and can include nausea, vomiting, diarrhoea, hypotension, and in toxic doses decreased level of consciousness, confusion, blurred vision, visual hallucinations, loss of coordination and balance, seizures, coma, and death. No doses with such toxic adverse effects have ever been recommended in the treatment of conditions in humans.

Unique antiviral properties of ivermectin

An initial study from the Monash Biomedicine Discovery Institute showed that ivermectin could prevent SARS-CoV-2 infection in vitro (ref 6). Further studies exploring this finding are underway (ref 7). One in vivo placebo controlled investigation noted patients treated with ivermectin had lower viral loads and less viable viral cultures, suggesting an anti-SARS-CoV-2 activity (ref 8).

The possible mechanisms (ref 9) conferring ivermectin a protective role in Covid-19 infection include:
1. Direct action on SARS-CoV-2
Blocking spike protein facilitated virus entry into host cells via the ACE receptor
2. Action on host targets important for viral replication
Protease inhibition of virus replication
Blockage of nuclear transport essential for viral replication.
3. Action on host targets important for inflammation
An anti-inflammatory role preventing cytokine storm
4. Action on other host targets
Preventing clotting/thrombotic processes and enhancing mitochondrial ATP production protecting cardiac function

Re-purposed drugs like ivermectin have broad effects on changing the internal milieu of cells in a way that inhibits assemblage of whole virus (ref 9). Many target points can usually be identified, reflecting their biological sources and probable protective roles. The mechanisms identified above suggest that ivermectin would have a role in preventing Covid-19 infection (as a prophylactic), in treating early stages of infection, and in treating established severe cases.

Review of evidence-base for ivermectin use in Covid-19

Since the start of the Covid-19 pandemic the re-purposed use of ivermectin for the prevention and treatment of SARS-CoV-2 has been studied extensively in case reports and randomised, placebo controlled trials. The scientific quality of these studies has varied considerably, but most have found a consistent beneficial effect for ivermectin in reducing rates of infection, reducing severity of disease, reducing hospitalisations, reducing intensive care admission, and reducing deaths.

In summary, to date there have been 75 clinical studies, 54 of which have been peer reviewed, and 32 of which are randomised controlled trials (RTC's). Seven systematic reviews by experienced epidemiologists noted a reduction in mortality of between 59% and 81% (ref 10). The findings for other outcome measures in these RCT's have favoured ivermectin. Prophylaxis was achieved in 84% (range 25-96%), and significant improvement in clinical condition was noted following early treatment 62% (45-74) and late treatment 23% (1-46). Over 7,000 patients were included in the 32 RCT's, performed by 361 authors. This database has been described by leading epidemiologist Dr Tess Lawrie as "in excess of data usually submitted for a regulatory drug approval" (ref 11).

While a number of supportive systematic reviews have been published, a meta-analysis by the Cochrane group (ref 12) found insufficient evidence to recommend ivermectin as a treatment for Covid-19. This analysis has been criticized on methodological grounds as being an unreliable assessment of the efficacy of ivermectin (ref 13).

Beyond clinical case series and controlled trials, ivermectin has been used as part of public health measures in whole countries, states and regions across the world. In some jurisdictions ivermectin was provided as one of a suite of drugs and vitamins for citizens to take to prevent or treat Covid-19 infection. In other jurisdictions ivermectin was strongly recommended to the public and made readily available as a prophylactic or treatment of Covid-19 infection. Interventions with community-wide administration of ivermectin have been undertaken in India, Mexico, regions of Peru and Argentina, Japan, Dominican Republic and Brazil. In these opportunistic and uncontrolled trials the notable consistent findings were dramatic reductions in Covid-19 infections, hospitalisations and Covid-related deaths within one to two weeks following the widespread availability of ivermectin.

In a quasi-experimental Mexico City study symptomatic Covid-19 subjects receiving a medical kit including ivermectin 12mg for two days (along with paracetamol and aspirin) were 55% to 77% less likely to be hospitalised than those not using the kit (ref 14).

A large propensity-matched real-world citywide study of adults in Brazil demonstrated a 67% reduction in hospitalisations and a 70% reduction in deaths in the subjects who took ivermectin for two days each fortnight. The benefit of ivermectin prophylaxis was independent of known risk factors for Covid-19 infections (ref 15). A follow-up publication from this group demonstrated a substantially reduced rate of hospitalization and death in a dose-dependent relationship among ivermectin treated individuals (ref 16).

An informative comparison unblinded trial can be derived by observing the pattern of Covid-19 between Indian states that used ivermectin to greater or lesser degrees (ref 17). The starkest difference in policy and outcomes was between Uttar Pradesh (population 241 million) that pursued a proactive widespread ivermectin early treatment and prophylaxis roll-out similar to ITT (ivermectin, zinc, vitamin D3, doxycycline, multivitamin) plus personal protective equipment and pulse oximeter delivered door to door, compared with Kerala (35 million) that banned ivermectin and relied on vaccines.

While total cumulative Covid-19 deaths by late August 2021 in Uttar Pradesh were 22,700 and those in Kerala were 20,000 were similar, the Uttar Pradesh population was 7-fold greater, and deaths plummeted in Uttar Pradesh following the ivermectin protocols (ref 17).

In the 2021 September reporting fortnight period Indian media reported 199 active cases, 11 new daily cases (from 226,000 tests) and zero deaths in Uttar Pradesh (ref 18), whereas there were 180,842 active cases, 19,325 new cases (from 121,070 tests) and 143 deaths in Kerala (ref 19). The positive case rate of <0.01% in Uttar Pradesh versus 15.96% in Kerala is observational data worthy of noting.

Vaccination status was unrelated to the Covid-19 performance of these two Indian states: by late August 2021 less than 5% of adults in Uttar Pradesh were fully vaccinated (two administrations of vaccine) compared with 20% in Kerala (ref 20).

By 15 January 2022, Uttar Pradesh's Covid death toll had remained almost static at 22,953 with 3 to 6 deaths per day from the omicron wave, whereas in the ivermectin-suppressed state of Kerala the death toll had now more than doubled to 50,674 with deaths having continued at over 100 per day for months (ref 21).

The Australian experience with ivermectin for Covid-19

Intracellular infections such as TB, H pylori, HBV, HCV and HIV – all require mostly 3 drugs combined to treat the infection effectively. For TB we would not be promoting the use of isoniazid alone nor amoxycillin alone for H pylori eradication. Similarly ivermectin should not be used alone for Covid-19. Furthermore when used alone in parasite infections resistance against ivermectin has been reported (ref 22). So in the Australian study ITT was used, rather than ivermectin alone.

Australian 'real-world experience' with ITT for Covid-19 has been substantial. A 600 subject prospective observational trial of consecutive patients is now complete (ref 22). This study used ivermectin 24mg daily plus doxycycline (100 mg bd), and zinc (50mg daily) for 10 days within 48 hours of a positive PCR test and diagnosis of Covid-19. Side effects were minimal – only 7% of patients had minor gut symptoms. No patient ceased the trial due to adverse events. 90% of patients completed the study in full.

Over the course of the trial only 5 patients (0.8%) were admitted to hospital, and there were no deaths. Symptoms of Covid-19 declined significantly and oximetry readings improved substantially. Although this trial did not have a control group, comparison of the results to historical outcomes of hospitalizations and deaths among non-ivermectin treated patients is dramatic – 70 patients would have been expected to be hospitalized and there would have been 6 deaths (ref 23).

Another consecutive series of 24 of severely ill but not hospitalized patients treated with a similar combination of ivermectin and doxycycline, zinc and vitamins D and C in the USA had comparable success to the Australian

study (ref 24). In all subjects symptoms resolved quickly and oxygen saturation improved within 24 h of the start of treatment. There were no hospitalizations or deaths in the treated cohort.

Conclusion

The information presented in this statement clearly shows the benefit of ivermectin for a prophylactic role in Covid-19, as well as the value of using ivermectin for early and established Covid-19 infections. In the light of the massive spread of Covid-19 infection occurring at the moment despite high levels of immunization, Australian governments (federal, state and territory) should encourage the medically supervised use of ivermectin in ITT for preventing and treating of Covid-19, and support controlled trials of this medication to prevent and treat early and established Covid-19 infections. The previous argument of suppressing the use of ivermectin because it would take away from the focus on getting widespread uptake of vaccination in the community no longer holds because government authorities are now invested in introducing antiviral drugs for Covid-19 treatment. We consider widespread use of ivermectin would contribute to the control of Covid-19 within weeks, as it has done in other jurisdictions.

Group members

Disclosures

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

TO

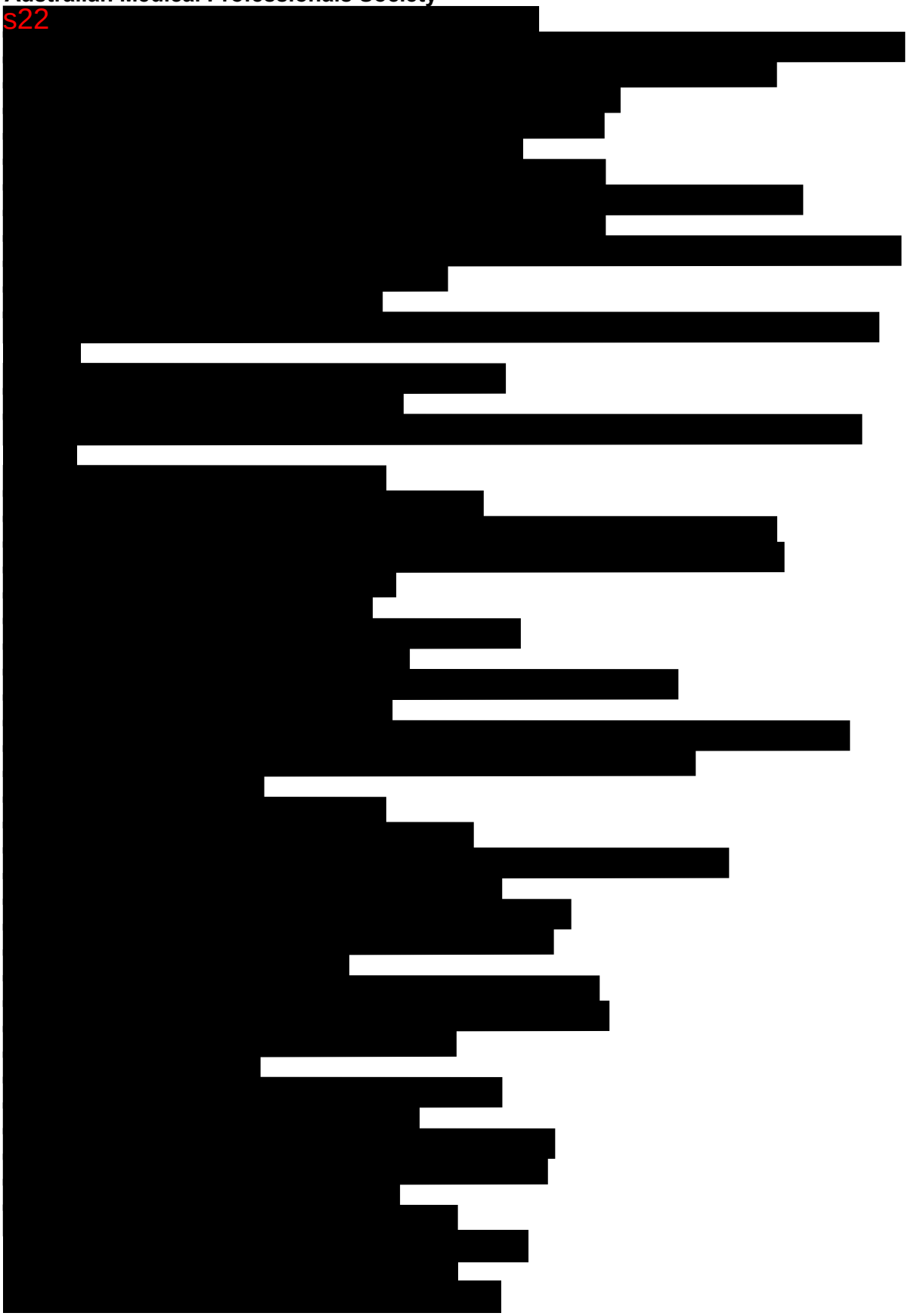
AMEND THE SCHEDULING OF IVERMECTIN - DELETION OF APPENDIX D, ITEM 10 FROM THE CURRENT S4 POISONS SCHEDULING

26 September 2022

SUBMISSIONS BY (collectively the 'Co-Signatories'):

Australian Medical Network
Australian Medical Professionals Society

s22



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:

Name: s22 [redacted]

[redacted]

Submissions Editor acting for and on behalf of the Co-Signatories

Address: s22 [redacted]

Email: s22 [redacted]@aussiebroadband.com.au

All correspondence and notices to s22 [redacted] (but copies to any and all co-signatory organisations and individuals as appropriate)

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

s22 [redacted]

[redacted]

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 thses 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:

[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*

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[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].

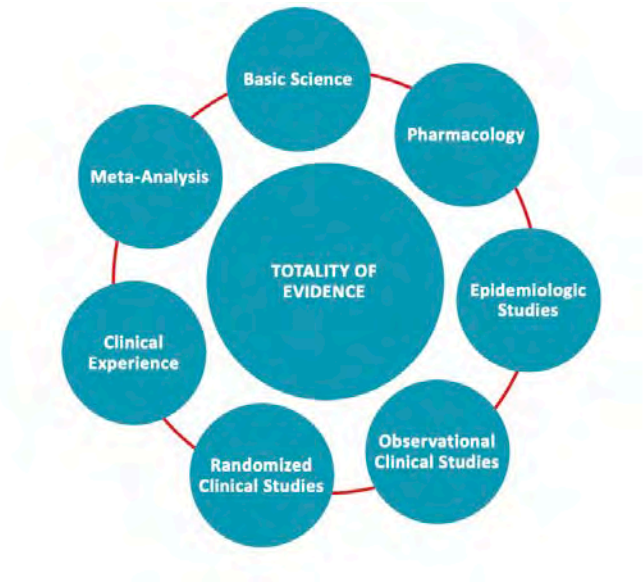
72. Ivermectin, in contrast to these two antiviral medications, has a much wider therapeutic index and has a relatively high level of safety following many years of use in many millions of individuals treated for parasitic infections such as river blindness. It should also be noted, in contrast to ivermectin, 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".

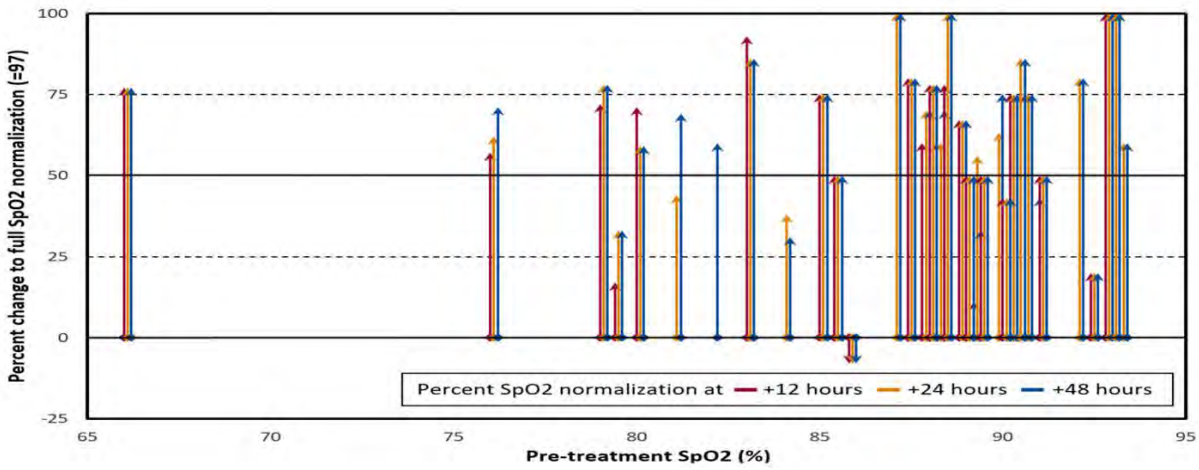
82. In a mini-review of ivermectin safety in the treatment of COVID-19 it was concluded that ivermectin "has been safely used in 3.7 billion doses since 1987" and that the medicine has been "used without serious [adverse effects] in multiple COVID-19 studies[39].

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 s22 s22 dated 21 August 2021 (together with a Commentary by s22 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
Office of the Attorney General
2115 STATE CAPITOL BUILDING
LINCOLN, NE 68509-8920
(402) 471-2682
TDD (402) 471-2682
FAX (402) 471-3297 or (402) 471-4725

DOUGLAS J. PETERSON
ATTORNEY GENERAL

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 canceled 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/world/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] Beasley & Davey, *supra*.

[8] Neb. Rev. Stat. §§ 38-102 & 38-164.

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. § 38-1703.

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 *Peor v. State*, 266 Neb. 183, 190, 663 N.W.2d 102, 115 (2003); *Davis v. Wright*, 213 Neb. 831, 830-37, 333 N.W.2d 814, 818 (1983).

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 these same lines, the regulation governing physicians states that unprofessional conduct includes:

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

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

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

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17 *Langvardt v. Horton*, 254 Neb. 878, 895, 581 N.W.2d 69, 79-71 (1998).

18 Neb. Rev. Stat. § 38-179.

19 172 Neb. Admin. Code § 88-009(C).

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(L).

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

23 172 Neb. Admin. Code § 88-009(E).

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* [redacted] (last visited Oct. 14, 2021).

[29] U.S. Food & Drug Administration, Understanding Unapproved Use of Approved Drugs "Off Label" (Feb. 5, 2018), [redacted] (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* [redacted] (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 camamotem therapy with hydroxychloroquine and azithromycin reduces mortality in 10,429 COVID-19 outpatients*, 22 Reviews in Cardiovascular Medicine 1063, 1063 (Sept. 2021), [illegible] (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* [illegible] (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* [illegible] (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. 202[illegible]), [illegible] (last visited Oct. 14, 2021).

These groups of physicians have established protocols for early treatment, and ivermectin and hydroxychloroquine are staples of those treatments.[39] 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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[39] E.g., McCullough, *Multifaceted*, *supra*, at 519 Table 1 (listing early treatment kits that include both ivermectin and hydroxychloroquine); McCullough, *Pathophysiological*, *supra*, at 18 (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* [redacted] (last visited Oct. 14, 2021) (finding that "the use of nitazoxanide, ivermectin[,] and hydroxychloroquine demonstrated unexpected improvements in COVID-19 outcomes when compared to untreated patients").

[42] Andy Crump, *Ivermectin: enigmatic multifaceted 'wonder' drug continues to surprise and exceed expectations*, 70 The Journal of Antibiotics 495, 495 (2017), *available at* https://www.nature.com/articles/ja2017111.pdf (last visited Oct. 11, 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* [redacted] (last visited Oct. 14, 2021).

[45] Andrew Bryant et al., *Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines*, 28 American Journal of Therapeutics 434, 435 (Jul./Aug. 2021), *available at* [redacted] (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 [redacted] 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), [redacted] (last visited Oct. 14, 2021).

49 Crump, *Ivermectin*, *supra* at 508.

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* [redacted] (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* [redacted] (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 Ozlen 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* [redacted] (last visited Oct. 14, 2021).

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

to surprise and excite scientists, offering more and more promise to help improve global public health by treating a diverse range of diseases."[56]

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."[57] 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* [illegible] (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, [illegible] (last visited Oct. 14, 2021) ("hereinafter, "NIH, COVID-19 and Ivermectin").

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

[58] Lehrer, Cully, 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 (FWC) for the indication of Scabies at 16 (Dec. 2018), *available at* [illegible] (last visited Oct. 14, 2021).

[61] VigiAccess, Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, [illegible] (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* https://jia-contents.wdc-jp.com/pdf/JJA7401/74-1-opeof/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/14329/46795_CE[Ra]_F(Sh)_PF1(SY_OM)_PFA_(OM)_PN[KM].pdf (last visited Oct. 14, 2021).

ivermcotin, 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 Behéra study in India tested ivermectin as a prophylaxis in a group of 3,632 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] Priyamadhaba Behera et al., *Prophylactic Role of Ivermectin in Severe Acute Respiratory Syndrome Coronavirus 2 Infection Among Healthcare Workers* Cureus at 1 (Aug. 2021) *available at* [illegible] (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* [illegible] (last visited Oct. 14, 2021).

[85] Morteza Shakiba, 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 268, 268 (2021), *available at* [illegible] (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 45% 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 46.

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 [redacted] (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 [redacted] (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*, MSF Preprints, at 7 (Sept. 3, 2021), available at [redacted] (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 [redacted] (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* [redacted] (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 [redacted] (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* [redacted] (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] These 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 55 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, 578 (Sept./Oct. 2021), *available at* [redacted] (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. ", 2021), *available at* [redacted] 139739.pdf (last visited Oct. 14, 2021).

[105] Ivermectin for COVID-19: Real-time meta analysis of 64 studies (Oct. 8, 2021), [redacted] (last visited Oct. 14, 2021).

[106] *Id.*

[107] *Id.*

[108] *Id.*

[109] Alessandro D. Santin et al., *Ivermectin: a multifaceted drug of Nobel prize-honored distinction with indicated efficacy against a new global scourge, COVID-19*, New Microbes New Infections (Aug. 2021), *available at* [redacted] (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."[10]

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.[11] 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.[12] The research revealed that "countries with routine mass drug administration of prophylactic . . . ivermectin have a significantly lower incidence of COVID-19."[13] 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.[14] 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."[15]

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[9] *Id.* at 4.

[10] *E.g.*, U.S. National Library of Medicine, ACTIV-6: COVID-19 Study of Repurposed Medications, [redacted] (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), [redacted] (last visited Oct. 14, 2021) (purpose of this trial involving 1,100 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").

[11] Varkin D. Hellwig & Anaeska Mara, *A COVID-19 prophylaxis? Lower incidence associated with prophylactic administration of ivermectin*, International Journal of Antimicrobial Agents (2021), available at [redacted] (last visited Oct. 14, 2021)).

[12] *Id.* at 1.

[13] *Id.*

[14] *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 < 0.0012 for effect by state, then 13-fold increase after ivermectin use restricted* (Mar. 2021), *available at* https://osf.io/9egh4/ (last visited Oct. 14, 2021); *see also* Santin, *supra*, at 3–4 (discussing the Peruvian data); Kory, *supra*, at 311–13 (same).

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

[118] Santin, *supra*, at 3.

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

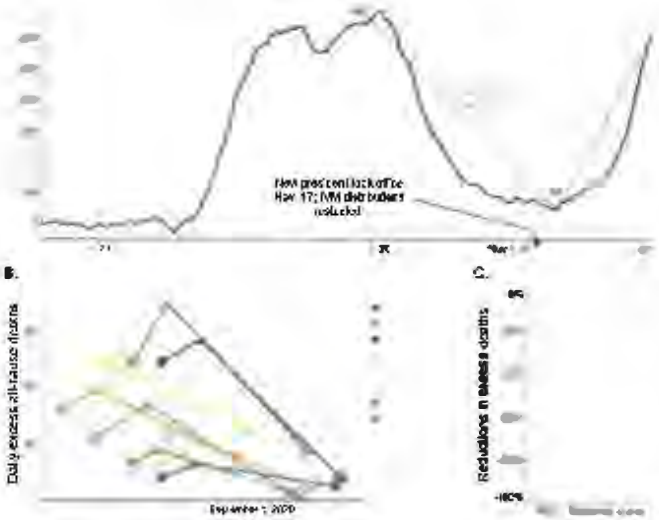
[120] *Id.*

[121] *Id.*

[122] *Id.*

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

Daniel Chamie-Quintero, Jennifer A. Kibbe, David E. Schein



*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-7311799/ (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-BB1qDp5U (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/20210305[illegible]/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/20210902[illegible]/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 antiviral 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), [redacted] (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) [redacted] (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), [redacted] (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/1429059702448922639 (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*

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

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

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

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

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

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COVID-19, Health Advisory, at 1 (Aug. 26, 2021), *available at* [redacted] (last visited Oct. 14, 2021).

[156] *Id.*

[157] *Id.* at 3.

[158] Emma Goldberg, *Demand Surges for Deworming Drug for Covid Despite No Evidence It Works*, New York Times (Aug. 30, 2021), *available at* [redacted] (last visited Oct. 14, 2021) (emphasis added).

[159] Emma Goldberg, *Demand Surges for Deworming Drug for Covid, Despite No Evidence It Works*, New York Times (amended Sept. 28, 2021), *available at* [redacted] (last visited Oct. 14, 2021).

Doctor Says."[152] Soon thereafter, one the hospitals where this doctor supposedly works denied that claim, and "the doctor [did] not respond[] to requests for further comment."[153] 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."[154] In addition, the magazine added an "update" message stating, among other things, that "[n]one 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."[155] 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."[156] 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.[157] 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 79 per 1,000 chance of death.[158] Also, the WHO considered only

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[152] Peter Wade, *Gunshot Victims Left Waiting as Horse Dewormer Overdoses Overwhelm Oklahoma Hospitals, Doctor Says*, Rolling Stone (Sept. 3, 2021) *available at* [redacted] (last visited Oct. 14, 2021).

[153] 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* [redacted] (last visited Oct. 14, 2021).

[154] *Id.*

[155] *Id.*

[156] World Health Organization, Therapeutics and COVID-19: Living Guideline, at 20 (July 6, 2021), *available at* [redacted] (last visited Oct. 14, 2021) (hereinafter, "WHO COVID-19 Guidelines").

[157] *Id.*

[158] *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 Sladitya 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/[illegible] (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* [illegible] ("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 B1.

[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-mck-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://www.[illegible] (last visited Oct. 14, 2021).

[182] Lewis Krauskopf & Manojna Maddipatla, *Merck COVID-19 pill success slams Moderna shares, stalks US healthcare sector*, Reuters (Oct. 1, 2021), *available at* https://www.[illegible] (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://www.[illegible] (last visited Oct. 14, 2021).

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

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

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

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[184] *Id.*

[185] *Id.*

[186] 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).

[187] *Id.*

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

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

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

4. Hydroxychloroquine

A. History of Hydroxychloroquine

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

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

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[191] National Institutes of Health, COVID-19 Treatment Guidelines: Chloroquine or Hydroxychloroquine and/or Azithromycin, [illegible] (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 [illegible] (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 [illegible] (last visited Oct. 14, 2021).

[195] Elisa-Laura Virkelall, *Hydroxychloroquine in rheumatic autoimmune disorders and beyond*, EMBO Molecular Medicine, e. 1 (Aug. 2020), available at [illegible] (last visited Oct. 14, 2021).

[196] *Id.*

[197] Fram, *supra*, at 389.

[198] ClinCalc, Hydroxychloroquine Drug Usage Statistics, United States, 2013-2019, https://[illegible] (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 [illegible] (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 Marlin J. Vincent et al., *Chloroquine is a potent inhibitor of SARS coronavirus infection and spread*, Virology Journal, at 1 (Aug. 2005), *available at* [illegible] (last visited Oct. 14, 2021).

201 Ponticelli & Moroni, *supra*, at 411; *see also* Ewa Helady et al., *Antimalarials – are they effective and safe in rheumatic diseases?*, 56 Reumatologia 164, 171–72 (2018), *available at* [illegible] (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®), [illegible] (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), [illegible] (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* [illegible] (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/[illegible] (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 26,759 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 (Jul. 2021), *available at* https://www.sciencedirect.com/science/article/pii/S1567576921002721 (last visited Oct. 14, 2021).

[210] *Id.*

[211] *Id.*

[212] Million, *supra*, at 1063.

[213] *Id.* at 1066.

[214] *Id.* at 1063.

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

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

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

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215 *Id.*

216 Eva Harras 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://[illegible].biomedcentral.com/articles/10.1186/s12879-021-06574-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 Imards 408, 408 (2020), *available at* https://[illegible] (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 Chiwese 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://[illegible] (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://[illegible] (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 > 50% 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 .58 and the odds ratio of death was .25. In other words, his meta-analysis demonstrated that when hydroxychloroquine is administered as an early COVID-19 treatment, it can reduce the risk of death by 75%.

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

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230 Million, *supra*, at *070.

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 [redacted] (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 [redacted] (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 [redacted] (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 Iara 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/S2052297520301057#! (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.[242] These kinds of concerns prompted one group of scholars to conduct a systematic review of the hydroxychloroquine safety literature pre-COVID-19. Their review of the data indicated that people taking that medication in appropriate doses "are at very low risk of experiencing cardiac [adverse events], particularly with short term administration of the drug."[244] The pre-COVID-19 data showed that heart issues occurred—albeit infrequently—only when patients took hydroxychloroquine in dangerously high doses or for many years on end.[245]

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

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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, [redacted] (last visited Oct. 14, 2021).

244 Pram, *supra*, at 391.

245 *Id.* at 390, 92.

246 *Id.* at 393.

247 *Id.* at 392.

248 *Id.* at 393.

249 *Id.* at 394.

250 *Id.*

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

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

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

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[250] Shivraj Padiyar & Deepashish Dandia, *Revisiting cardiac safety of hydroxychloroquine in rheumatological diseases during COVID-19 era: Facts and myths*, 6 European Journal of Rheumatology 100, 100 (2021), available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8133989/pdf/ejr-8-2-100.pdf (last visited Oct. 14, 2021).

[251] *Id.*

[252] *Id.* at 102.

[253] *Id.* at 102.

[254] *Id.* at 100.

[255] Khalid Elias y 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).

[256] *Id.*

[257] 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",[259] 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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[257] *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-go-one-of-the-biggest-retractions-of-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-chloroquine/indonesia-major-advocate-of-hydroxychloroquine-told-by-who-to-stop-using-it-idUSKBN2327L (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/us-health-coronavirus-safety-idUKKBN2327L (last visited Oct. 14, 2021).

[263] Beseley & Davey, *supra*.

[264] Davey, *supra*.

[265] Rabin, *supra*.

[266] Beseley & Davey, *supra*.

[267] *Id.*

[268] Heathers, *supra*.

of what happened," the Lancet has "declined to provide details regarding the retracted study[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, [redacted] (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, [redacted] (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 [redacted] (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) (May 29, 2020), *available at* [redacted] (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* [redacted] (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 concentrations" 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* [redacted] (last visited Oct. 14, 2021) (hereinafter, "FDA EUA Revocation Memo").

280 *Id.* at 4.

281 *Id.*

282 Xue-ling 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* [redacted] (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 acoually 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 hydroxychloroquine for COVID-19.

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

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

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

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

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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. 4, 2021).

for an individual patient."[249] 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."[250] 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."[251] 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."[252] 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."[253] 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."[254]

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."[255] It reached this recommendation after concluding that hydroxychloroquine

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249 FDA, Bringing Perspective, *supra*.

250 *Id.*

251 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).

252 *Id.*

253 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).

254 *Id.*

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

"probably do[es] not reduce mortality" and that its "effect on . . . admission to hospital . . . remains uncertain."[295] 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.[296] In addition, the WHO's statistics on hospitalization rates, which consisted of one RCT that included 405 outpatients, suggests hydroxychloroquine's efficacy.[298] 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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[295] *Id.* at 27.

[296] *Id.* at 28.

[297] RECOVERY Collaborative Group, *supra*, at 2060.

[298] 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 [redacted] (last visited Oct. 14, 2021).

[302] The COPCOV Trial's position statement on "A living WHO guideline on drugs to prevent COVID-19," NORU Tropical Health Network (Mar. 5, 2021), [redacted] (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.[104]

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

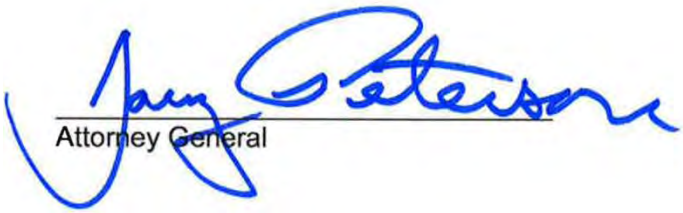
Very truly yours,

DOUGLAS J. PETERSON
Attorney General

James A. Campbell
Solicitor General

Mindy L. Lester
Assistant Attorney General

Approved by:



Attorney General

ANNEXURE 2

OPEN LETTER

21 August 2021

s22
National Covid Clinical Evidence Taskforce
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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,

s22
s22
[redacted]

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Review of the Emerging Evidence Demonstrating the Efficacy of Invermectin in the Prophylaxis and Treatment of COVID-19. American Journal of therapeutics 28, e299-e318 (2021.

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.

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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,

s22 [redacted]
Clinical Trials and Regulatory Affairs Consultant

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The uses and abuses of systematic reviews: the case of ivermectin in Covid-19.
EbMCsquared CIC, Northgate House, Upper Borough Walls, Bath BA1 1RG, UK

The Pharmacy Guild of Australia

PROPOSED AMENDMENTS TO POISONS STANDARD

ACMS and Joint ACMS-ACCS Meeting November 2022

Comments by The Pharmacy Guild of Australia to the proposed amendments to the Poisons Standard

1. Ivermectin

s22 S2 [redacted]

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Date 29 September 2022

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IVERMECTIN

Proposal

The application is proposing to delete the Appendix D entry for ivermectin. This would remove the current restrictions on the prescribing and use of ivermectin for oral administration for human use, allowing prescribing without restrictions on prescriber speciality and potential for off-label indications such as the prevention and treatment of COVID-19.

Scheduling considerations

The purposes for which a substance is to be used and the extent of use of a substance

Ivermectin belongs to the anthelmintics group of medicines. It is indicated for the treatment of parasitic infections including onchocerciasis, strongyloidiasis and crusted scabies, as well as papulopustular rosacea.[1] The Australian Medicines Handbook also lists other intestinal nematode infections, cutaneous larva migrans and lymphatic filariasis as accepted indications.

In Australia, the precise prevalence of parasitic infections treated with ivermectin is relatively unknown, making it difficult to determine the extent of use of ivermectin. For instance, the prevalence of strongyloidiasis is estimated to be between 35-60% in Indigenous Australian communities, however it is difficult to detect and not routinely tested for.[2] Similarly, whilst scabies is considered common across Australia, crusted scabies is considered a rare but highly infections variant.[3] Review of Pharmaceutical Benefit Scheme data would provide further insight into the use of ivermectin for permitted indications.

The COVID-19 pandemic led to some medicines being repurposed for the prevention and treatment of COVID-19. There were suggestions that ivermectin had the potential to be used for this indication due to its ability to inhibit the replication of viruses in vitro. An updated Cochrane systematic literature review assessing the efficacy and safety of ivermectin for the prevention of infection with SARS-CoV-2 (post exposure) and treatment of COVID-19 was published in June 2022. The review '*found no evidence to support the use of ivermectin for treating COVID-19 or preventing SARS-CoV-2 infection'.*[4]

The current Appendix D entry enables ivermectin to be used for the purpose of clinical trials and does not act as a barrier for further research on the use of ivermectin for COVID-19 prevention and treatment. The Guild believes that it is appropriate to retain the current Appendix D entry until there is sufficient and definitive evidence that ivermectin is effective for the prevention or treatment of COVID-19.

Any other matters necessary to protect public health

Vaccination is the mainstay for prevention of vaccine-preventable diseases such as COVID-19. In Australia, consumers are fortunate to have free access to COVID-19 vaccines through the National COVID-19 vaccination rollout. COVID-19 vaccination protects against severe illness and death from COVID-19; helps prevent complications such as long COVID; and reduces the burden on the health system by preventing hospitalisations.[5] Vaccination is not 100% effective at preventing infection and means access to treatments for COVID-19 is also required.

[1] https://amhonline.amh.net.au/chapters/anti-infectives/anthelmintics/other-anthelmintics/ivermectin
[2] https://theconversation.com/strongyloidiasis-is-a-deadly-worm-infecting-many-australians-yet-hardly-anybody-has-heard-of-it-81687
[3] https://www.racgp.org.au/afp/2017/may/scabies-a-clinical-update
[4] https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD015017.pub3/full
[5] https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/about-rollout#benefits-of-vaccination

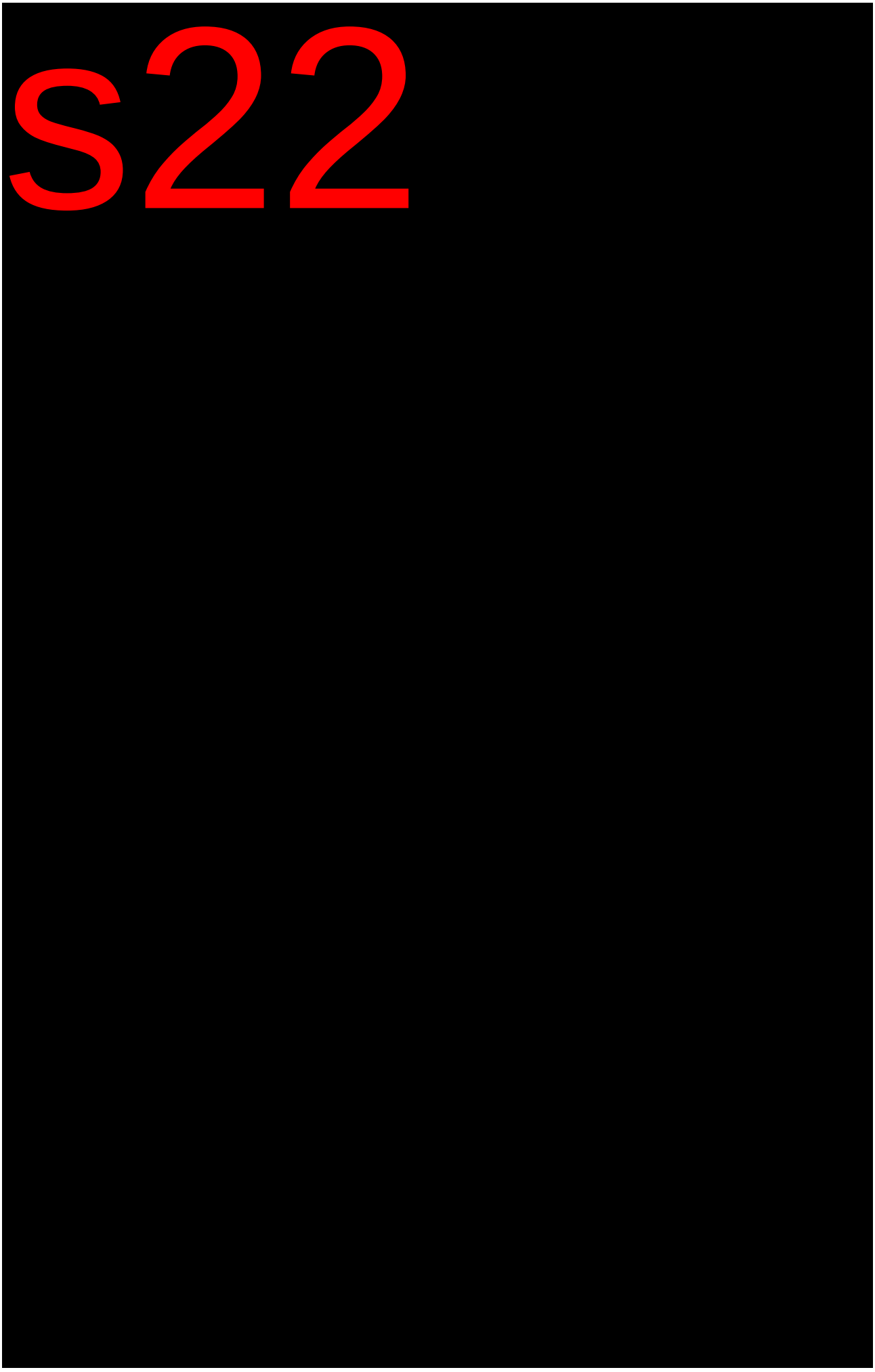
The Therapeutic Goods Administration has granted provisional registration to many treatments for use in COVID-19 positive patients. These treatments have been determined to meet the safety, efficacy and quality standards required for use in Australia.[6] The treatments that have been granted provisional registration enable patients access to safe and effective treatment of COVID-19 regardless of whether they are being managed in the community setting by primary care providers or in hospital.

The Guild believes that it is important to retain the current Appendix D entry for ivermectin to ensure patients continue to utilise vaccination for the prevention of COVID-19 infection and access COVID-19 treatments that are safe and effective.

Summary

The Guild opposes the proposed amendment to remove ivermectin from Appendix D. Studies conducted on the use of ivermectin for the prevention and treatment of COVID-19 have so far failed to conclude that it is effective for this indication. As a matter of public safety, the Guild believes that the current restrictions remain appropriate to ensure individuals receive safe and effective treatment for COVID-19.

[6] https://www.tga.gov.au/products/covid-19/covid-19-treatments/covid-19-treatments-provisional-registrations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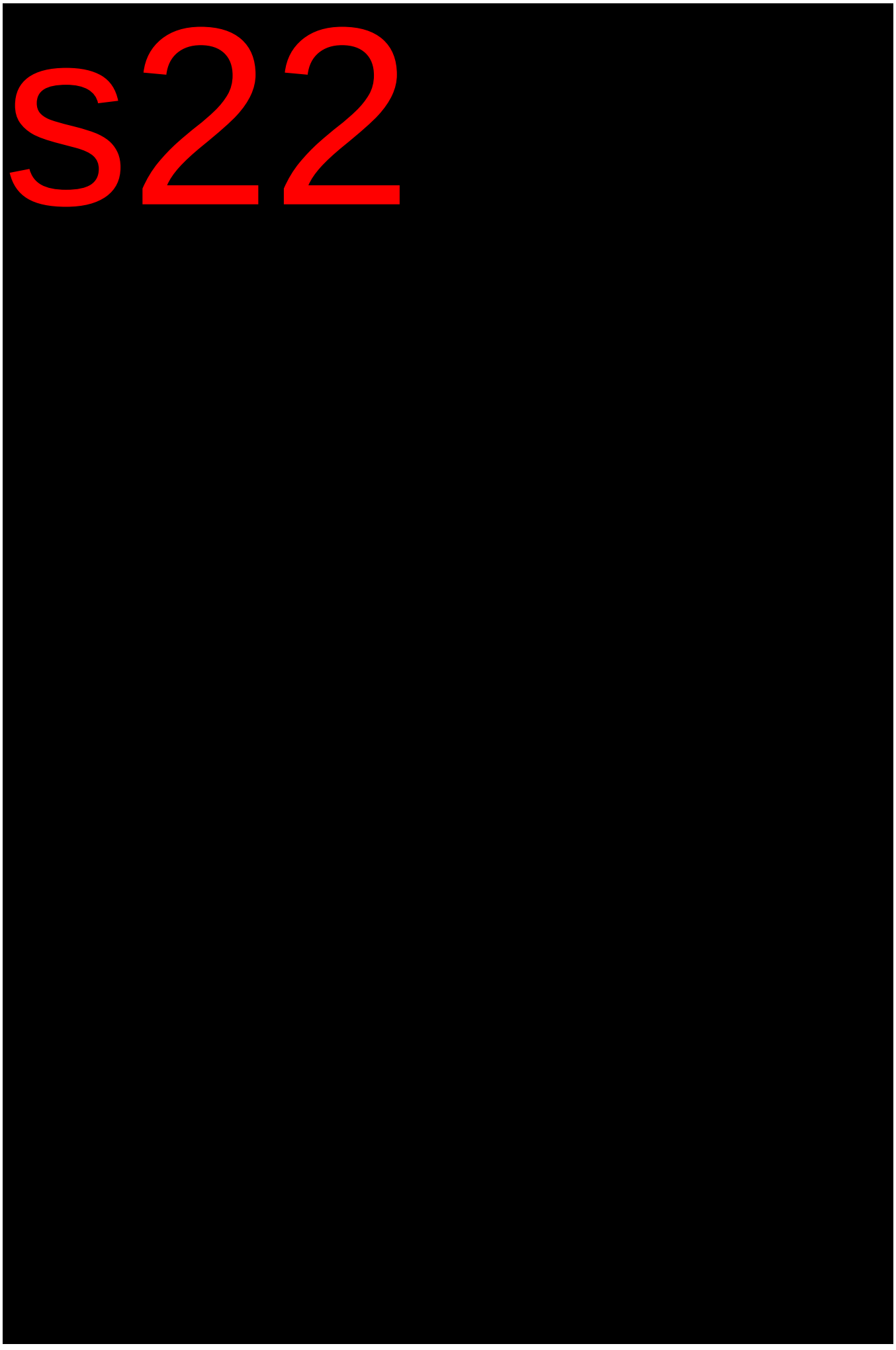
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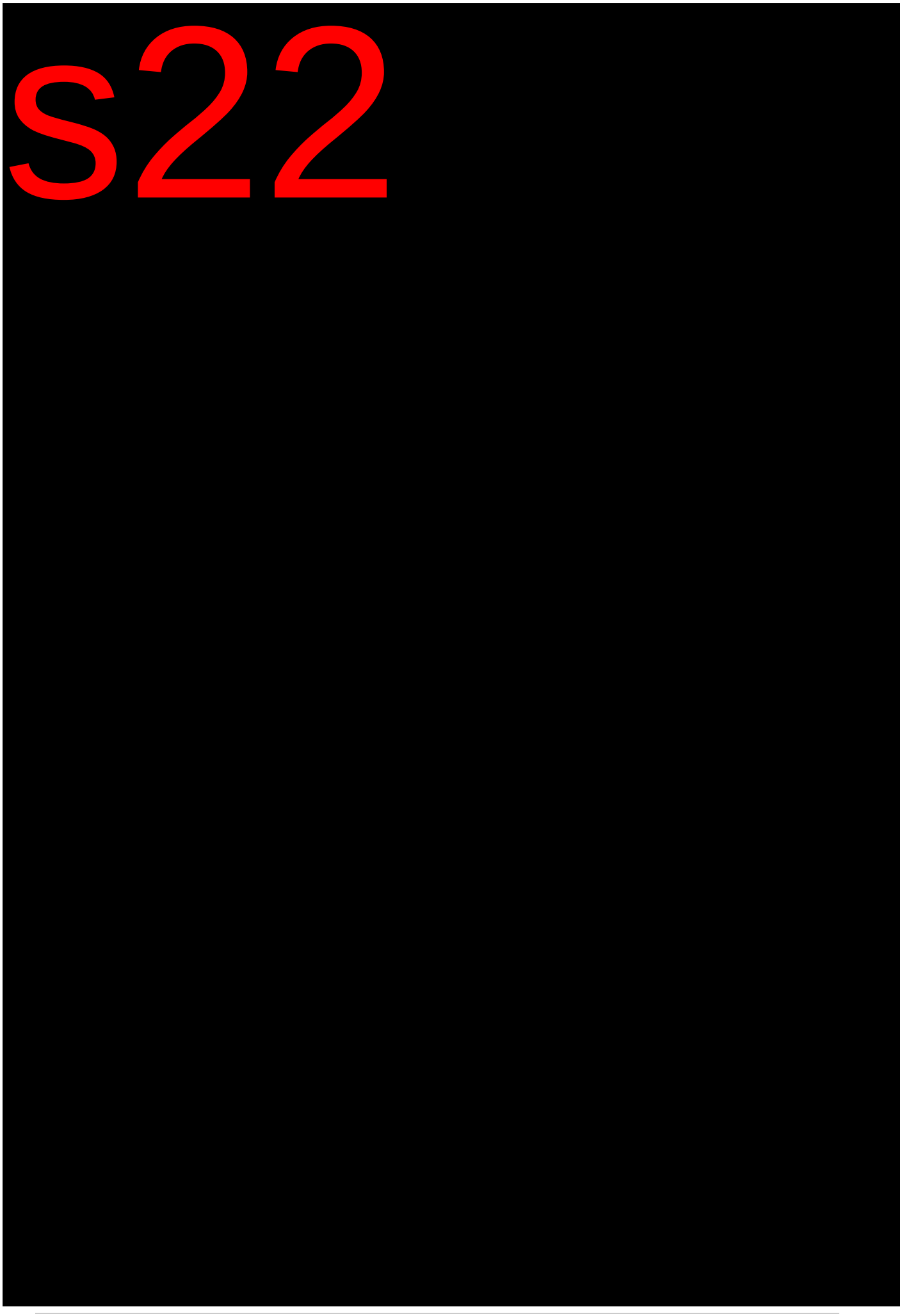
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29 September 2022

Submission to the Commonwealth Department of Health

Therapeutic Goods Administration

To

Amend The Scheduling of Ivermectin

Deletion of Appendix D, Item 10 from The Current S4 Poisons Scheduling

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DECLARATION:

We declare that we have no competing interests or conflicts of interest in making this submission. We represent the Australian Medical Professionals Society (AMPS). We believe the views expressed in this document are consistent with those of our members. The information provided in the submission is, as far as we know, true and accurate.

We agree to maintain confidentiality in relation to notifications of intermediate and final decisions on this consultation and submission until they are published in accordance with subsections 42ZCZP and 42ZCZS of the Therapeutic Goods Regulations Act 1990, as applicable (i.e., following referral to an expert advisory committee).

Co-Signatories:
s22 [redacted]

Date 29/9/2022

Contents

Introduction

On 10 September 2021, a delegate of the Secretary of the Department of Health considered the advice provided by the Advisory Committee on Medicines Scheduling (ACMS) and made the decision to amend the Poisons Standard by creating a new Appendix D listing for ivermectin and thus eliminated its use as an off-label treatment option for COVID-19. This occurred with reference to subsection 52E(1) of the Therapeutic Goods Act 1989, in particular paragraph (f), which empowers the Secretary to act on any *other matters* that the Secretary considers necessary to protect public health[1]. We consider this change to the Poison Scheduling for ivermectin to be inappropriate and not in the best interests of medicine in Australia[2].

The role of the Therapeutic Goods Administration is to apply scientific and clinical expertise to decision making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines[3]. However, the reasons outlined for placing constraints on the prescription of ivermectin for the treatment of COVID-19 do not appear to be based on a thorough risk benefit analysis to consumers and appear to contradict earlier authoritative safety analysis (AusPAR 2013). The use of ivermectin was restricted in a very specific context, in which the priority for public health agencies was maintaining the focus on vaccine uptake in the community, whilst maintaining control of messaging.

The Australian Medical Professionals Society (AMPS) is a growing association of medical professionals in Australia. AMPS welcomes the opportunity to make a submission to amend the scheduling of ivermectin, through deletion of Appendix D, Item 10 from the current S4 Poisons Scheduling. In seeking to provide our Society's perspective, we will discuss the set of rationales outlined by the TGA at the time of the original decision. Importantly, it is our belief that to meet our Code of Conduct obligations, we must seek to have safe, affordable and efficacious medicines available to our patients. As such, we seek to have ivermectin reinstated and available at the present time, as was the case pre-pandemic.

Prior to the amendment of September 2021, ivermectin had been available for off-label prescribing, in accordance with the clinical judgement of doctors. In a climate where clinicians became used to looking to the government for guidance on numerous pandemic-related issues in daily practice, it is true that there were no positive statements made by government bodies or associated committees, in support of the use of ivermectin for COVID-19 disease. However, many Australian doctors felt from their own analysis that the case for ivermectin was very reasonable (often in combination with other medications) and were able to use this medicine off-label, as confirmed by Minister Hunt, in a letter from August 2020[4]. Clearly no sponsor was likely to approach the TGA to seek a formal indication

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[1] https://www.tga.gov.au/resources/publication/scheduling-decisions-final/notice-amendment-current-poisons-standard-under-paragraph-52d2a-therapeutic-goods-act-1989-0

[2] https://www.tga.gov.au/resources/publication/scheduling-decisions-final/notice-amendment-current-poisons-standard-under-paragraph-52d2a-therapeutic-goods-act-1989-0

[3] https://www.tga.gov.au/about-tga/what-we-do/role-tga#:~:text=The%20TGA%20is%20responsible%20for%20regulating%20the%20supply%2C%20import%2C%20export,be%20lawfully%20supplied%20in%20Australia.&text=The%20TGA%20is%20a%20part%20of%20the%20Australian%20Government%20Department%20of%20Health.

[4] https://www.tga.gov.au/products/covid-19/covid-19-treatments/covid-19-treatments-provisional-registrations#:~:text=Off%2Dlabel%20prescribing%20refers%20to,the%20setting%20of%20informed%20consent.

of ivermectin in the treatment of COVID-19 disease, given that its patent expired, but this was not a significant barrier to physician-driven off-label treatment.

With this background, the pressure and concern of the vaccine rollout and a potential negative impact on ivermectin availability, which itself implied that significant numbers of doctors were prescribing the drug, appear to have been the primary motivations in introducing Appendix D in its current form. These reasons will be discussed subsequently. As will also be discussed, AMPS members have assessed the full range of studies on ivermectin and believe that the initial hesitancy, in which claims that ivermectin was unsafe thrived, is unsupported by the overall body of literature[5]. In fact, the evidence base continues to grow that this is a safe, cost effective, efficacious and essential medicine.

In the changing context of SARS-CoV2 and COVID-19 disease, which remains prevalent despite high rates of vaccination, our view is that Australian doctors should have the maximum options available for use, based on their clinical judgement. Cognisant of our Code of Conduct obligations and placing patient care as our primary concern, we believe that ongoing restrictions on ivermectin prescribing is not suited to the current conditions of the pandemic. AMPS therefore strongly supports the deletion of Appendix D, Item 10 from the Current S4 Poisons Scheduling, in the best interest of Australian doctors and their patients.

Professional Responsibilities

AMPS has been established as a platform of advocacy for medical professionals in this country. We advocate for policies and practices which support the health and safety of the Australian public, are supremely focussed on patient care and are consistent with the Good Medical Practice Code of Conduct. The Code sets out professional obligations to ensure patient care is our highest priority. Doctors are obliged to act honestly, ethically and in a trustworthy manner. Public trust in medical professionals is a bedrock of public health. Australians expect their doctors to act competently, providing advice openly and with full disclosure and to display qualities of integrity, truthfulness, dependability and compassion[6].

AMPS undertook a survey of membership to solicit feedback on the potential removal of Appendix D and can advise that 100% of respondents were fully supportive of the proposal to reschedule this medicine. Additionally a recent survey conducted by the Royal Australian College of General Practitioners found that the majority (54%) of doctors believe there should be no restrictions on being able to prescribe ivermectin for COVID-19[7]. Our members expressed their determination and saw it as their duty to advocate strongly for patients to have access to ivermectin, being confident of the supporting evidence-base with regard to safety, as well of its benefits in the treatment of COVID-19 disease at various stages.

In this regard, our society makes note of the 2013 AusPar Report which found no significant safety concerns reported with the use of ivermectin. Given the fiduciary obligation doctors

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[5] https://ivmmeta.com/

[6] file:///C:/Users/danan/Downloads/Medical-Board---Code---Good-medical-practice-a-code-of-conduct-for-doctors-in-Australia---1-October-2020%20(15).PDF

[7] https://www1.racgp.org.au/newsgp/poll

have when unwell patients present to them, to treat them to the best of their knowledge and ability, we believe that the changes to Appendix D place all doctors who are aware of the safety profile of ivermectin, in a situation which breaches our primary obligations. Furthermore, to our membership, it is of great concern that restrictions on the availability of this product has prevented vast numbers of Australians, who wished to do so, from accessing a safe treatment option that showed genuine promise.

We are not opposed to the approval and availability of other medicines for early treatment of COVID-19 disease. However, we note that decisions have been made to provisionally approved medicines with less supporting evidence than ivermectin, especially with regard to safety, and with significantly higher cost and adverse event profile, such as Remdesivir, Paxlovid and Molnupiravir[8].

On first principles, an early treatment strategy is both separate and complementary to a vaccination strategy. However, it is now clear that mRNA vaccines have been less effective than anticipated. It is now clear that less protection is offered by currently available vaccines against new and prevailing variants of SARS-CoV2. Unfortunately, the phenomenon of waning immunity, in which protection of any kind is very limited after 4-6 months, is well documented and publicly acknowledged. With this in mind, if there was at one time a basis for a 'vaccine only strategy', it is certainly no longer the case. We believe it is now time to liberalise decision making about best clinical care to medical practitioners, who should be free to draw on their years of expertise and subject knowledge to make recommendations for the benefit of patients, at their discretion.

Given these considerations, the statement that there is not enough evidence to support the safe and effective use of ivermectin drugs (used as monotherapy or in combination with doxycycline and zinc) to prevent or treat COVID-19[9] does not accord with the current body of evidence, amassed historically and recently. This being the case, with ivermectin being a safe and accepted item of the pharmacopoeia decades before the pandemic, we wish to highlight that the persistence of Appendix D in its current form, limits the ability of doctors to exercise their judgement on behalf of patients and thus may compromise them in their fiduciary duty to individual patients above all else.

To summarise, we have made the case that a restrictive policy regarding ivermectin does not accord with the professional opinions of our membership, nor with a large proportion in the wider medical community. We believe that, in practice, such a policy contradicts our Codes of Conduct and wish to highlight that this can be remedied by the deletion of Appendix D, Item 10.

8https://mail-attachment.googleusercontent.com/attachment/u/0/?ui=2&ik=614ed1668c&attid=0.1&permmsgid=msg-f:1743540180858574027&th=18324c8e8bb214cb&view=att&disp=inline&realattid=f_l7v5qnoy0&sadnir=2&saddbat=ANGjdJ9BgyYZBQpBGpL4ZmYvV9fj1xekMYbqPr_qyoMkcsvEmyvwaYSrl1qXRmi82_s0BUm-cvwQkYMUFKh0Fm7goGs8ZhqqmZOYG1YR6_N0K36uxNFu59R3E5PzUOniupo130hjZJqUoY8MANRcBcVhEWqCXZVu_rmZSPM2QPOYPL89E3sicJn5bnYZlFY6sShMz-yFI8d58h0qdsK_WQ8srP8JyvoLtoQg5IelAc2D4DukO2P_t8BpqII5vA-WTdx027GC555tZfxgq9ybId74vazzE8RVSzwlprirguuK2qtEVR0-V934pvQ0oSVchpkWahuJ5Kl--hcNym62Ty-0dci4KBvHipT8SWbq-M8hMq0JvYLqVhIBkncnZZzp9NDmg9-BINV-CawttzoC8tSyIaKrKFbBnIukBYd8csp638a_c1u3sGW8cSpcjex40J-eCHM7W3m1jope--6f4P2IcPL-8Kd0OhXkg-kUxPLZ2Vpaoom-zYLxWPbfAX8OB8bhffWtWsoZ9Rii1Ii5o-tJSjYpBPp1CbOjWoemCGHJlQTEvQleOF4XfKQiPpvMZwFY7iJ2wVJ4mgKEsYxHIZNSysC5hSOXURdX1k44AFUK8sDdry6mcdcsYPysHagyxe9gRrA17eNkc1Jtn34qkOh1YtWw4Ocmx9Lj8iRL-8QX70S-0eh5TaHQfIs_bItcuQtaVB_uU1SzAnHOwGvAJr1Qd7sSRRlPuCyvvsjd8eMzYVQW0bW2P0iEhcnPyKY

9 https://www.health.gov.au/health-alerts/covid-19/treatments/about

Reasons given for the Rescheduling of Ivermectin

On 10 September 2021 a delegate of the Secretary of the Department of Health considered the advice provided by the Advisory Committee on Medicines Scheduling (ACMS) and decided to amend the Poisons Standard by creating a new Appendix D listing for ivermectin, in effect banning it for use as an off-label treatment option for COVID-19. In statements made by the TGA[10], this change to Poison Scheduling was backed up with reference to subsection 52E(1) of the Therapeutic Goods Act 1989, paragraph (f)[11], together with 3 stated reasons relating to public health, considered in the remainder of this section:

> **Reason 1.** *Serious concerns that there are significant public health risks associated with the prescribing of ivermectin for COVID-19. This includes the likelihood that people who have been prescribed the substance for this purpose may believe themselves to be protected from the disease and not get vaccinated or tested and seek appropriate medical care if they develop symptoms.*
>
> **Reason 2.** *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.*
>
> **Reason 3.** *Concern that if action is not taken to address these concerns, it is possible that oral ivermectin will be in shortage in Australia for the treatment of the conditions for which it has been properly evaluated and approved in accordance with scientific data.*

AMPS does not believe Reason 1 justified the prohibition of ivermectin prescribing for the treatment of COVID-19. We believe that every intervention has to be judged on its own merits and that doctors and patients should be able to make these decisions together, in an atmosphere free from undue pressure for any other party. We further believe that the decision of an individual to be vaccinated is a separate and complementary one to any treatment strategy employing ivermectin. Regarding Reason 3, supply has not been reported to be a problem in Australia or world-wide.

AMPS is of the understanding that the role of the TGA is to determine the safety of medicines and regulate products based on an assessment of risks against benefits[12][13]. In this spirit, we do not take the view that the legislative provisions within the Therapeutic Goods Act necessarily allow the TGA to restrict access to acceptable pre-existing medical options, as a means of encouraging public behaviour to meet other policy objectives. This

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[10] https://www.tga.gov.au/resources/publication/scheduling-decisions-final/notice-amendment-current-poisons-standard-under-paragraph-52d2a-therapeutic-goods-act-1989-0

[11] https://www.tga.gov.au/resources/publication/scheduling-decisions-final/notice-amendment-current-poisons-standard-under-paragraph-52d2a-therapeutic-goods-act-1989-0

[12] https://www.tga.gov.au/about-tga/what-we-do/role-tga#:~:text=The%20TGA%20is%20responsible%20for%20regulating%20the%20supply%2C%20import%2C%20export,be%20lawfully%20supplied%20in%20Australia.&text=The%20TGA%20is%20a%20part%20of%20the%20Australian%20Government%20Department%20of%20Health.

[13] https://www.tga.gov.au/how-we-regulate/advertising/legal-framework/act-regulations-and-code-offences/how-tga-regulates

kind of justification, implicitly present in Reason 1 with regard to uptake of provisionally approved vaccines, was not subjected to wide consultation.

As stated previously, early treatment is a separate and complementary strategy, which can and does coexist in the treatment of Australians facing COVID-19 disease. In regards to currently available provisionally approved vaccines against SARS-Cov2, we note with significant concern, the unprecedented rates of adverse event reports, including deaths, injury and disablement, being seen in Australia and across the world[14]. Regardless of this, however, we note that consequent to Appendix D, Item 10, vaccinated Australians who suffer COVID-19 are currently being denied access to the full range of early treatment options, despite the objective of high vaccination rates having already been achieved in Australia.

Also with regarding Reason 2, in consideration of safety, the (NCCET) conducted a review of the clinical data regarding the use of ivermectin in the management of COVID-19 and concluded;

> *"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.[15]"*

We note that the term "reasonable certainly" is ambiguous in terms of drug regulation, in that the threshold for what is reasonable is not defined and may be viewed differently by different parties. We point out that this recommendation has been challenged by experts both National and Internationally[16][17][18]. We believe there is ample controlled evidence to support the effectiveness of ivermectin both alone and in combination, in addition to the notable documented experience of countries such as India and Peru, in which a strong correlation has been reported between ivermectin use and mortality reductions. Nevertheless, efficacy was not a reason outlined by the TGA as a consideration in the scheduling decision[19][20][21].

Therefore, in the following section, we will focus on addressing safety concerns and the claim that ivermectin has the potential to cause severe adverse events, pertinent to Reason

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14 https://8630368.fs1.hubspotusercontent-na1.net/hubfs/8630368/AMPS/Altman%20Report%20Final%20Version%2011-8-22%20(1).pdf?utm_source=hs_email&utm_medium=email&_hsenc=p2ANqtz-8HS0cEyUJuQHjoxCYMYvaYAqn1CWxMNk_F4VyGSiymi6QxgE6AEh9SJNXh6yR0hIVEAxxC

15 https://covid19evidence.net.au/wp-content/uploads/NC19CET_Published_Guideline_V48_0.pdf

16 file:///C:/Users/danan/Downloads/COCHRANE%20Fordham-Review%20of%20Cochrane%20Report%20copy.pdf

17 https://quadrant.org.au/opinion/qed/2021/08/commentary-on-nccet-statement-on-ivermectin/

18 https://quadrant.org.au/opinion/public-health/2021/10/we-cant-vaccinate-this-pandemic-away/

19 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8383101/

20 https://osf.io/9egh4/

21 https://indianexpress.com/article/cities/lucknow/uttar-pradesh-government-says-ivermectin-helped-to-keep-deaths-low-7311786/

2, above. We will focus on peer reviewed data, rather than the potential dangers associated with data sourced from social media posts, as considered in the TGA reasoning.

Ivermectin Safety and Clinical Benefits

The essential issue is that in the case of a repurposed compound with documented safety and excellent tolerability, such as ivermectin, doctors should not be hindered in evaluating such pre-existing treatments and adopting them if they so choose, in pursuit of the best care of their patients. This simply reflects a reasonable and time-honoured approach, employing critical appraisal, risk benefit analysis and informed consent, in keeping with good medical practice. In the context of a novel health concern, we argue that a responsible physician-directed process is eminently suitable when the compounds under consideration are familiar to doctors and have excellent known safety profiles. This is the case with ivermectin, especially where considered in the pre-hospital phase of COVID-19 treatment, where other options have been more limited.

As outlined in the TGA's 2013 AusPar Report for ivermectin, no significant safety concerns were found with the use of ivermectin[22]. Very importantly, the report found no safety concerns even at 10 times the (then) current approved dose of 200ug/kg[23]. The U.S. National Institute of Health (NIH) has recognised that "ivermectin has been widely used and is generally well tolerated"[24]. A recent systematic review stated "ivermectin at the usual doses is considered extremely safe for use in humans"[25]. In 2018, ivermectin was added to the WHO list of Essential Medicines and in supporting the submission for inclusion in the list, the WHO concluded that the adverse events associated with ivermectin are "*primarily minor and transient*". The clinical evaluator in the WHO Report found that there were no significant safety concerns or serious adverse events reported with the use of ivermectin[26].

In February 2021, an expert toxicology report on the safety of ivermectin was collated based on a review of over 500 articles. This unprecedented work is well worth considering in detail and outlined the following:

> "*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*....

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22 https://www.tga.gov.au/sites/default/files/auspar-ivermectin-131030.pdf

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

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

[25] 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

[26] 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)

> *…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[27].”*

In this regard, a decisive legal opinion from the U.S. Nebraska State Attorney General’s Office (14 October 2021) is highly instructive. It provided a detailed analysis of the arguments regarding ivermectin and off-label prescribing and a copy of this ruling forms Annexure 1 to this Submission. The Co-signatories rely upon this opinion in full as it pertains to ivermectin.

The opinion states in part:

> “*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. This number is incredibly low considering that “more than 3.7 billion doses” of ivermectin have been administered to humans worldwide since the 1980s[28]*.”

The brief but comprehensive review of the safety of ivermectin provided here does not provide any clear or convincing evidence that ivermectin poses such a threat to public health and safety that it required sudden rescheduling in the middle of a pandemic as a poison when prescribed for COVID-19. In truth, no data exists in support of serious harm. It is likely that the absence of safety concerns relating to ivermectin was the very reason for the rapid commencement of multiple early controlled trials in COVID-19 disease overseas, after widespread interest in the potential benefits of this highly versatile drug.

Ivermectin has documented pharmacological mechanisms that led clinicians to believe this extremely safe medicine could be repurposed effectively for the treatment of COVID-19. It has been known for over 10 years that ivermectin demonstrated antiviral activity against several RNA viruses by blocking the nuclear trafficking of viral proteins[29]. A comprehensive systematic review summarises the antiviral effects of ivermectin, including in vitro and in vivo studies over the past 50 years [30]. Another paper titled, “Ivermectin: an award-winning drug with expected antiviral activity against COVID-19” put forward that Ivermectin, an FDA-approved broad-spectrum antiparasitic agent, had demonstrated antiviral activity against a number of DNA and RNA viruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[31]. As well as ivermectin’s antiviral benefits there is also research literature that outlines its recognised “anti-inflammatory capacity”[32].

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[27] 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

[28] 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

[29] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7539925/

[30] https://pubmed.ncbi.nlm.nih.gov/32533071/

[31] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7539925/

[32] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7476419/

A review titled “Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19” 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 [33].”*

Finally, an online real time meta-analysis of the clinical safety and efficacy of ivermectin in COVID-19 disease is well worth considering and can be found at www.ivmmeta.com: as of 9 September 2022, this includes 91 studies, of which 41 were randomised controlled trials involving 11,141 patients[34]). This resource illustrates the high level of international interest in the clinical submission of ivermectin for potential use in COVID-19. When taken in totality, the clinical data presented at www.ivmmeta.com presents a compelling case for the safety and efficacy of ivermectin. 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, hospitalisation, progression, recovery, [number of] cases, viral clearance, and in pooled analysis... Meta-analysis using the most serious outcome measure shows 62% [57-70%] and 83% [74-89%] improvement for early treatment and prophylaxis”.

At this stage, public health officials and the medical profession generally have had time to review the accumulating data regarding ivermectin, in addition to the rapid mutation rate of the SARS-CoV2 and waning vaccine efficacy. We believe it is vital to reconsider the role of ivermectin in the arsenal of available drugs. It is important to point out that we are not aware of any other occasion on which an established drug in the Australian pharmacopoeia that has previously been considered very safe, has been rescheduled in such a way as to make its prescription illegal for doctors.

AMPS can find no clear and conclusive evidence to support the TGA claims that ivermectin poses a safety risk to the public with the potential for a high incidence of severe adverse events. Rather, our review of the evidence demonstrates that ivermectin is a fully approved, AurPar reviewed, Nobel prize winning WHO essential medicine, that has been given in billions of doses with minimal adverse reaction reported. We consider that Australian doctors should again be afforded professional discretion with regard to ivermectin use, which may translate to benefit in future seasonal outbreaks of SARS-CoV2/COVID-19 disease, with flow-on benefits to the hospital system, with very little downside, as we have summarised.

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

34 https://ivmmeta.com/

Conclusion

AMPS believes in the primacy of the doctor/patient relationship within medicine and stands firmly opposed to the placement of excessive constraint on the clinical judgement of doctors. Now that Australian vaccination rates have risen to such high levels, we assert that it is consistent at this time to freshly reevaluate historic decisions in the full light of today's context.

In making this submission, foremost in the thinking of our Society is that ivermectin cannot be construed to be a hazard to the health of the Australian people. This assertion contradicts the most extensive drug safety review of ivermectin in the literature[35], the well known evaluation of the WHO in 2018[36], the decisive legal opinion of the Nebraska State Attorney General's Office[37], as well as the TGA's own 2013 AusPar Report[38]. As such, we contend that in the current context, the use of off-label ivermectin cannot plausibly be said to constitute a threat to the public health of Australians, in the spirit of subsection 52E(1) of the Therapeutic Goods Act 1989, particular paragraph (f)[39].

As a Society, we applaud this move of the TGA to open consultation with regard to Appendix D, Item 10. AMPS believes that the continuing restriction of ivermectin would at this stage represent a serious error in judgement. In this regard, we draw attention to the humility recently expressed by Dr Rochell Walensky the Director of the CDC told, who told employees recently:

> *"To be frank, we are responsible for some pretty dramatic, pretty public mistakes from testing, to data, to communications[40]"*

As we have outlined in this document, we consider that the Australian Regulators now have the opportunity to reconsider these questions, in a way which is not only likely to benefit the health of Australians, but reinforce the invaluable role of doctors' clinical judgement and expertise in the use of safe repurposed therapies in individualised patient care.

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[35] 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

[36] 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)

[37] 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

38 https://www.tga.gov.au/sites/default/files/auspar-ivermectin-131030.pdf

[39]https://www.tga.gov.au/resources/publication/scheduling-decisions-final/notice-amendment-current-poisons-standard-under-paragraph-52d2a-therapeutic-goods-act-1989-0

[40] https://www.washingtonpost.com/opinions/2022/08/18/cdc-changes-next-pandemic-preparation/

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/26/questions-raised-over-hydroxychloroquine-study-which-caused-who-to-halt-trials-for-covid-19 (last visited Oct. 14, 2021).

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

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

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

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

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

ANALYSIS

1. The Nebraska Uniform Credentialing Act and Other Relevant Law

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

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7 Boseley & Davey, *supra*.

8 Neb. Rev. Stat. §§ 38-102 & 38-104.

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

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

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

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

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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(6), (24).

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

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

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

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

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17 *Langvardt v. Horton*, 254 Neb. 878, 895, 581 N.W.2d 80, 70-71 (1998)

18 Neb. Rev. Stat. § 38-179.

19 172 Neb. Admin. Code § 88-009(Q).

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

21 172 Neb. Admin. Code § 88-009(B)

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

23 172 Neb. Admin. Code § 88-009(B)

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

25 *Id.* (collecting cases).

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

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

2. COVID-19 and SARS-CoV-2

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

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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=3f3YCJGw6sEC&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-expended-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, 495 (2017), *available at* https://www.nature.com/articles/ja201711.pdf (last visited Oct. 14, 2021) (hereinafter, "Crump, *Ivermectin*").

[43] *Id.*

[44] Andy Crump & Satoshi Ōmura, *Ivermectin, 'wonder drug' from Japan: the human use perspective*, 87 Proceedings of the Japan Academy, Series B, Physical and biological sciences 13, 13 (2011), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3043749/pdf/pjab-87-013.pdf (last visited Oct. 14, 2021).

[45] Andrew Bryant et al., *Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines*, 28 American Journal of Therapeutics 434, 435 (Jul./Aug. 2021), *available at* https://journals.lww.com/americantherapeutics/fulltext/2021/08000/ivermectin_for_prevention_and_treatment_of_7.aspx (last visited Oct. 14, 2021) (hereinafter, "Bryant, *Ivermectin*").

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

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

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

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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*, 28 American Journal of Therapeutics 299, 301 (2021), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8068823/ (last visited Oct. 14, 2021).

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

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

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

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

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

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

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

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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/s8.6_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://ja-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] Priyamedhaba 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/84807/20210904-4912-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 Shalkhsi 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 451.

89 *Id.* at 436.

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/pegqj/ (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/ait-28-e576.pdf (last visited Oct. 14, 2021)

102 *Id.*

103 *Id.* at 578.

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

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

106 *Id.*

107 *Id.*

108 *Id.*

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

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

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

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

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

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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/NCT04510947?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/9eqh4/ (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.*

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

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

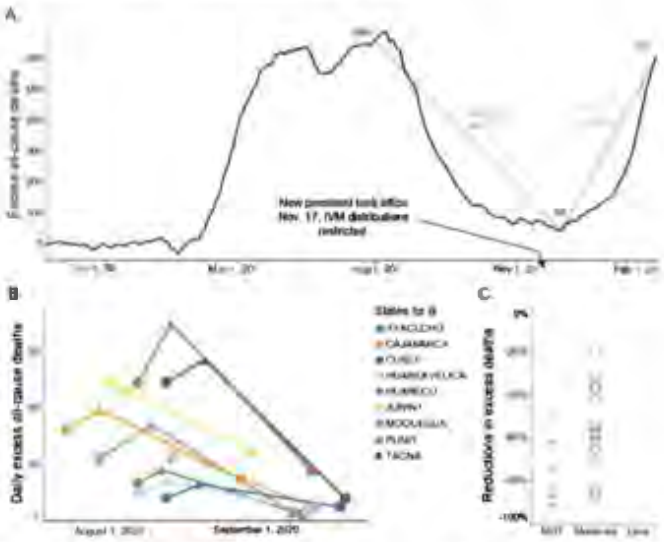

Figure 1. A) **Excess all-cause deaths (all ages), national population of Peru.** These decreased 14-fold August 1-through December 1, 2020 (mandate after IVM use was restricted, increased 13-fold through February 1. All y values are 7-day moving averages (for D.C. ages ≥ 50). Data are from Peru's National Death Information System (SINADEF).[42] B) Drops in excess deaths for all states of operation *MOT*, an array-led program of mass IVM distributions, but Pasco, which had them on 3 dates. ■ *MOT* start date; ▲ peak deaths; ■ day of peak deaths + 10 days. Junin also distributed IVM 13 days before *MOT* start. C) Reductions in excess deaths at +10 days after peak deaths for the 25 states by extent of IVM distributions: maximal-*MOT* (+), mean -74%; moderate-local distributions (o), mean -53%; and minimal-Lima (x), -25%. These reductions for the 25 states correlated with extent of IVM distributions with Kendall τ_b p=0.002.

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

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

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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-sotu-vpx.cnn (last visited Oct. 14, 2021).

[135] *Id.*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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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).

[155] *Id.*

[156] *Id.* at 3.

[157] Emma Goldberg, *Demand Surges for Deworming Drug for Covid, Despite No Evidence It Works*, New York Times (Aug. 30, 2021), *available at* https://web.archive.org/web/20210830091030/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 Wailing as Horse Dewormer Overdoses Overwhelm Oklahoma Hospitals, Doctor Says*, Rolling Stone (Sept. 3, 2021), *available at* https://web.archive.org/web/20210903231939/https://www.rollingstone.com/politics/politics-news/gunshot-victims-horse-dewormer-ivermectin-oklahoma-hospitals-covid-1220608/ (last visited Oct. 14, 2021).

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

161 *Id.*

162 *Id.*

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

164 *Id.*

165 *Id.* at 23.

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

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

iv. Professional Associations and Physicians on Ivermectin

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

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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).

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

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

170 *Id.*

171 *Id.*

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

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

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172 *Id.*

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

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

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

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

177 *Id.*

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

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

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

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

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

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184 *Id.*

185 *Id.*

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

187 *Id.*

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

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

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

4. Hydroxychloroquine

A. History of Hydroxychloroquine

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

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

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

196 *Id.*

197 Fram, *supra*, at 389.

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

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

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

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

B. Hydroxychloroquine and COVID-19

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

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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/PMC1232569/pdf/1743-422X-2-69.pdf (last visited Oct. 14, 2021).

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

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

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

204 CDC, Malaria Travel, *supra*.

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

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

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

i. Hydroxychloroquine Studies and Meta-analyses

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

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

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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 (Jul. 2021), *available at* https://www.sciencedirect.com/science/article/pii/S1567576921002721 (last visited Oct. 14, 2021).

210 *Id.*

211 *Id.*

212 Million, *supra*, at 1063.

213 *Id.* at 1066.

214 *Id.* at 1063.

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

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

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

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215 *Id.*

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

217 *Id.*

218 *Id.*

219 *Id.* at 606.

220 *Id.* at 603.

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

222 *Id.*

223 *Id.*

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

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

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

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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 > 80% reduction in mortality."[233] And another scholar, Dr. Harvey A. Risch, Professor of Epidemiology at Yale School of Public Health, has published online a non-peer-reviewed meta-analysis of ten studies exploring hydroxychloroquine as an early COVID-19 treatment.[234] He concluded that for people receiving that treatment the odds ratio of hospitalization was .56 and the odds ratio of death was .25. In other words, his meta-analysis demonstrated that when hydroxychloroquine is administered as an early COVID-19 treatment, it can reduce the risk of death by 75%.

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

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

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

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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 confounder."[255]

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

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

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

[252] *Id.*

[253] *Id.* at 102.

[254] *Id.* at 102.

[255] *Id.* at 100.

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

[257] *Id.*

[258] Mehra, *supra*.

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

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

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259 *Id.* at 1.

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

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

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

263 Boseley & Davey, *supra*.

264 Davey, *supra*.

265 Rabin, *supra*.

266 Boseley & Davey, *supra*.

267 *Id.*

268 Heathers, *supra*.

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

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

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

iii. U.S. Public Health Agencies on Hydroxychloroquine

The public health agencies in the United States have addressed the topic of hydroxychloroquine and COVID-19. The NIH "recommends against" its use "for the treatment of COVID-19 in hospitalized patients . . . and in nonhospitalized patients."[272] To justify its position against hydroxychloroquine for nonhospitalized patients, the NIH relied heavily on a RCT conducted by Mitja.[273] While that study did not show great advantages in the hydroxyehloroquine 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 Xueting Yao et al., *In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)*, Clinical Infectious Diseases, at 13 (2020), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7108130/pdf/ciaa237.pdf (last visited Oct. 14, 2021)

283 *Id.* at 2.

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

285 *Id.* at 6.

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

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

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

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

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

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

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

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

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

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

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

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289 FDA, Bringing Perspective, *supra*.

290 *Id.*

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

292 *Id.*

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

294 *Id.*

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

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

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

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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.

s22

Page 4B

Very truly yours,

s22

Approved by:

s22 s22

SHPA response to Proposed amendments to the Poisons Standard – ACCS, ACMS and joint ACCS/ACMS November 2022 meetings (ivermectin), September 2022

Introduction

The Society of Hospital Pharmacists of Australia (SHPA) is the national, professional organisation for the 6,100+ Hospital Pharmacists, and their Hospital Pharmacist Intern and Hospital Pharmacy Technician colleagues working across Australia's health system, advocating for their pivotal role improving the safety and quality of medicines use. Embedded in multidisciplinary medical teams and equipped with exceptional medicines management expertise, SHPA members are progressive advocates for clinical excellence, committed to evidence-based practice and passionate about patient care.

SHPA convenes an Infectious Diseases Specialty Practice Group, consisting of a network of pharmacists who have expertise or interest in infectious diseases, including general infectious diseases, critical care, tropical medicine, antimicrobial stewardship, antimicrobial therapeutic drug monitoring, surgical prophylaxis, HIV, and sexual health.

SHPA is also a member of the National COVID-19 Taskforce and represented on the National Steering Committee and National Guidelines Leadership Group. SHPA members who are subject matter experts in their field, are also represented on various specialist expert writing group panels convened by the National COVID-19 Taskforce, including the acute and critical care panel, disease modifying treatment and chemoprophylaxis panel.

After consultation with SHPA members in the Infectious Diseases, Medication Safety, Dispensing and Distribution Specialty Practice Group and SHPA members in the National COVID-19 Taskforce, SHPA would like to provide the following comments for the Delegate's consideration in making a decision regarding the Appendix D listing for ivermectin, and that any decisions made that limit its access are proportional to the risks of misuse.

Applicant's intent and evidence for ivermectin as a COVID-19 treatment

SHPA is strongly concerned at the applicant's clear intention and view that access to ivermectin for the treatment of COVID-19 should be more readily available, despite not being listed as a recommended treatment on the National COVID-19 Clinical Evidence Guidelines.[1] The evidence base for ivermectin remains poor, with a Cochrane Review in 2021 assessing the evidence base for ivermectin in prevention and treatment of COVID-19 concluding uncertainty in the limited evidence base and noting that most studies were small, biased and of poor quality.[2]

Given that Therapeutic Goods Administration-approved treatments for the treatment and prevention for COVID-19 are readily available, SHPA recognises that patients who are prescribed and dispensed ivermectin by their doctors and pharmacists are being treated with sub-optimal treatment that is not supported by National COVID-19 Clinical Evidence Guidelines.[1]

Evidence of inappropriate ivermectin use

With the increased availability of approved treatments for COVID-19, SHPA members report relatively low levels of inappropriate prescribing of ivermectin seen in practice. Data surrounding inappropriate prescribing or use of ivermectin since approved COVID-19 treatments became readily available, are lacking and would need to be assessed prior to forming a decision regarding this proposal.

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Impact on use and access to ivermectin for approved TGA indications

It is essential that the treatment of parasitic infections must not be impeded by any restriction placed on ivermectin access, however, SHPA acknowledges that evidence demonstrating this is lacking. Members have raised that other antimicrobials have the potential to be inappropriately prescribed, but do not have measures limiting their access placed on them, as such measures are not proportional to the risk. SHPA believes appropriate clinical oversight by antimicrobial stewardship pharmacists is essential in ensuring that appropriate prescribing and dispensing for medicines to treat infectious diseases are maintained. Such clinical pharmacy services in all settings of care complement regulatory measures and oversight to mitigate the risk of inappropriate use of antimicrobials.

If you have any queries or would like to discuss our submission further, please do not hesitate to contact Jerry Yik, Head of Policy and Advocacy on jyik@shpa.org.au.

References

[1] National COVID-19 Clinical Evidence Taskforce. Living Guidelines. (2022) Available at: https://covid19evidence.net.au/#living-guidelines

[2]Popp M., Stegemann M., Metzendorf M-I., Gould S., Kranke P., Meybohm P., Skoetz N., Weibel S.(2021). Ivermectin for preventing and treating COVID-19.Cochrane Database of Systematic Reviews 2021, Issue 7. Art. No.: CD015017.DOI: 10.1002/14651858.CD015017.pub2.

Name	Responder type	Written submission
Pharmaceutical Society of Australia	Organisation or peak body	**Ivermectin** PSA opposes the proposal, noting that: • the recommendation against the use of ivermectin for the treatment of COVID-19 issued by the National COVID-19 Clinical Evidence Taskforce remains • in future, measures other than the use of an Appendix D entry in the Poisons Standard to regulate off-label prescribing may need to be considered. Brimonidine PSA supports the proposal, noting that: • the indications, lower strength (0.025%) and use in adults appear to be consistent with safety profile and scheduling factors for S2 • it is consistent with approved use in Canada • patient education will be important to minimise any confusion with higher strength brimonidine eye drops • there may be advantages over other ophthalmic decongestants which are alpha-1 or mixed alpha-1/alpha-2 adrenergic receptor agonists. Fexofenadine PSA supports the proposal, noting that: • similar antihistamine substances such as loratadine in larger packs are currently available for general sale • access through general sale is not necessarily more convenient than through a community pharmacy and should not be considered as a rationale for rescheduling for exemption from the S2 entry. Ibuprofen PSA does not support the proposal, noting that: • there is an increased risk of consumer confusion and possibly duplication of therapy as multiple immediate-release and modified-release products would become available for self-selection (in the majority of jurisdictions) • there are many ibuprofen (and other) products available for the management of acute pain conditions and therefore, rescheduling modified-release ibuprofen may not necessarily lead to a reduction in GP consultations for acute pain management.
s22	s22	s22 I am familiar with the profile of ivermectin (IVM) and its use. It seems inconceivable that eminent medical organisations and bureaucracies, even including a Cochrane Collaboration Review, should seek to prevent the use of such an inexpensive, safe, effective antiviral treatment for Covid-19.
s22	s22	Reconsideration to make ivermectin readily available on prescription for covid, without the current restriction to certain medical specialists This is what I wish to be considered by the ACMS in its November review of the use of ivermectin, alone or in combination, for covid. Thank you

		s22 [redacted] There is Lucy Kerr et al's recently reported work: https://www.cureus.com/articles/111851-regular-use-of-ivermectin-asprophylaxis- for-covid-19-led-up-to-a-92-reduction-in-covid-19-mortalityrate- in-a-dose-response-manner-results-of-a-prospective- observationalstudy- of-a-strictly-controlled-population-of-88012-subjects and Jackie Stone et al's: https://www.mdpi.com/2673-8449/2/3/15/htm There is a local trial: See https://c19ivermectin.com/borody.html, as well of course, all the information in c19ivermectin.com. There are particular studies of interest such as the Tlaxcala study: See https://www.ijidonline.com/article/S1201-9712(21)00100-4/pdf In relation to the population wide study in Mexico City, I note that the reasons given for withdrawing the paper by SocArXiv do not directly relate to the science in the paper: They were: " Our grounds for this decision are several: The paper is spreading misinformation, promoting an unproved medical treatment in the midst of a global pandemic. The paper is part of, and justification for, a government program that unethically dispenses (or did dispense) unproven medication apparently without proper consent or appropriate ethical protections according to the standards of human subjects research. The paper is medical research – purporting to study the effects of a medication on a disease outcome – and is not properly within the subject scope of SocArXiv. The authors did not properly disclose their conflicts of interest." Ground 1 is silly. Credible public health officials from a major world city wrote up their findings from a covid strategy in the midst of a pandemic so that others might benefit from those findings, just as any published paper aims to do. Ground 2. There were reasonable grounds for thinking ivermectin might have an impact. And the ethics differed little from those applied to the covid vaccines, which have not lived up to the initial expectations of them, and in relation to which doctors here have been officially threatened for fully outlining their pros and cons. Ground 3. The journal initially accepted the paper. Ground 4 is also silly. It was perfectly clear who the authors were and who they worked for. Safety On the safety of ivermectin, there is the TGA's published review from 2013, and long and wide experience in its usage, including in Australia's north. Very few if any serious adverse events emerged during the many reported trials. Some adverse events have been reported where people were unable to access the medicine on prescription, and sought other sources. Further In early January 2021, this is what Andrew Hill of the University of

		Liverpool said: " We are working on a project funded by UNITAID as part of the WHO ACT-Accelerator project on COVID-19 treatment. We have combined the results from 18 different randomised controlled trials of ivermectin. I have attached the most recent version of the results. We are seeing strong effects of ivermectin on viral clearance, clinical recovery, time in hospital and survival. The results will be presented to the World Health Organisation treatment guidelines group within the next week. The aim is to gain a recommendation for treatment with ivermectin for patients with COVID-19 infection. " Dr Tess Lawrie et al's metaanalysis at the same time backed this up. See https://journals.lww.com/americantherapeutics/fulltext/2021/08000/ivermectin_for_prevention_and_treatment_of.7.aspx Later, finding one trial which had been included was doubtful, did not alter the essential conclusions, and Bryant and Fordham successfully challenged the Popp critique of the Lawrie et al metaanalysis. See https://ebm.bmj.com/content/27/3/187 and https://www.researchgate.net/publication/355132966_The_uses_and_abuses_of_systematic_reviews and https://medicalupdateonline.com/2021/08/critical-questions-on-theivermectin- meta-analysis/. (I note that in order to have this submission accepted, I have to state that it is all true, with a penalty if not. I cannot vouch for the truth of others' work in the links provided; whether they are accepted as truth is a matter for the reviewing committee. This is as you would expect where there are competing discourses.)
s22 [redacted]		ACMS Ivermectin There is a bit of a backstory to my first submission to the ACMS lodged recently, which I think is important, because it goes to explain my motivation for submitting. Like a lot of Australians, s22 [redacted] were excluded from those permitted to receive the new antivirals sotrovimab, nirmaltrevir/ritonavir or molnupiravir. So the authorities had consigned us, along with all those in our cohort, to the dustbin of history. We were to be sacrificial fodder to a blinkered policy. We were not to be treated with anything likely to attack the virus until the disease had progressed far enough to land us in hospital. No policy of "health in the home"packs, as issued in some countries overseas. Ivermectin prescribed by a doctor wasn't going to kill us, and it had the potential to be better than doing nothing. The alternative was possible death or long term health issues, after a potentially very unpleasant hospital stay, seriously stretching health staff support. In late August 2022, I wrote to a doctor, saying in February I had applied to the TGA to be allowed to be prescribed ivermectin. Access to an early treatment antiviral could have meant the difference between life and

		death for us. The TGA said it wasn't their decision. I then wrote to the Health Department secretary. After phone calls in which I was told key officers wouldn't take my calls, eventually I got a reply (see it and my comment below at *1), saying the matter rested with the Secretary's delegate, apparently a senior medical officer, that the Secretary had no power to vary it for my wife and I, and that any decision to vary the September 2021 decision on ivermectin would not be considered until November 2022. This was with covid deaths running at about 12 times the road toll, worse than the previous two years, and afflicting a greater proportion of the elderly. They still are running at about ten times. I was sent from pillar to post, totally disappointed in the Ombudsman's attitude, and six months and about 8500 covid deaths later, I was yet to find out who the delegate to the Secretary for Health was. I still don't. I cited legal authority back then to the Ombudsman for the fact that a delegator does not lose their decision making power even if they appointa delegate. (Huth vs. Clark). The Ombudsman had said they lacked medical expertise, even though I had raised a matter of administrative procedure, not medicine per se. The AAT when contacted pointed out that Parliament had severely circumscribed, in the enabling Act, their power to oversight the TGA, limiting appeals to certain aspects, largely offering drug and device companies appeal routes but not ordinary members of the public. Small wonder then that I became actively interested in another way of trying to save our lives with early treatment, if needed, and that is the use, based on several reported trials eg. Koshak, Ashraf, of Nigella sativa, the seed found on Turkish bread. The rules around antivirals changed again later in 2022, an[s22] and are now eligible, but many still aren't. Having said that, in inquiries at our local level, there was inadequate current knowledge at the GP pharmacies about the new antivirals from about February 2022 to July 2022, even with an RACGP online seminar occurring in April 2022. Parallel approaches to early stage treatment I should also note the marked lack of medico-scientific drive in Australia since 2020 to carry out any trials of potential early effect-ameliorating treatments, even at the simple level of iodine or other throat gargles, and nasal sprays. Cepharanthine, an OTC drug in Japan, noted in 2020 by the NSW treatment guidelines authority, was not trialled, even though it showed promise in combination with ritonavir in in vitro trials in China by HH Fan, in in vitro trials by Ohashi, and it was reviewed by Rogoznitsky. I even offered to buy some for Monash University to try against covid in vitro. Pointing out to a number of people in the public arena about the potential benefits of promising treatment (even a ten percent reduction in hospital admissions due to early stage treatment of ambulant patients would reduce the stresses on the health system and its staff) fell on deaf ears. It is worth remembering too that Ramos, a cardiopulmonary specialist in Peru wrote up success with ivermectin in May 2020, and Aguirre Chang, Chesler and Tavares in three separate countries also noted beneficial effects around that time. Chetty in Kwazulu also noted in October 2020

		the benefits of of early treatment of incipient hypoxia with antihistamine and steroid. *1 “RE: Request for exemption from your decision of 10.9.21 [SEC=OFFICIAL] I have no authority or delegation to provide the approval you request for two reasons. Firstly, I was not the decision-maker regarding the changes to ivermectin access. Secondly, the decision is implemented in law by your state government not the commonwealth. If you are seeking an ivermectin prescription I suggest you make an appointment with a relevant specialist who can prescribe if they see it medically appropriate. Note however the approved oral antivirals are now available in every state and territory. Adjunct Prof John Skerritt FTSE FIPAA (Vic) Deputy Secretary for Health Products Regulation Australian Government Department of Health PO Box 100 Woden ACT 2606 AUSTRALIA” Comment: Yet the states and territories take their lead from the Commonwealth, and secondly there was a very low chance of getting a script early enough in the course of the disease, given the pressure on GPs and the time it would take to get an appointment with a designated type of specialist with a referral in the midst of the pandemic pressure.
s22 [redacted]		Supplementary Submission Is it true that in the weeks after the September 2021 decision on ivermectin, at least some members who attended that ACMS meeting were unwilling to account for their vote to the public they represented?
s22 [redacted]	[redacted]	The applicant proposes removal of the appendix D entry for ivermectin. In preparing this response I have considered both the summary on the TGA website for consultation, and a copy of the application (dated 13th of August, resubmitted 20th of August) shared by the applicant on his public twitter account. The proposal asserts: - The original appendix D listing was “possibly criminal” - Ivermectin is an effective agent in the prevention of covid-19 - Ivermectin is an effective agent in the treatment of covid-19 - There is “black market” use of veterinary ivermectin - Vaccines have been less effective than hoped - African countries use ivermectin and have low rates of covid-19, providing evidence ivermectin works. Firstly, I am not able to comment on any purported criminality of the Appendix D listing, however I will attempt to address the rest. Secondly the assertion that ivermectin prevents or treats covid 19 is not in line with the best available evidence syntheses, including a Cochrane review and the National Covid-19 Evidence Taskforce. The application lists a handful of low quality studies not systematically selected, and a single (more than 1 year old) meta-analysis in which the only study to show a significant decrease in death has since been retracted. It also

		ignores many major major trials from reputable journals such as NEJM and JAMA which failed to show a benefit from ivermectin in Covid. The capacity of a non-systematic evidence review such as the one presented here to meaningfully alter assessments of efficacy (in the face of gold standard structured syntheses reaching the opposite conclusion) is negligible. Thirdly the assertion of veterinarian [sic] ivermectin use in Australia is not supported by any objective evidence, the application does not identify any instance in which veterinary ivermectin has been used in this way in Australia, and this should be considered a theoretical consideration at most. Fourthly the relative effectiveness of vaccines (which remains high against serious disease) is not a directly relevant consideration for altering the listing of ivermectin. Fifthly direct comparison of sub-Saharan African countries' official rates of diagnosis to rates of diagnosis in other (often higher income) countries is not meaningful, as it will largely be a marker for the development and comprehensiveness of public health surveillance and monitoring infrastructure. That is, differences that represent ascertainment bias should not be ascribed to ivermectin. In a recent BMJ Global Health article (10.1136/bmjgh-2022-008477) rates of underdiagnosis greater than 13 times, the highest in the world, were observed in Kenya, the only African country with data included. Finally, under the provision to consider "any other matters necessary to protect public health" I would make that point that the decision on whether to remove the appendix D listing in response to this (heavily reported) application is not simply about whether the original appendix D listing was justified. This application specifically argues that ivermectin is effective at treating and preventing covid-19 and the acceptance of this application by the TGA would be publicly perceived as a de facto endorsement of ivermectin for these indications. While I am not saying that no application could be prepared that would justify such a change in listing (I neither support nor reject such a proposition), I am saying that is not possible to accept this particular application which is explicitly and publicly based around purported efficacy of the drug for treating covid without the TGA being taken to publicly endorse it for this indication.
s22	s22	As a s22 , I followed the covid 19 response from early 2020 and became aware of the work overseas doctors were doing in finding effective early treatment options. Clinical reports and clinical trials in numerous countries demonstrated that ivermectin was effective in both treatment and prophylaxis. It may be that these trials were not large, but the totality of evidence is convincing and it continues to build (see supporting references in Dr. Fidge's application). Also, it should be recalled that the principles of evidencebased medicine include the knowledge of experienced physicians and informed patient choice. Denying real world medical experience and relying solely on incomplete data provided by pharmaceutical companies can have deleterious outcomes. I obtained ivermectin in case I contracted covid 19, which subsequently occurred in January 2022. I took ivermectin as indicated in protocols

developed by doctors who had collectively and successfully treated thousands of patients overseas and in Australia. My illness was mild and lasted only five days.s22 [redacted],
I recovered very well.
The hysteria in the press about ivermectin as a 'horse-dewormer' did a great disservice to the public and possibly influenced the thinking of health professionals. Nobel prizes in medicine are not given for veterinary treatments. And as the TGA is aware from its own safety study, ivermectin is safer than many over-the-counter (OTC) products and is on the WHO list of essential medicines.
The effective banning of ivermectin in September 2021 was a huge shock
to me. I could not fathom that a government agency would deprive people of a safe and effective medicine. The 'rationale' published by the TGA at the time was unconvincing, devoid of evidence, and frankly embarrassing. The impact of the ban, I believe, led to a much-increased number of severe covid 19 infections, overwhelmed hospitals, and quite likely the unnecessary deaths of numerous Australians. Harmful lockdowns would not have been required had widespread early treatment with ivermectin (and other useful medicines and nutraceuticals) been supported by the TGA and public health officials. The advice to 'not treat' was unconscionable.
A 'vaccines are the only solution' approach was reductionist, poorly researched, coercive, and overlooked the wider holistic approaches on which many past public health successes were founded.
I support a Royal Commission into the handling of the pandemic, with terms of reference that include the actions of the TGA. The Commission should investigate the banning of GPs from prescribing ivermectin, and also the inadequate process for collecting adverse events. As a novel and rushed vaccine, there should have been a serious research program established to ensure thorough collection of adverse events data in Australia. Ongoing education should have been provided to doctors about the emerging range of adverse events, many not previously encountered in traditional vaccines, to enable informed responses and patient support.
The TGA's current reporting system is complex and time-consuming. There are widespread anecdotes of doctors commenting that they do not have time to enter reports, or even that they were unaware of this reporting system. Doctors also act as gatekeepers, making uninformed decisions about whether to report potential vaccine injuries, which contributes to under-reporting of adverse events.
The participation of the TGA in enabling vaccine coercion in this country has most likely contributed to a higher number of vaccine adverse events (including deaths) than would have occurred if ivermectin had remained available as a treatment option.
Issues such as those raised above are deserving of investigation.
Many countries and jurisdictions around the world have employed ivermectin against covid 19 and the number continues to grow. For example:
• Worldwide, over two billion people in multiple countries and

		jurisdictions are now covered by ivermectin: https://ivmstatus.com/ • In April 2022, Tennessee legislated to enable OTC purchase of ivermectin: https://www.einnews.com/pr_news/572339675/ivermectinnow-available-over-the-counter-from-pharmacists-in-tennessee • Twenty-eight US states have now legislated to promote ivermectin access: https://www.beckershospitalreview.com/pharmacy/28-stateshave- legislation-to-promote-ivermectin-access.html Hundreds of thousands of people, possibly millions, have benefitted from this treatment, and many are aware of unjustified attacks and bans on ivermectin, particularly in Western countries. As a medicines regulator that is globally admired, the TGA risks devaluing its well-earned reputation by continuing to make ivermectin unavailable to the majority of Australians. At least nine anti-viral drugs were provisionally approved over the period 2020-2022, some with less evidence than was available for ivermectin. Approval and purchase of these patented drugs transferred millions of taxpayer dollars to the pharmaceutical industry, while the banning of ivermectin - safe, effective, and cheap - disenfranchised GPs and harmed the public. Finally, covid 19 variants will likely emerge in future and 'updated' vaccines be developed in response. As vaccine development lags behind the ability of a respiratory virus to mutate, such vaccines could have low effectiveness. Ivermectin has demonstrated in vitro effectiveness against a range of covid variants (Delandre et al 2022: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9024598/) and its availability for prescription by GPs could provide a more nimble response to future outbreaks. Much damage has been done in Australia by policies that were, in hindsight, misguided. Erosion of trust in our health institutions, who are meant to put the interests of Australians first, is a regrettable outcome of many poor decisions made during the pandemic. The denial of ivermectin to the population is, in my opinion, one of the most serious. Divisions have arisen in the medical profession, and between doctors and their professional associations and regulators. But perhaps the worst outcome is that patients no longer can count on their GPs for effective early treatment against covid 19, or for informed consent. In conclusion, I fully support Dr Fidge's application to delete the appendix D, item 10 listing for ivermectin, which was inserted on 11 September 2021. I respectfully request that the TGA find a way to enable GPs to prescribe ivermectin as an antiviral drug.
s22 [redacted]	[redacted]	Ivermectin should NEVER have been removed by the TGA, because of its world-wide long-term use since 1998. As per the Spectator article 24.7.2021 https://spectator.com.au/2021/07/ivermectin-its-as-aussieas-vegemite/ (extract):

		"...The TGA says more robust clinical trials are needed yet officials in Mexico showed a quicker way to test ivermectin's efficacy and save lives in a pandemic. They organised a trial last year and distributed an ivermectin therapy to anyone who tested positive and wanted to take the drug between November and January. Of 200,000 people who tested positive, there was a 76 per cent reduction in hospitalisation in the 80,000 that used ivermectin. As for safety, 3.7 billion doses of ivermectin have been used since 1987 and in 30 years, only 20 deaths following its use have been reported to the UN's Vigi-Access database. Compare that to remdesivir, which has been given emergency use authorisation to treat Covid in Australian hospitals. In 12 months, there have been 551 deaths reported. Indeed, a study published in the prestigious Journal of the American Medical Association this week found remdesivir did not increase survival, just time spent in hospital. As for the Covid vaccines, in six months 8,589 deaths have been reported to the UN database and 1,490,915 adverse reactions. In Australia, the TGA has confirmed 83 cases of thrombosis with thrombocytopenia, 24 treated in ICU, 3 fatal, 31 reports of suspected immune thrombocytopenia, one fatal, 52 reports of Guillain-Barre syndrome, one death of a patient who died from multi-organ failure and had signs of capillary leak syndrome, 50 cases of suspected myocarditis/pericarditis, all linked to Covid vaccinations. In addition, there are another 373 deaths and almost 40,000 adverse reports that may later be linked to vaccination...." Notably the TGA 48-page "Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and joint ACCS/ACMS meetings November 2022", specifically pages 12-13 is highly misleading information with regards the TGA DAEN information on Ivermectin i.e. 32 case reports and 5 deaths. The TGA should have truthfully advised that the first ever DAEN case report on this drug was dated back in 1998. Hence in 24 years, only 32 case reports and sadly 5 deaths. Compare this to the global trial COVID-19 injectable products on the TGA DAEN with under 2 years of use and yet has caused outright massive harm to Australians with over 132,000 single suspected 'medicine' reports and 937 deaths (including 8 children aged under 18). This COVID-19 data does NOT include the under-reporting factor, as most cases can individually take up to 20 mins to enter on the complicated TGA DAEN website. Please refer to these links for real-time analysis and relevant studies involving Ivermectin for COVID-19 treatment: 1. https://c19early.com COVID-19 early treatment: real-time analysis of 2,158 studies Analysis of 47 COVID early treatments, approvals in 74 countries, database of 1,713 treatments (including Ivermectin) 2. https://c19ivermectin.com Invermectin for COVID-19 - 92 studies 979 scientists, 134,148 patients across 27 countries. Quote: "Statistically significant improvement for mortality, ventilation, IC, hospitalization, recovery, cases and viral

		clearance". Please note a study was published on https://c19ivermectin.com on "Sep 8" and has since been suspiciously or 'conveniently' removed from this website. However, in anticipation of the possible event of censorship, I screenprinted 2 images from this study (originally published on Sept 8) and sent it to a Cardiologist in Melbourne on Sept. 15, 2022. I have placed those 2 screenprint images into the attached PDF as EVIDENCE REMOVED about ivermectin treatment for COVID-19. Quote shown from this removed publication (as indicated in saved screenprint image: "Over 20 countries adopted ivermectin for COVID-19. The evidence base is much larger and has much lower conflict of interest than typically used to approve drugs." Please see 2 screenprint images in PDF attached to my submission. I completely support the amendment for the re-introduction i.e. registered for use approval of Ivermectin. One suggested improvement is for the TGA. In future, the TGA should not hastily withdraw an obviously successful product, without widespread open-debate and with transparency for an openconsultation process (with no conflicts of interest of $ factor influence). Please advise the outcome of this "Public Consultation". Thank you. Rgds, Sharon Cousins Independent Researcher & Writer
s22 [redacted]	[redacted]	Ivermectin should NEVER have been witheld from the public as a cure for covid. The TGAs lack of research on the safety and efficacy of Ivermectin for both prophylactic and therapeutic treatment of SARS-COV-2 has compromised the health outcomes of millions of Australians. The largest study available on the effectiveness of Ivermectin which since 1975 has been used by humans has proven that Ivermectin could have saved hundreds of Australians from SARS-COV-2. The Daily Sceptic Ivermectin Cuts Covid Mortality by 92%, Major Study Finds – Why is it Still Not Approved? BY WILL JONES 3 SEPTEMBER 2022 5:55 PM Ivermectin: Cheap Covid Treatment Shown to be Highly Effective in New Peer-Reviewed Study Regular use of ivermectin led to a 100% reduction in hospitalisation rate, a 92% reduction in mortality rate and an 86% reduction in the risk of dying from a COVID-19 infection when compared to non-users, a major new study has found. The study, published in the medical journal Cureus, analysed data from 223,128 people from the city of Itajaí in Brazil and is the largest study of its kind, giving its findings a high degree of certainty. Senior author Dr. Flavio A. Cadegiani wrote on Twitter: “An observational study with the size and level of analysis as ours is hardly achieved and infeasible to be conducted as a randomised clinical trial. Conclusions are hard to be refuted. Data is data, regardless of your beliefs.” The study compared those who took ivermectin regularly, irregularly and

		not at all prior to being infected with COVID-19 (i.e., as prophylaxis), and found a dose-dependent relationship, confirming that the difference in outcomes is very likely to be due to the drug and not other factors, such as differences between the groups. The authors used a technique called 'propensity score matching' to control for confounding factors that may otherwise have biased the study in one direction or another. For example, those taking ivermectin tended to be older than those not taking it (average age 47 years vs 40 years), but by matching people of similar age in each group and comparing outcomes this confounding factor was controlled for. Here is the abstract of the study, which summarises the methods and results. Background We have previously demonstrated that ivermectin used as prophylaxis for coronavirus disease 2019 (COVID-19), irrespective of the regularity, in a strictly controlled citywide program in Southern Brazil (Itajaí, Brazil), was associated with reductions in COVID-19 infection, hospitalisation, and mortality rates. In this study, our objective was to determine if the regular use of ivermectin impacted the level of protection from COVID-19 and related outcomes, reinforcing the efficacy of ivermectin through the demonstration of a dose-response effect. Methods This exploratory analysis of a prospective observational study involved a program that used ivermectin at a dose of 0.2 mg/kg/day for two consecutive days, every 15 days, for 150 days. Regularity definitions were as follows: regular users had 180 mg or more of ivermectin and irregular users had up to 60 mg, in total, throughout the program. Comparisons were made between non-users (subjects who did not use ivermectin), and regular and irregular users after multivariate adjustments. The full city database was used to calculate and compare COVID-19 infection and the risk of dying from COVID-19. The COVID-19 database was used and propensity score matching (PSM) was employed for hospitalisation and mortality rates. Results Among 223,128 subjects from the city of Itajaí, 159,560 were 18 years old or up and were not infected by COVID-19 until July 7th 2020, from which 45,716 (28.7%) did not use and 113,844 (71.3%) used ivermectin. Among ivermectin users, 33,971 (29.8%) used irregularly (up to 60 mg) and 8,325 (7.3%) used regularly (more than 180 mg). The remaining 71,548 participants were not included in the analysis. COVID-19 infection rate was 49% lower for regular users (3.40%) than non-users (6.64%) (risk rate (RR): 0.51; 95% CI: 0.45-0.58; $p < 0.0001$), and 25% lower than irregular users (4.54%) (RR: 0.75; 95% CI: 0.66-0.85; $p < 0.0001$). The infection rate was 32% lower for irregular users than non-users (RR: 0.68; 95% CI: 0.64-0.73; $p < 0.0001$). Among COVID-19 [infected] participants, regular users were older and had a higher prevalence of type 2 diabetes and hypertension than irregular and non-users. After PSM, the matched analysis contained 283 subjects in each group of non-users and regular users, [283] between regular users and irregular users, and 1,542 subjects between non-users

		and irregular users. The hospitalisation rate was reduced by 100% in regular users compared to both irregular users and non-users ($p < 0.0001$), and by 29% among irregular users compared to non-users (RR: 0.781; 95% CI: 0.49-1.05; $p = 0.099$). Mortality rate was 92% lower in regular users than non-users (RR: 0.08; 95% CI: 0.02-0.35; $p = 0.0008$) and 84% lower than irregular users (RR: 0.16; 95% CI: 0.04-0.71; $p = 0.016$), while irregular users had a 37% lower mortality rate reduction than non-users (RR: 0.67; 95% CI: 0.40-0.99; $p = 0.049$). Risk of dying from COVID-19 [once infected] was 86% lower among regular users than non-users (RR: 0.14; 95% CI: 0.03-0.57; $p = 0.006$), and 72% lower than irregular users (RR: 0.28; 95% CI: 0.07-1.18; $p = 0.083$), while irregular users had a 51% reduction compared to non-users (RR: 0.49; 95% CI: 0.32-0.76; $p = 0.001$). Conclusion Non-use of ivermectin was associated with a 12.5-fold increase in mortality rate and a seven-fold increased risk of dying from COVID-19 compared to the regular use of ivermectin. This dose-response efficacy reinforces the prophylactic effects of ivermectin against COVID-19. The authors draw particular attention to the dose-dependent relationship as confirming the efficacy of the treatment: The response pattern of ivermectin use and level of protection from COVID-19-related outcomes was identified and consistent across dose related levels. The reduction in COVID-19 infection rate occurred in a consistent and significant dose-dependent manner, with reductions of 49% and 32% in regular and irregular users, when compared to nonusers. The most striking evidence of ivermectin's effectiveness was the 100% reduction in mortality for female regular users. The data in the study come from official government databases and, according to the authors, "conclusively show that the risk of dying from COVID-19 was lower for all regular and irregular users of ivermectin, compared to non-users, considering the whole population". The study, while not a randomised controlled trial (RCT), used a "strictly controlled population with a great level of control for confounding factors" and was larger than would be feasible in an RCT. The authors highlight a "notable reduction in risk of death in the over 50- year-old population and those with comorbidities". They conclude that the evidence provided by the study is "among the strongest and most conclusive data regarding ivermectin efficacy". Many governments have suppressed the use of ivermectin to treat COVID-19, claiming there is a lack of evidence of efficacy. However, this purported lack of evidence often relies on poorly designed trials and biased conclusions. For example, a recent widely-reported RCT concluded the study "did not show adequate support for the effectiveness of this drug" – yet its own results showed statistically significant benefits for speed of recovery as well as large (though not, in that study, statistically significant) benefits for mechanical ventilation and death. Participants also were not given the treatment until over a week into having symptoms and the study may have been confounded by people in the placebo arm also taking the drug.

		One of the new study's authors and a seasoned proponent of repurposed treatments like ivermectin, Dr. Pierre Kory, made clear his thoughts on Twitter in April as he responded to an FDA tweet reminding the public that ivermectin is not approved: "Messaging BS with one corrupt study while ignoring 82 trials (33 RCTs) from 27 countries, 129K patients – sum showing massive benefits. Stop lying man, people are dying. #earlytreatmentworks." Social media companies have censored information about ivermectin, often considering any suggestion that it is an effective treatment for COVID-19 to be misinformation. Yet ivermectin is a cheap, safe drug that many studies have shown brings considerable benefit in treating and preventing COVID-19. The latest study impressively confirms this efficacy as a prophylactic, with a reduction in mortality of up to 92%. Shockingly, most governments still do not have a protocol for early treatment or prevention of COVID-19. The NHS says treatment is only available for those at high risk of serious disease who have a positive test and symptoms that are not getting better. Its guidance on self-care for people ill at home only recommends paracetamol and ibuprofen. Yet here is a highly controlled study of over 200,000 people that shows huge benefit – 92% reduction in mortality, 100% reduction in hospitalisation – for the prophylactic use of a cheap, widely available drug, and which confirms the results of multiple earlier studies. What are our governments waiting for? What more do they need to approve drugs that have been shown to save lives?

JAMA | Original Investigation

Effect of Ivermectin vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19
A Randomized Clinical Trial

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IMPORTANCE The effectiveness of ivermectin to shorten symptom duration or prevent hospitalization among outpatients in the US with mild to moderate symptomatic COVID-19 is unknown.

OBJECTIVE To evaluate the efficacy of ivermectin, 400 µg/kg, daily for 3 days compared with placebo for the treatment of early mild to moderate COVID-19.

DESIGN, SETTING, AND PARTICIPANTS ACTIV-6, an ongoing, decentralized, double-blind, randomized, placebo-controlled platform trial, was designed to evaluate repurposed therapies in outpatients with mild to moderate COVID-19. A total of 1591 participants aged 30 years and older with confirmed COVID-19, experiencing 2 or more symptoms of acute infection for 7 days or less, were enrolled from June 23, 2021, through February 4, 2022, with follow-up data through May 31, 2022, at 93 sites in the US.

INTERVENTIONS Participants were randomized to receive ivermectin, 400 µg/kg (n = 817), daily for 3 days or placebo (n = 774).

MAIN OUTCOMES AND MEASURES Time to sustained recovery, defined as at least 3 consecutive days without symptoms. There were 7 secondary outcomes, including a composite of hospitalization or death by day 28.

RESULTS Among 1800 participants who were randomized (mean [SD] age, 48 [12] years; 932 women [58.6%]; 753 [47.3%] reported receiving at least 2 doses of a SARS-CoV-2 vaccine), 1591 completed the trial. The hazard ratio (HR) for improvement in time to recovery was 1.07 (95% credible interval [CrI], 0.96-1.17; posterior *P* value [HR >1] = .91). The median time to recovery was 12 days (IQR, 11-13) in the ivermectin group and 13 days (IQR, 12-14) in the placebo group. There were 10 hospitalizations or deaths in the ivermectin group and 9 in the placebo group (1.2% vs 1.2%; HR, 1.1 [95% CrI, 0.4-2.6]). The most common serious adverse events were COVID-19 pneumonia (ivermectin [n = 5]; placebo [n = 7]) and venous thromboembolism (ivermectin [n = 1]; placebo [n = 5]).

CONCLUSIONS AND RELEVANCE Among outpatients with mild to moderate COVID-19, treatment with ivermectin, compared with placebo, did not significantly improve time to recovery. These findings do not support the use of ivermectin in patients with mild to moderate COVID-19.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04885530

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Visual Abstract

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV-6) Study Group and Investigators appear in Supplement 4.

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Despite advances in treatment of COVID-19, additional therapies are needed, particularly in the outpatient setting. Novel oral antivirals have been authorized for high-risk individuals in high-income countries[1,2]; however, efficacy of these drugs in vaccinated people is unclear and access globally is limited. For individuals in the US not considered at high risk, no COVID-19 therapy is currently recommended.

Numerous repurposed drugs have been investigated for COVID-19.[3-6] To date, the study of repurposed drugs has been largely in the inpatient setting for the treatment of severe COVID-19.[7-9] In the outpatient setting, repurposed drug studies have been challenged by small sample sizes, design limitations, and variable results, limiting the impact on clinical practice.

Ivermectin, an antiparasitic drug used worldwide for onchocerciasis and strongyloidiasis, emerged in 2020 as a potential repurposed drug for COVID-19 due to an in vitro study suggesting possible antiviral activity.[10] Numerous ivermectin studies have been completed across the spectrum of COVID-19 disease severity.[10] While early studies, particularly in the inpatient setting, suggested potential treatment effect, variability in dosing and overall study quality, followed by multiple article retractions, has resulted in controversy.[11-13] The largest randomized outpatient trial to date, TOGETHER, enrolled patients in Brazil with symptomatic mild to moderate COVID-19. No clinical benefit of ivermectin (400 µg/kg daily for 3 days) was observed for preventing disease progression.[14]

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV-6) is an ongoing, fully remote (decentralized), double-blind, randomized, placebo-controlled, platform trial investigating repurposed drugs for the treatment of mild to moderate COVID-19 in the outpatient setting. This article reports the effect of ivermectin, 400 µg/kg, daily for 3 days, compared with placebo, for the treatment of early mild to moderate COVID-19.

Key Points

Question Does ivermectin, 400 µg/kg, daily for 3 days, compared with placebo, shorten symptom duration among adult (≥30 years) outpatients in the US with symptomatic mild to moderate COVID-19?

Findings In this double-blinded, randomized, placebo-controlled platform trial conducted in the US during a period of Delta and Omicron variant predominance, and that included 1591 adult outpatients with COVID-19, the posterior probability of improvement in time to recovery in those treated with ivermectin vs placebo had a hazard ratio of 1.07, with a posterior probability of benefit of .91. This did not meet the prespecified threshold of posterior probability greater than .95.

Meaning These findings do not support the use of ivermectin in outpatients with mild to moderate COVID-19.

Methods

Trial Design and Oversight

This double-blind, randomized, placebo-controlled platform protocol was designed to be flexible, allowing for use in a wide range of settings within health care systems and the community. The platform protocol enrolls outpatients with mild to moderate COVID-19 with a confirmed positive polymerase chain reaction or antigen test result for SARS-CoV-2, including home-based testing. Each repurposed medication (study drug group) is further described including drug-specific exclusion criteria in each drug-specific appendix. The trial protocol and statistical analysis plan are available in Supplement 1 and Supplement 2, respectively.

A governing institutional review board for each site approved the protocol. Informed consent was obtained from each enrolled participant either via electronic consent or (in-person consent) written process. An independent data monitoring committee oversaw the monitoring of participant safety, efficacy, and trial conduct.

Participants

Recruitment into the platform trial opened on June 11, 2021, and is ongoing. Participants were enrolled in the ivermectin group or identical matched-placebo or contributing-placebo group from June 23, 2021, through February 4, 2022, at 93 sites in the US. The group was closed after meeting the prespecified accrual goal. Participants were either identified by sites or self-identified by contacting central study telephone hotline(s).

Sites verified eligibility criteria including age 30 years or older, confirmed SARS-CoV-2 infection within 10 days, and 2 or more symptoms of acute COVID-19 for 7 days or less from enrollment. Symptoms included fatigue, dyspnea, fever, cough, nausea, vomiting, diarrhea, body aches, chills, headache, sore throat, nasal symptoms, and loss of sense of taste or smell. Exclusion criteria included hospitalization, study drug use within 14 days, or known allergy or contraindication to study drug (Supplement 1). Vaccination was allowable, as were standard-of-care therapies for COVID-19.

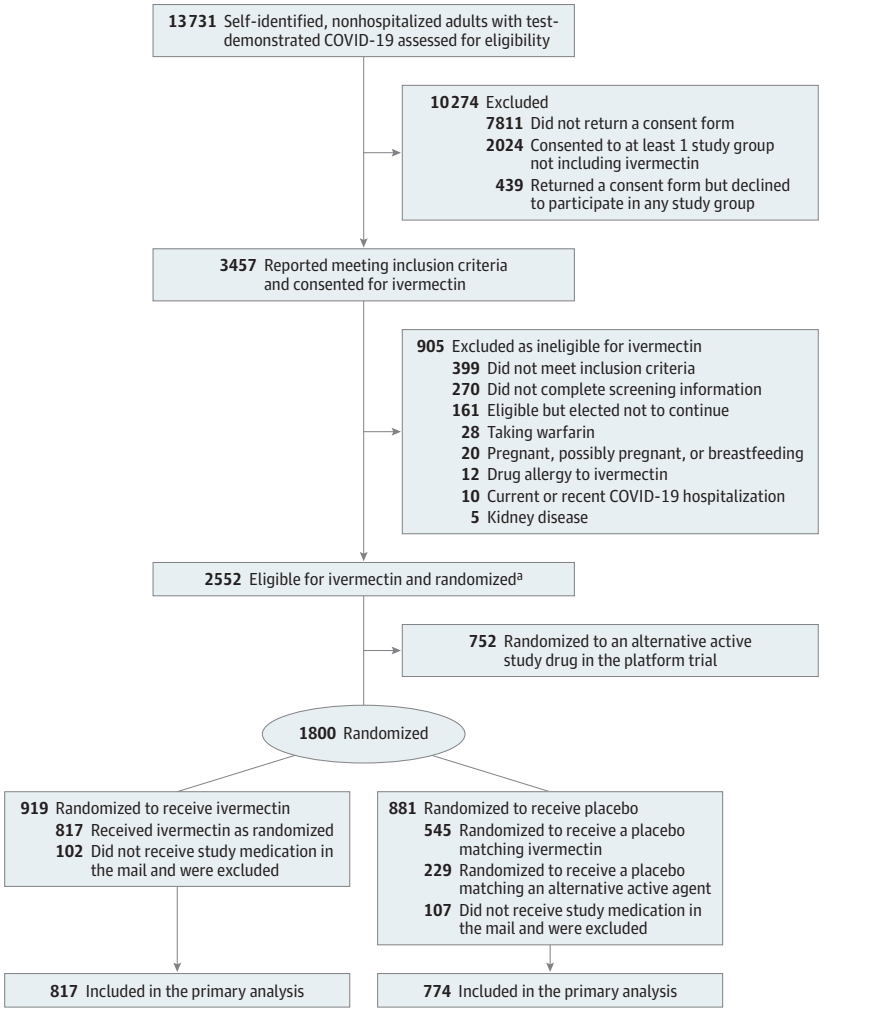
Randomization

Participants were randomized, using a random number generator, in a 2-step process (**Figure 1**). First, participants were randomized with equal probability among the study drugs actively enrolling for which participants were eligible. Participants could choose to opt out of specific study drugs if they or the site investigator did not feel there was equipoise. After randomization among study drugs, participants were randomized to active agent or placebo in a ratio of *m*:1 where *m* is the number of study drugs for which the participant was eligible. The more study groups a participant was eligible for, the greater the chance of receiving an active study drug. Participants eligible for the ivermectin study drug group and another group(s) but randomized to placebo for a different study drug were included and contributed to the placebo group for ivermectin.

Interventions

A central pharmacy supplied ivermectin or placebo to participants via direct home delivery. Ivermectin was supplied as a bottle of 15 7-mg tablets. Participants were instructed to take a prespecified number of tablets for 3 consecutive days based on their weight for a daily dose of approximately 400 µg/kg (Supplement 1). Packaging for matched placebo was identical to that of ivermectin. Packaging for other contributing placebo was identical to that of the associated study drug.

Figure 1. Flow Diagram of Participants in the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV-6) Trial



[a] In this platform trial with multiple study drugs, participants were able to choose to which agents they were willing to be randomized. Participants were first randomized 1:*m* between placebo and study drug, where *m* was the number of study groups for which the participant was eligible and consented to participate. Then, participants were randomized with 1/*m* probability among the study drugs for which they were eligible.

Outcome Measures

The primary measure of effectiveness was based on time to sustained recovery, defined as achieving at least 3 consecutive days without symptoms; this was selected a priori from among the 2 co-primary end points that remained available to other study drugs in the platform (Supplement 2). Time to sustained recovery was the number of days between receipt of study drug and the third of 3 consecutive days without symptoms. Participants who died, by definition, did not recover regardless of reported symptom freedom. Time to recovery was administratively censored at 28 days. Secondary outcomes included the composite of hospitalization or death by day 28; the difference in mean time spent unwell estimated from a longitudinal ordinal model; the COVID Clinical Progression Scale on days 7, 14, and 28; mortality through day 28; and hospitalization, urgent care visit, or emergency department visit through day 28. The final secondary outcome per the statistical analysis plan, PROMIS-29, is planned to be assessed through day 90. Due to the longer 90-day follow-up, it is not reported in this article.

Trial Procedures

The study was designed as a fully remote, or decentralized, trial. Screening and eligibility confirmation were participant reported and site confirmed. A positive SARS-CoV-2 polymerase chain reaction or antigen test result was verified prior to randomization. At screening, participant-reported demographic information was collected and included race and ethnicity, eligibility criteria, medical history, concomitant medications, symptom reporting, and quality of life questionnaires. Participant-reported race and ethnicity were collected due to the disparity in the burden of COVID-19 infection carried by marginalized communities based on race and ethnicity. Participants were asked about ethnicity separately from race and were able to select any combination of race designations, including the option to not report any designation. While demographic data remained participant-reported, screening and enrollment could occur in person at sites and unplanned study visits could occur in person or remotely, as deemed appropriate by site investigators.

A central investigational pharmacy distributed the study drug. Shipping and delivery were tracked. Participants must

have received the study drug to be included in the analysis; receipt of the study drug was defined as day 1 for this study.

Participants were asked to complete daily assessments and report adverse events via the study portal through day 14, then at other intervals through day 28, and at the final study visit at day 90. Assessments included symptoms and severity, health care visits, and medications. If participants were still reporting symptoms at day 14, they continued to be assessed until they experienced 3 consecutive days without symptoms or until day 28. At days 28 and 90, all participants completed assessments. Additional details are available in Supplement 1.

Statistical Analysis Plan

This ongoing platform trial was designed to be analyzed accepting the possibility of adding and dropping groups as the trial progresses. The general analytical approach was regression modeling. Proportional hazard regression was used for time-to-event analysis, and cumulative probability ordinal regression models were used for ordinal outcomes. In addition, mean time spent unwell was estimated using a longitudinal ordinal regression model as a quantification of benefit (Supplement 2).

The planned primary end point analysis was a bayesian proportional hazards model. The primary inferential (decision-making) quantity was the posterior distribution for the treatment assignment hazard ratio (HR), with HR >1 indicating benefit. If the posterior probability of benefit exceeded .95 at any of the interim or final analyses, the trial would conclude efficacy of the intervention. To preserve type I error less than .05, the prior for the treatment effect parameter (on the $\log_e$ relative hazard scale) was a normal distribution centered at 0 and scaled to an SD of 0.1. All other parameter priors were noninformative, using the software default of 2.5 times the ratio of the SD of the outcome divided by the SD of the predictor variable. The study design was estimated to have 80% power to detect an HR of 1.2 in the primary end point.

The primary end point model included the following predictor variables in addition to randomization assignment: age (as restricted cubic spline), sex, duration of symptoms prior to receipt of study drug, calendar time (as restricted cubic spline), vaccination status, geographic region (Northeast, Midwest, South, West), call center indicator, and baseline symptom severity. The proportional hazards assumption of the primary end point was evaluated by generating visual diagnostics such as the log-log plot and plots of time-dependent regression coefficients for each predictor in the model, a diagnostic that indicates deviations from proportionality if the time-dependent coefficients are not constant in time.

Secondary end points were analyzed with bayesian regression models (either proportional hazards or proportional odds). Noninformative priors were used for all parameters. Secondary end points were not used for formal decision-making, and no decision threshold was selected. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. The same set of covariates used in the primary end point model was used in the analysis of secondary end points, provided the end point accrued enough events to be analyzed with covariate adjustment.

To achieve this sample size in an ongoing platform trial, once 1200 participants had been randomized to the study group or to matching placebo and had received study drug, enrollment into the study group was halted. Some participants had already consented to participate but had not received study drug, and these participants continued in their assigned study group.

As a platform trial, the primary analysis is implemented separately for each study drug, where the placebo group consists of contemporaneously randomized participants who meet the eligibility criteria for that study drug; this includes both matched and contributing placebo. From other remote trials,[3,6] it was recognized that medication delivery (placebo or active study drug) may not always occur (eg, failure of delivery, participant withdrawal, or interval hospitalization). For this trial, the full analysis set for the primary analyses included all participants who received study drug and participants were analyzed as assigned. All available data were used to compare each active study drug vs placebo control, regardless of postrandomization adherence to study protocols. In both the primary and secondary end point analyses, missing data among covariates were addressed with conditional mean imputation because the amount of missing covariate data was small (<4%).

A prespecified analysis tested for differential treatment effects as a function of preexisting participant characteristics. Analysis of heterogeneity of treatment effect included age, number of days of symptoms, body mass index, day 1 symptom severity, calendar time (surrogate for SARS-CoV-2 variant), sex, and vaccination status; continuous variables were modeled as such without creating subgroups.

Analyses were performed with R version 4.1 with the following primary packages: rstanarm, rmsb, and survival.[15]

Results

Study Population

Of the 3457 participants who met inclusion criteria and consented to be evaluated for inclusion in the ivermectin group, 1591 were eligible for this study group; randomized to ivermectin, 400 µg/kg (n = 817), or placebo (n = 774); and received study drug (Figure 1). Of participants receiving placebo, 545 (70%) received matching placebo and 229 (30%) received placebo as part of a concurrent study group and contributed to the pooled placebo group.

The mean (SD) age of the participants was 48 (12) years, and 43% were aged 50 years or older (**Table 1**). The population was 59% female, 7% identified as Black/African American, 81% identified as White, and 10% reported being of Latino/Hispanic ethnicity. Although not required for enrollment, high-risk comorbidities were prevalent, including body mass index (calculated as weight in kilograms divided by height in meters squared) greater than 30 (41%), diabetes (11.5%), hypertension (26%), asthma (15%), and chronic obstructive pulmonary disease (4%). Overall, 47% of participants reported

Table 1. Baseline Characteristics

Variable	Group, No. (%)	
	Ivermectin	Placebo
No.	817	774
Age, median (IQR), y	47.0 (39.0-56.0)	48.0 (39.0-56.0)
<50 y	476 (58.3)	435 (56.2)
Sex		
Female	508 (62.2)	424 (54.8)
Male	309 (37.8)	349 (45.1)
Prefer not to answer	0	1 (0.1)
Race, not mutually exclusive[a]		
American Indian or Alaska Native	18 (2.2)	9 (1.2)
Asian	20 (2.5)	18 (2.3)
Black or African American	57 (7.0)	56 (7.2)
Middle Eastern or North African	31 (3.8)	23 (3.0)
Native Hawaiian or Other Pacific Islander	3 (0.37)	3 (0.39)
White	659 (80.7)	627 (81.0)
Ethnicity		
Hispanic/Latino	93 (11.4)	70 (9.0)
Not Hispanic/Latino	724 (88.6)	704 (91.0)
Region[b]		
Midwest	157 (19.2)	166 (21.5)
Northeast	85 (10.4)	68 (8.8)
South	475 (58.1)	455 (58.8)
West	100 (12.2)	85 (11.0)
Recruited via call center[c]	127 (15.5)	112 (14.5)
BMI, median (IQR)	28.3 (24.9-33.2)	28.3 (24.9-33.3)
>30	334/816 (40.9)	314 (40.6)
Weight, median (IQR), kg	81.6 (70.3-98.9)	83.9 (70.3-100.2)
No.	816	
Weight, >88 kg, No./total (%)	322/816 (39.5)	343/774 (44.3)
Medical history, No./total (%)[d]		
High blood pressure	212/804 (26.4)	203/756 (26.9)
Asthma	121/804 (15.1)	120/756 (15.9)
Smoked, past year	134/804 (16.7)	103/756 (13.6)
Diabetes	96/804 (12.0)	88/756 (11.6)
Heart disease	34/804 (4.2)	36/756 (4.8)
COPD	34/804 (4.2)	23/756 (3.0)
Malignant cancer	26 (3.2)	22 (2.8)
Chronic kidney disease	6/804 (0.75)	6/756 (0.79)
COVID-19 vaccine status		
Not vaccinated	420 (51.4)	394 (50.9)
Vaccinated, 1 dose	12 (1.5)	12 (1.6)
Vaccinated, ≥2 doses	385 (47.1)	368 (47.6)
Days between symptom onset and receipt of drug, median (IQR)	6 (5-8)	6 (4-7)
Symptom burden on study day 1		
None	55 (6.7)	54 (7.0)
Mild	490 (60.0)	434 (56.1)
Moderate	221 (27.1)	247 (31.9)
Severe	51 (6.2)	39 (5.0)
Remdesivir	2 (0.24)	2 (0.26)
Nirmatrelvir and ritonavir (Paxlovid)	1 (0.12)	1 (0.13)
Monoclonal antibodies	22 (2.7)	25 (3.2)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease.

[a] Participants may have selected any combination of the race descriptors, including prefer not to answer.

[b] The following state groups define each region: Northeast includes Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, and Pennsylvania; Midwest includes Indiana, Illinois, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota; South includes Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma, and Texas; and West includes Arizona, Colorado, Idaho, New Mexico, Montana, Utah, Neveda, Wyoming, Alaska, California, Hawaii, Oregon, and Washington.

[c] Alternatively, patients may have been recruited at local clinical sites.

[d] Medical history was provided by participants, responding to the prompts: "Has a doctor told you that you have any of the following?" and "Have you ever experienced any of the following (select all that apply)" and "Have you ever smoked tobacco products?"

Table 2. Primary and Secondary Outcomes

	Group, No. (%)		Adjusted estimate (95% CrI)[a]	Posterior *P* value (efficacy)
	Ivermectin	Placebo		
No.	817	774		
Primary end point, time to recovery[b]				
Skeptical prior (primary analysis)			HR, 1.07 (0.96 to 1.17)	.91
Noninformative prior (sensitivity analysis)			HR, 1.09 (0.97 to 1.22)	.93
No prior (sensitivity analysis)			HR, 1.09 (0.98 to 1.22)[c]	
Secondary end points				
Mortality at day 28	1 (0.12)	0		
Hospitalization or death through day 28	10 (1.22)	9 (1.16)	HR, 1.1 (0.4 to 2.6)[c,d]	NE[e]
Hospitalization, urgent care, ED visit, or death through day 28	32 (3.9)	28 (3.6)	HR, 1.2 (0.6 to 1.8)	.32
Clinical progression ordinal outcome scale[f]				
Day 7			OR, 0.81 (0.50 to 1.13)	.88
No.			1582	
Day 14			OR, 0.76 (0.39 to 1.13)	.89
No.			1570	
Day 28			OR, 1.11 (0.52 to 1.91)	.45
No.			1555	
Time unwell, mean (95% CrI), d	10.96 (10.78 to 11.15)	11.45 (11.28 to 11.60)	Δ, −0.49 (−0.82 to −0.15)	.99

Abbreviations: CrI, credible interval; ED, emergency department; HR, hazard ratio; NE, not estimated; OR, odds ratio.

[a] Unless otherwise noted, a highest-density credible interval. Adjustment variables for time to recovery, mortality, composite clinical end points, and clinical progression in addition to randomization assignment: age (as restricted cubic spline), sex, duration of symptoms prior to receipt of study drug, calendar time (as restricted cubic spline), vaccination status, geographic region (Northeast, Midwest, South, West), call center indicator, and baseline symptom severity.

[b] The mean time unwell is estimated from receipt of study drug to achieving sustained recovery. For direct comparison to studies that use the first day of recovery, 2 days should be subtracted from these estimates. Adjustment variables for mean time unwell in addition to randomization assignment: age and calendar time. HR >1.0 is favorable for faster recovery for ivermectin compared with placebo.

[c] Confidence interval.

[d] Low event rate precluded covariate adjustment.

[e] Due to the low event rate, a posterior probability was not estimated.

[f] The description of the 8 levels of the clinical progression ordinal outcome scale is reported in the eMethods in Supplement 3. Proportional odds were not evaluated because most participants were either at home with limitations or at home without limitations, resulting in a model that is approximately a logistic regression. For the clinical progression ordinal outcome scale, an OR <1.0 is favorable for less progression for ivermectin compared with placebo.

receiving at least 2 doses of a COVID-19 vaccine. The median time from symptom onset to receipt of study drug was 6 days (IQR, 4-8). Baseline symptom prevalence and severity are described in eTable 1 in Supplement 3. Receipt of therapies available under US Food and Drug Administration approval or authorization was uncommon (remdesivir, 0.3%; monoclonal antibody, 3%; ritonavir-boosted nirmatrelvir, 0.1%).

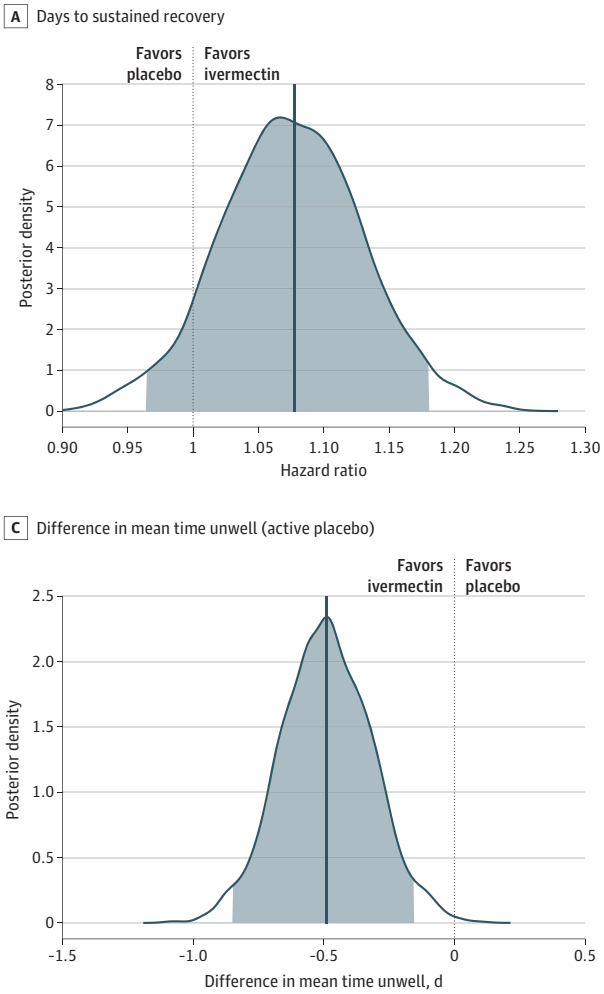
Primary Outcome

In the full analysis population, the posterior probability of benefit on the primary outcome of time to recovery between the ivermectin and placebo groups was .91 (hazard ratio [HR], 1.07 [95% credible interval [CrI], 0.96-1.17) where an HR >1 is for faster symptom resolution in the active drug group (**Table 2**, **Figure 2**A). The median time to recovery was 12 days (IQR, 11-13) in the ivermectin group and 13 days (IQR, 12-14) in the placebo group. This posterior probability of the primary outcome was below the prespecified threshold of .95 (Supplement 2). Diagnostics did not indicate a violation of the proportional hazard assumption. Because the rate of enrollment was so rapid, it was not possible to complete the interim analyses. The analyses of the primary end point unadjusted for interim looks at the data resulted in similar point and interval estimates (noninformative prior, no prior) (Table 2). The unadjusted Kaplan-Meier analysis was consistent with the model-based inference (**Figure 3**).

Secondary Outcomes

Hospitalization or death were uncommon, occurring in 1.2% (10/817) in the ivermectin group and 1.2% (9/774) in the placebo group (HR, 1.1 [95% CrI, 0.4-2.6], where an HR >1 favors placebo); there was 1 death in the ivermectin group (Table 2; eFigure 1A in Supplement 3). The composite secondary outcome of urgent or emergency care visits, hospitalizations, or death was similar for ivermectin (3.9% [32/817]) compared with placebo (3.6% [28/774]) (HR, 1.2 [95% CrI, 0.6-1.8], where an HR >1 favors placebo) (Table 2, Figure 2B; eFigure 1B in Supplement 3). For the ordinal outcome at day 14, the difference in the amount of time spent feeling unwell with COVID-19 was estimated to be 0.49 days (95% CrI, 0.15-0.82 days) in favor of ivermectin. The posterior probability that this benefit exceeds 1 day was less than 0.01 (Figure 2C). The posterior probability of any benefit observed with the COVID Clinical Progression Scale at days 7, 14, and 28 was .88, .89, and .45, respectively (Table 2; eFigure 2 in Supplement 3). Because most participants were home (the lowest 2 levels of the scale), the model was approximately a logistic regression and questions of proportionality were moot.

Figure 2. Posterior Distributions of Effects for (A) Time to Sustained Recovery (1257 Observed Events); (B) Hospitalization, Urgent Care Visits, Emergency Department Visits, or Death (60 Observed Events); and (C) Mean Time Unwell



Thick vertical lines denote the estimated mean of the posterior distribution. Density is the relative likelihood of posterior probability distribution. Outcomes with higher density are more likely than outcomes with lower density.

Heterogeneity of Treatment Effect Analyses

Tests for heterogeneity of treatment effect showed no overall influence of the putative subgrouping variables on treatment effects. The overall effect of symptom severity at day 1 was not significant (P = .12) and all subgroup analyses across symptom severity were neither controlled nor adjusted for multiple comparisons (eFigure 3 in Supplement 3). There was no evidence of a different treatment effect with ivermectin compared with placebo for timing of symptom onset to receipt of study drug, body mass index, calendar time, or vaccination status.

Adverse Events

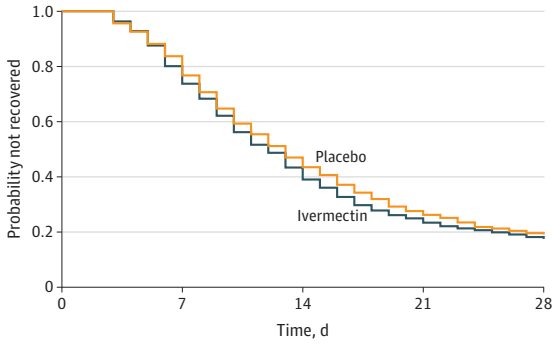
Adverse events were uncommon and similar in both groups (2.8% with ivermectin; 3.5% with placebo). All but 1 recorded event occurred in participants who confirmed taking their study drug; 1 participant who reported not taking the study drug experienced acute kidney injury. Ivermectin at 400 µg/kg was without additional serious adverse events compared with placebo (ivermectin [n = 10]; placebo [n = 9]) (eTable 2 in Supplement 3).

Discussion

Among outpatients with mild to moderate COVID-19, treatment with ivermectin, 400 µg/kg, daily for 3 days, compared with placebo, did not significantly improve time to recovery in this large trial that enrolled more than 1500 participants in the US. A lack of treatment effect was also seen for secondary clinical outcomes including hospitalization, death, or acute care visits. These findings do not support the use of ivermectin in patients with mild to moderate COVID-19.

Although there are numerous published studies reporting on the potential efficacy of ivermectin for the treatment of COVID-19, many are in the inpatient setting and the majority

Figure 3. Kaplan-Meier Curve for Primary Outcome of Time to Recovery



No. at risk

Ivermectin	817	641	339	192	138
Placebo	774	637	348	201	138

Recovery occurs on the third of 3 consecutive days without symptoms. Sixty-six participants were censored for nonresponse, and all others were followed up until recovery, death, or the end of short-term 28-day follow-up.

are small, variable in population and dosing, and some have been retracted.[11-13] In the outpatient setting, larger well-designed trials such as the current trial are emerging and do not support a clinical benefit of ivermectin when used at a dose of 400 µg/kg daily for 3 days.[14] Thus, this study adds to the growing evidence that there is not a clinically relevant treatment effect of ivermectin at this dose and duration.

This study has several strengths. This was a double-blind, randomized, placebo-controlled national study with enrolling sites in 28 states and a call center able to recruit participants from the remainder of the US. This ivermectin group of the platform trial enrolled rapidly due to the Delta and Omicron variant surges and included both vaccinated and unvaccinated patients, thus representing a highly relevant study population.

Limitations

This study has several limitations. First, the low mortality and hospitalization rates observed preclude drawing strict inferences on whether there are statistical differences in clinical event rates without much larger trials. Second, while the inclusion criteria allow for a broad study population, this study failed to achieve the level of representation desired for underrepresented populations in terms of racial and ethnic diversity. Third, ivermectin was dosed by weight to achieve a goal dose of 400 µg/kg, but the maximum dose of ivermectin provided by the study was 35 mg. While almost 42% of participants had a weight of more than 88 kg and thus did not achieve the goal dose, more than 75% of participants had a weight of less than 100 kg and so received at least 90% of the target dose. Fourth, due to the remote nature of the trial and constraints related to timing of randomization, the median time from start of symptoms to receipt of study drug was 6 days, which is later in the disease course than recent antiviral trials.[1,2] However, there was no evidence of a differential treatment effect based on the median time of symptom onset to receipt of study drug.

Conclusions

Among outpatients with mild to moderate COVID-19, treatment with ivermectin, compared with placebo, did not significantly improve time to recovery. These findings do not support the use of ivermectin in patients with mild to moderate COVID-19.

ARTICLE INFORMATION

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Author Contributions: Drs Naggie and Hernandez had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Naggie, Boulware, Lindsell, Stewart, Gentile, Collins, McCarthy, Thicklin, Felker, Ginde, Gabriel, Dunsmore, Adam, Wilson, Hernandez.
Acquisition, analysis, or interpretation of data: Naggie, Boulware, Lindsell, Stewart, Gentile, Jayaweera, Castro, Sulkowski, McTigue, Felker, Bramante, Slandzicki, Shah, Lenert, Dunsmore, DeLong, Hanna, Remaly, Wilder, Shenkman, Hernandez.
Drafting of the manuscript: Naggie, Boulware, Lindsell, Stewart, Collins, Thicklin, Gabriel, Wilson.
Critical revision of the manuscript for important intellectual content: Lindsell, Stewart, Gentile, McCarthy, Jayaweera, Castro, Sulkowski, McTigue, Felker, Ginde, Bramante, Slandzicki, Shah, Lenert, Dunsmore, Adam, DeLong, Hanna, Remaly, Wilder, Shenkman, Hernandez.
Statistical analysis: Lindsell, Stewart.
Obtained funding: Naggie, Adam, Hernandez.
Administrative, technical, or material support: Naggie, Boulware, Lindsell, Collins, Jayaweera, McTigue, Felker, Slandzicki, Gabriel, Lenert, Dunsmore, Adam, DeLong, Hanna, Remaly, Wilder, Wilson, Hernandez.
Supervision: Naggie, Lindsell, McCarthy, Jayaweera, Castro, Sulkowski, McTigue, Felker, Gabriel, Shah, Lenert, Hernandez.
Other - clinical protocol development and protocol oversight: Gentile.
Other - project management: Dunsmore.

Conflict of Interest Disclosures: Dr Naggie reported receiving grants from the National Institutes of Health (NIH) during the conduct of the study and grants from Gilead Sciences and AbbVie; personal fees from Pardes Biosciences, Personal

Health Insights Inc, and Bristol Myers Squibb/PRA Health Services; and stock options from Vir Biotechnology as well as providing unpaid consultation to Silverback Therapeutics outside the submitted work. Dr Boulware reported receiving grants from the NIH during the conduct of the study. Dr Lindsell reported receiving grants from the National Center for Advancing Translational Sciences (NCATS) during the conduct of the study and grants from the NIH, Centers for Disease Control and Prevention, and Department of Defense to his institution and contracts to his institution for research services from Endpoint Health, bioMerieux, Entegrion Inc, AbbVie, and AstraZeneca outside the submitted work. In addition, Dr Lindsell had a patent for risk stratification in sepsis and septic shock issued to Cincinnati Children's Hospital Medical Center. Dr Stewart reported receiving grants from the NIH NCATS during the conduct of the study and grants from the NIH outside the submitted work. Dr Gentile reported receiving personal fees from Duke University during the conduct of the study and grants from the NIH outside the submitted work. Dr Collins reported receiving personal fees from Vir Biotechnology during the conduct of the study. Dr Jayaweera reported receiving grants from NCATS during the conduct of the study and grants from Gilead, Pfizer, Janssen, and ViiV and serving as a consultant for Theratechnologies outside the submitted work. Dr Castro reported receiving grants from the NIH, American Lung Association, Patient-Centered Outcomes Research Institute, AstraZeneca, GlaxoSmithKline, Novartis, Pulmatrix, Sanofi, and Shionogi and personal fees from Genentech, Teva, Sanofi, Merck, Novartis, Arrowhead, OM Pharma, Allakos, Amgen, AstraZeneca, GlaxoSmithKline, Regeneron, and Elsevier outside the submitted work. Dr Sulkowski reported receiving personal fees from AbbVie, Gilead, GlaxoSmithKline, Atea Pharmaceuticals, Antios Therapeutics, Precision BioSciences, Viiv, and Virion and grants from Janssen to Johns Hopkins University outside the submitted work. Dr McTigue reported receiving grants to her institution from the NIH during the conduct of the study and research contracts to her institution from Pfizer and Janssen outside the submitted work. Dr Felker reported receiving grants from the NIH during the conduct of the study and grants from Novartis outside the submitted work. Dr Ginde reported receiving grants from the NIH during the conduct of the study and grants from the NIH, Centers for Disease Control and Prevention, Department of Defense, AbbVie (investigator-initiated), and Faron Pharmaceuticals (investigator-initiated) outside the submitted work. Dr Adam reported receiving funding from the US government (funding through Operation Warp Speed) during the conduct of the study. Dr DeLong reported receiving grants from NCATS during the conduct of the study. Dr Hanna reported receiving grants from the US Biomedical Advanced Research and Development Authority during the conduct of the study and personal fees from Merck & Co and AbPro outside the submitted work. Dr Remaly reported receiving grants from NCATS during the conduct of the study. Dr Wilder reported receiving grants from NCATS during the conduct of the study. Dr Wilson reported receiving grants from NCATS during the conduct of the study. Dr Hernandez reported receiving grants from American Regent, Amgen, Boehringer Ingelheim, Merck, Verily, Somologic, and Pfizer, and personal fees from AstraZeneca, Boston Scientific, Bristol Myers Squibb, Cytokinetics, and Merck outside the submitted work. No other disclosures were reported.

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Role of the Funder/Sponsor: NCATS participated in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV-6) Study Group and Investigators are listed in Supplement 4.

Data Sharing Statement: See Supplement 5

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Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Record of the 40th meeting of the Advisory Committee on Medicines Scheduling

16 November 2022

TRIM Reference no. D22-6160803

TGA Health Safety Regulation

Contents

1 Preliminary matters

1.1 Opening of the meeting

The 40th meeting of the Advisory Committee on Medicines Scheduling (the **Committee**) was held at the Department of Health and Aged Care's Fairbairn (ACT) office and via video conference on 16 November 2022.

The meeting was chaired by s22 [redacted], who opened the meeting at 10:03 am (AEDT) and welcomed attending members and observers.

Members were informed that the discussions and recommendations of the Committee are confidential until the interim decisions are published.

1.2 Attendance

A quorum was present for all decisions. Those present at the meeting were:

Committee members

Name	Representation
s22 [redacted]	Ministerial appointment
	Ministerial appointment
	Ministerial appointment
	Ministerial appointment
	Ministerial appointment
	Ministerial appointment
	Ministerial appointment
	Commonwealth
	NSW
	VIC
	QLD
	WA
	TAS
	ACT
	NT

Guest speakers

Name	Participation
s22 [redacted]	

Committee Secretariat (Commonwealth Department of Health and Aged Care)

s22 [redacted]	

Observers

Name	Items
Commonwealth Department of Health and Aged Care (Therapeutic Goods Administration)	
s22 [redacted]	All All All All All All
ACT	
s22 [redacted]	All
Pain Australia	
s22 [redacted]	s22 [redacted]

Apologies

s22 [redacted]

1.3 Conflict of interest

Conflicts of interest declared prior to the meeting by s22 [redacted] and s22 [redacted] were discussed.

s22 [redacted]

s22 [redacted]

[redacted]

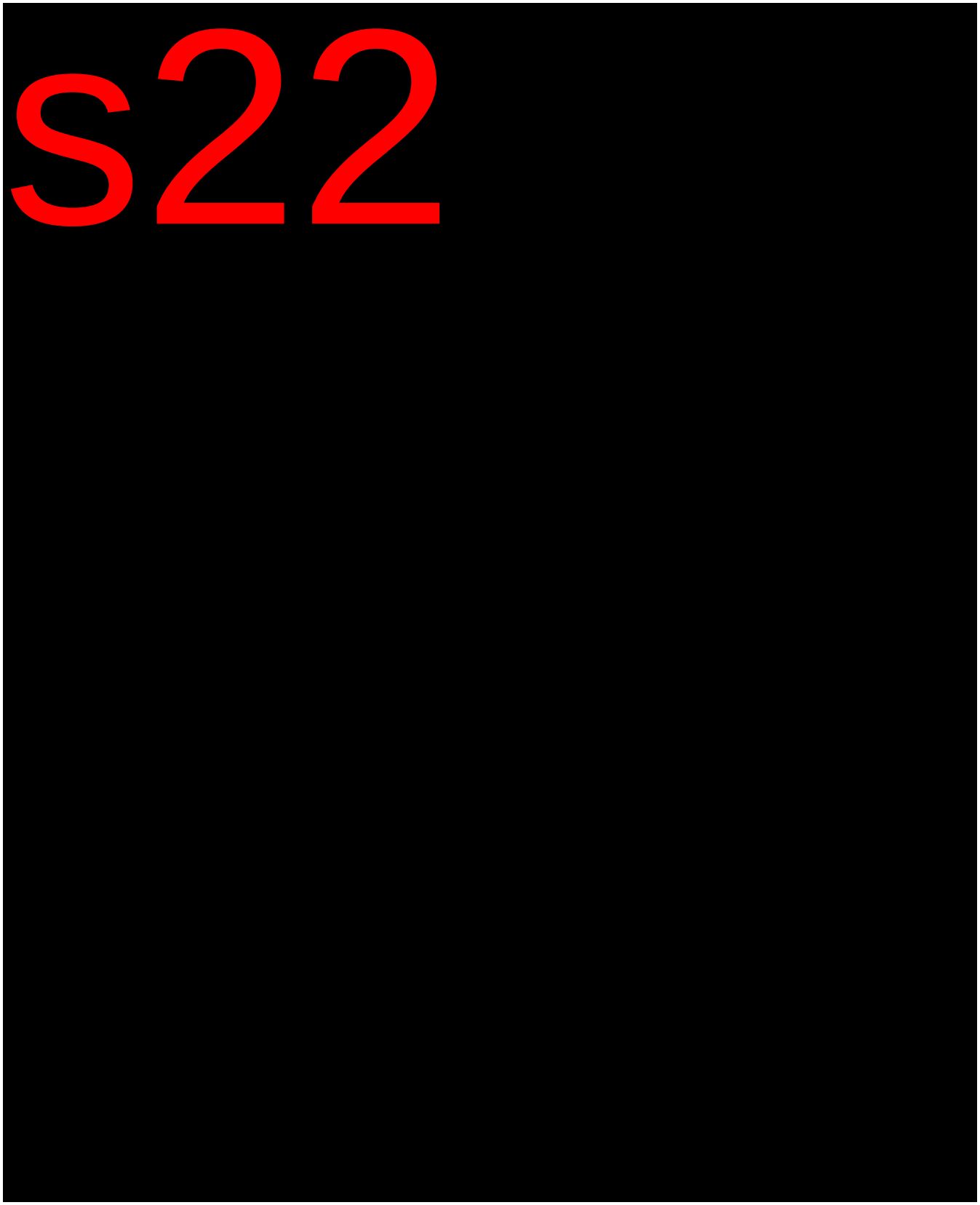
1.4 Procedural matters

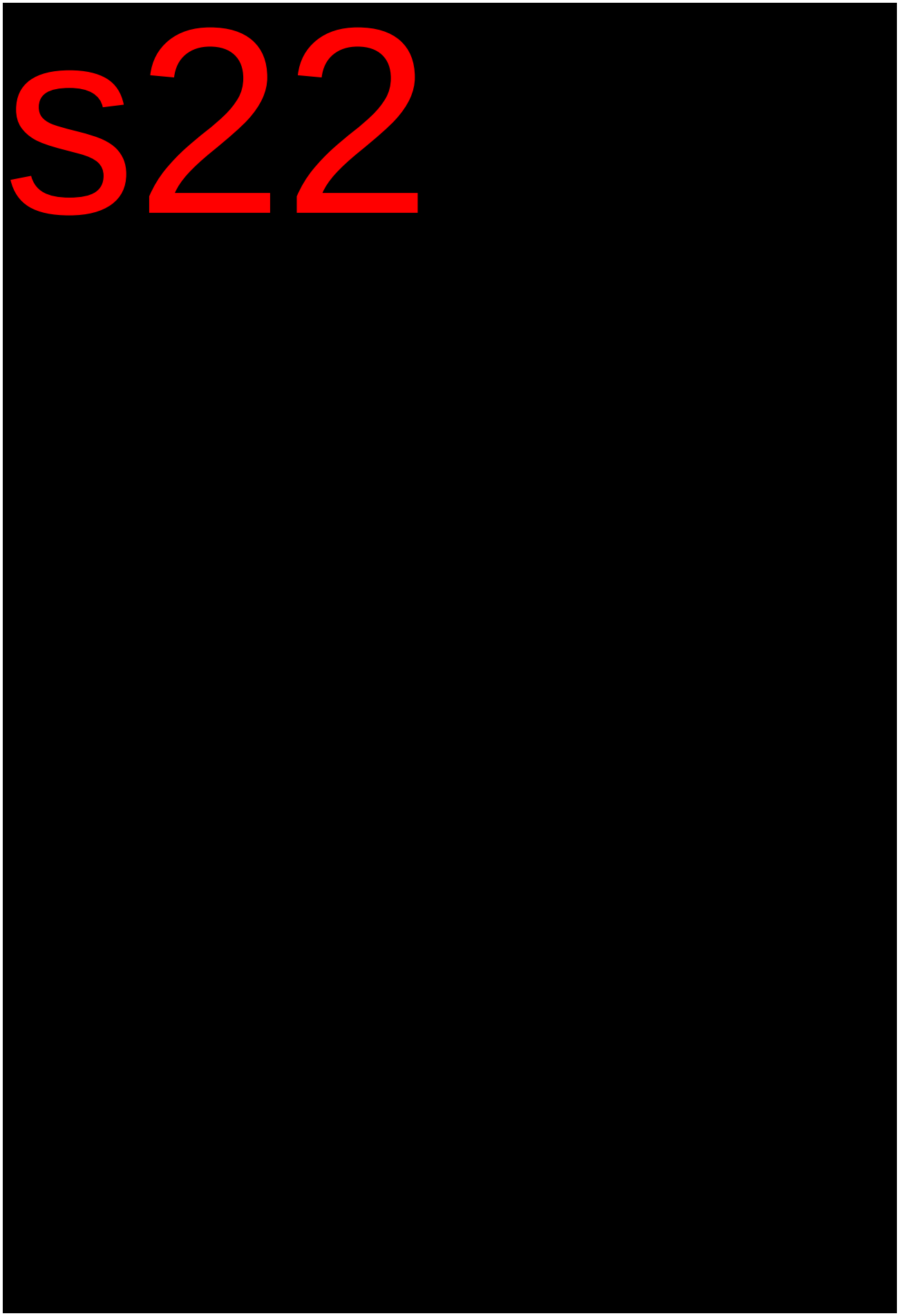
Members were informed of various housekeeping rules to ensure the smooth running of the meeting via videoconference.

All present were reminded of confidentiality in relation to all matters discussed by the Committee and that all decisions are to remain confidential until they are published along with

the interim decision of the delegate[1] of the Secretary of the Department of Health and Aged Care responsible for medicines scheduling (the **Delegate**).

2 Discussion Item

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2.2 Ivermectin

Advice for the Delegate's consideration

The Committee recommended that no change be made to the scheduling of ivermectin in the Poisons Standard.

Committee discussion

- The Committee considered the proposal that the Poisons Standard be amended to delete the Appendix D entry relating to ivermectin. This would remove the restriction on the prescribing of ivermectin for unapproved indications to medical specialists in nominated fields.
- There was unanimous agreement that there is currently a lack of safety data to support both the long-term and frequent use of ivermectin for unapproved indications. The regimens suggested for its use in relation to COVID-19 differ to the approved use for parasitic infections. Studies in relation to COVID-19 used variable dosing, often under different conditions (including as part of combination treatments). It was noted that one US based study using two doses of 200 µg/kg appeared to be safe, although there was no clinical benefit demonstrated.
- Members raised concerns that there is limited additional evidence of efficacy available from clinical studies from when the Committee last considered the scheduling of ivermectin, despite studies purporting to demonstrate efficacy (and, according to the applicant's proposal, supporting removal of the Appendix D entry). The clinical data available are from studies that are small (some neither controlled, nor peer-reviewed) and with various outcomes and endpoints. In addition, a large proportion of studies are conducted in countries with dissimilar standards of medical care compared to Australia.
- In October 2022, JAMA[5] published results of the ongoing ACTIV-6 trial into the effectiveness of ivermectin in treating mild to moderate COVID-19. The investigation detailed a randomised, double-blind, placebo-controlled study of 1800 participants. The study found that ivermectin did not significantly improve recovery time compared with placebo after 3 days of treatment and does not support use of ivermectin in patients with mild to moderate COVID-19.

[5] Effect of Ivermectin vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19: A Randomized Clinical Trial - PubMed (nih.gov)

- The Committee noted that the most recent Cochrane Review[6] still does not support the use of ivermectin for treating COVID-19 or preventing SARS-CoV-2 infection. However, noting that the evidence base has improved slightly but is still limited:
    - "For outpatients, there is currently low- to high-certainty evidence that ivermectin has no beneficial effect for people with COVID-19. Based on the very low-certainty evidence for inpatients, we are still uncertain whether ivermectin prevents death or clinical worsening or increases serious adverse events, while there is low-certainty evidence that it has no beneficial effect regarding clinical improvement, viral clearance and adverse events. No evidence is available on ivermectin to prevent SARS-CoV-2 infection. In this update, certainty of evidence increased through higher quality trials including more participants. According to this review's living approach, we will continually update our search".
- A Committee member noted that the National Covid Evidence Taskforce (NCET) does not recommend the use of ivermectin for the treatment of COVID-19 and this view was supported by the Pharmaceutical Society of Australia in their public submission.
- Members disagreed with the applicant's reasoning that the use of ivermectin is comparable to using provisionally registered antivirals. The reasons included that provisionally registered medicines must comply with a range of post-market conditions, including rolling submission of further data, follow up studies, a risk management plan (RMP) and are subject to the black triangle scheme—allowing the TGA to suspend or cancel products if safety concerns are identified.
- The Committee noted that, as per the considerations for amending Appendix D in the *Scheduling policy framework for medicines and chemicals* (SPF),[7] ivermectin poses a specific health risk that may be mitigated by restricting availability through specialist medical practitioners, and therefore the entry in Appendix D for ivermectin should be retained.
- The Committee discussed the opposition of leading peak bodies to the removal of the Appendix D entry as proposed by the applicant. The Society of Hospital Pharmacists of Australia (SHPA) stated that the evidence base for ivermectin remains poor. Further, the treatment of parasitic infections should not be impeded by these restrictions and that there are no restrictions on other TGA-approved treatments for the treatment and prevention for COVID-19. The NSW Poisons Information Centre (NSW PIC) are still receiving a number of calls regarding exposure to ivermectin since the scheduling restrictions were put in place, of which 17 calls were relating to veterinary products, further demonstrating the continued demand from consumers for the inappropriate use of ivermectin.
- In summary, as the Committee had identified insufficient new evidence for efficacy and safety to support the use of ivermectin for the prevention or treatment of COVID-19, it was agreed that its advice was not to remove the existing Appendix D entry for ivermectin.

The reasons for the advice

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included (a) the risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

[6] Ivermectin for preventing and treating COVID-19 | Cochrane

[7] Scheduling Policy Framework for Medicines and Chemicals (tga.gov.au)

The Committee's reasons were:

a) the risks and benefits of the use of a substance

Risks:

- Safety of higher doses used for prevention and treatment of COVID-19 is not well established.
- Evidence base for use in COVID-19 is not well established, in particular a lack of safety data to support use and for prolonged use.

Benefits:

- Established benefits for treatment of parasitic and helminth infections.
- Benefit in relation to COVID-19 unlikely: No current recommendation for the use of ivermectin in COVID-19, due to a lack of evidence.

b) the purposes for which a substance is to be used and the extent of use of a substance

- Ivermectin is a broad spectrum anti-parasitic agent.
- Registered indications include onchocerciasis, strongyloidiasis, crusted scabies in conjunction with topical therapy; human sarcoptic scabies when prior topical treatment has failed or is contraindicated.
- It is also used for rosacea (papulopustular), other intestinal nematode infections, cutaneous larva migrans and lymphatic filariasis.
- Not approved or recommended for prevention or treatment of COVID-19.

c) the toxicity of a substance

- When used in high doses for the prevention or treatment of COVID-19, can result in severe adverse events such as severe skin reactions accompanied by fever, chills and aching muscles, severe blisters and bleeding in the lips, eyes, mouth, nose and genitals, worsening asthma and swelling of the face, legs, ankles and feet.
- Common adverse events include diarrhoea, nausea, dizziness and somnolence.

d) the dosage, formulation, labelling, packaging and presentation of a substance

- Available in Australia as an oral dose form – Stromectol 3 mg tablets.
- Also available as a topical formulation.

e) the potential for abuse of a substance

- Nil.

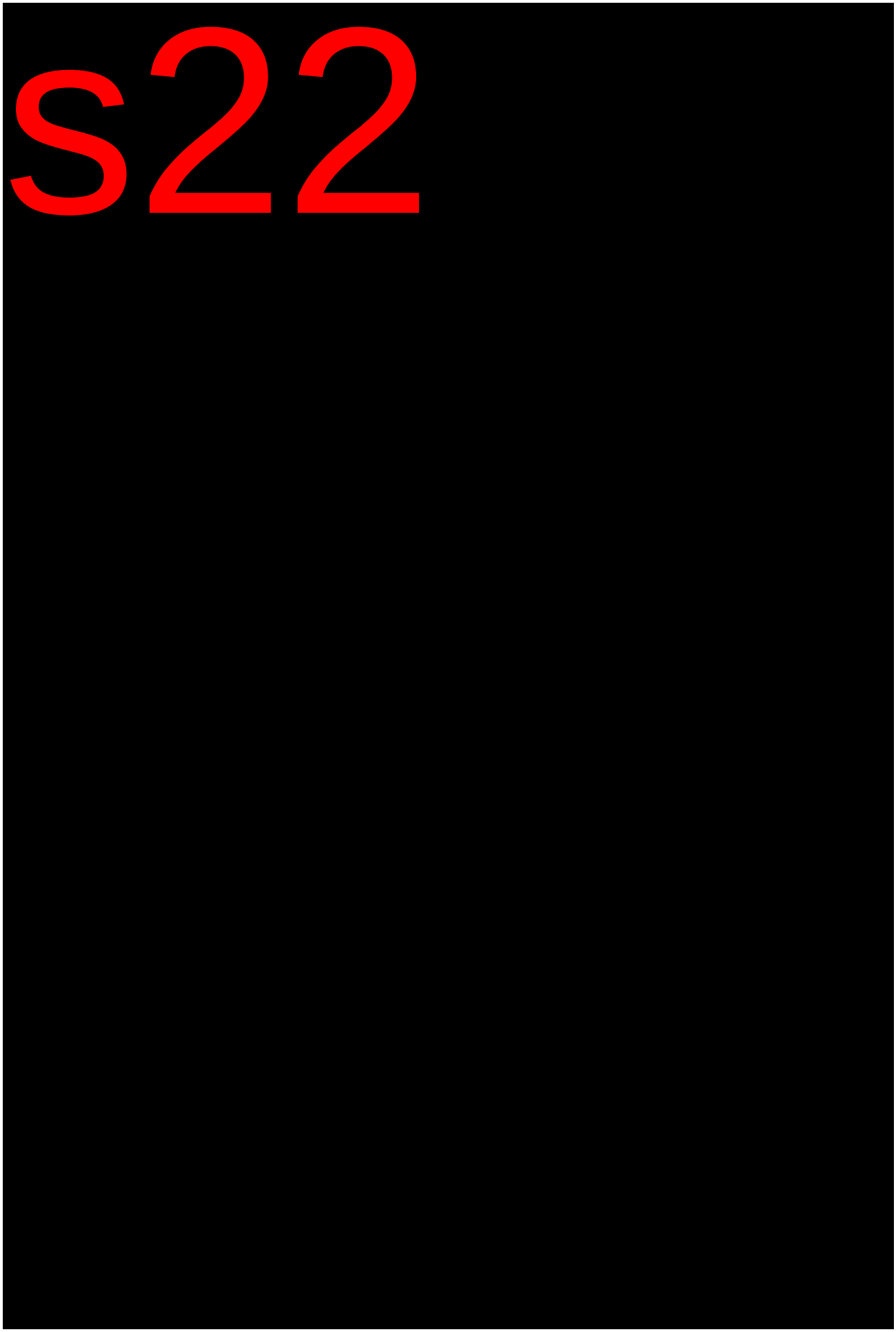
f) any other matters that the Secretary considers necessary to protect public health

- Appendix D entry is consistent with current recommendations for clinical indications and COVID-19.
- If removed from Appendix D there is potential to lead to shortages.
- A change in the current entry may lead to patients not seeking (or delay in seeking) appropriate medical treatment if infected with COVID-19.

– Allowing appropriate supplies for approved conditions.


s22


s22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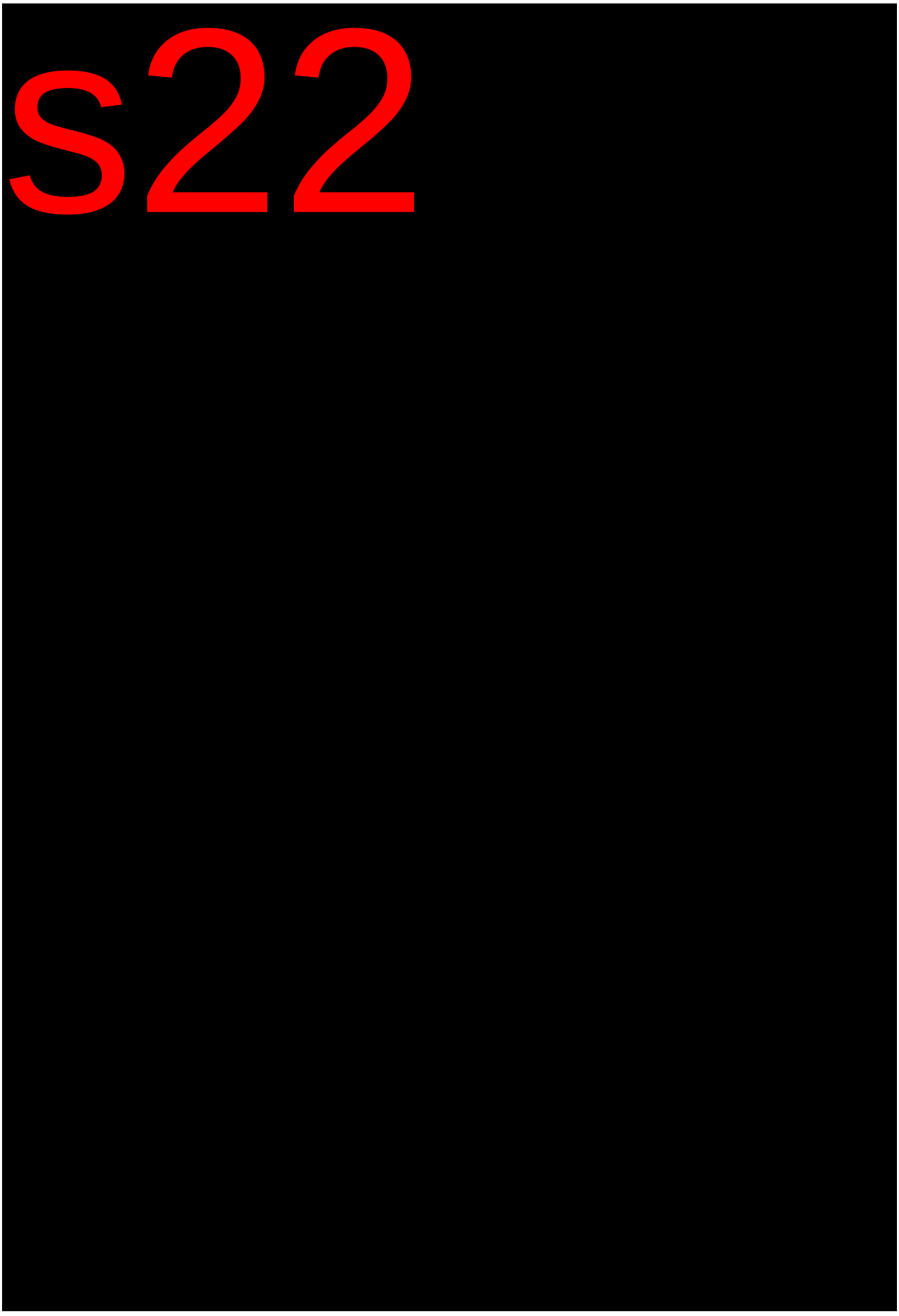
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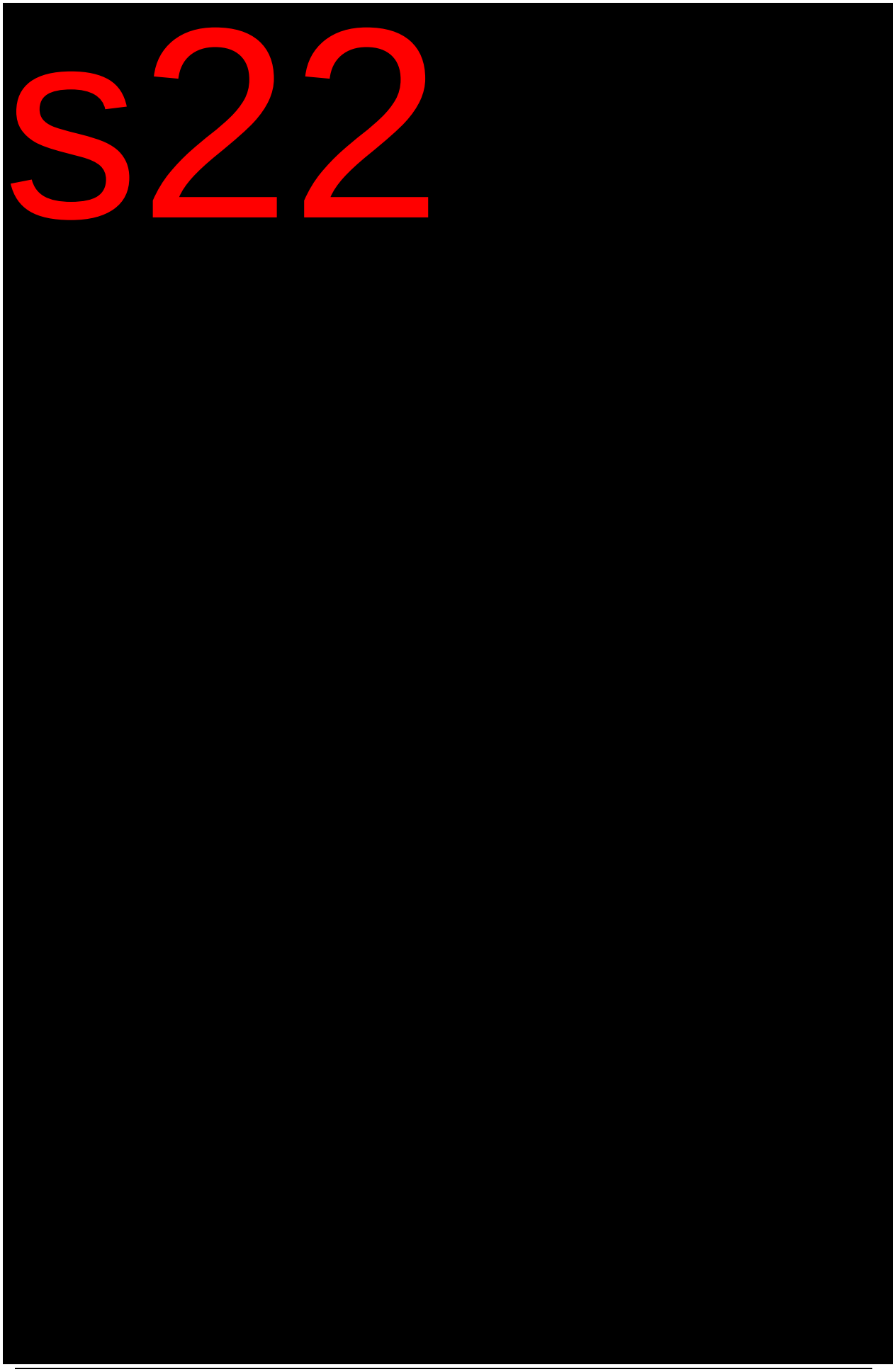
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3 Next meeting

The members noted that the next meeting of the Committee is scheduled for 14-16 March 2023.

4 Closure

The Chair closed the meeting at 5:30 pm, 16 November 2022.

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s22 Date XX January 2023

Chair

40th meeting of the Advisory Committee on Medicines Scheduling

Australian Government
Department of Health and Aged Care

COVID-19 vaccination – vaccination data – 24 March 2023

This data file contains statistical data about Australia's COVID-19 vaccinations.

Scroll down to access downloads and media.

Downloads

COVID-19 vaccination – vaccination data – 24 March 2023

Download Excel - 2.68 MB - 2 pages

We aim to provide documents in an accessible format. If you're having problems using a document with your accessibility tools, please contact us for help.

Publication date:
24 March 2023

Publication type:
Dataset

Audience:
General public

Language:
English

Part of a collection:

COVID-19 vaccination – vaccination data

Tags:

Immunisation | COVID-19 | COVID-19 vaccines

Document 7

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

(https://tga.gov.au/)

Database of Adverse Event Notifications (DAEN) - medicines

Back to tga.gov.au (https://tga.gov.au)

Inclusion in DAEN - medicines does not mean that the adverse event has been confirmed or that it was caused by a medicine or vaccine. +

Document 7

Search the DAEN - medicines

Reset

Date range

From 02/06/2019 To 31/03/2023

Search medicines - (2) Medicines selected

(Search by trade name/s or an active ingredient/s. Select one or multiple medicines from the list below to include in your search.)

ivermectin

- [x] Select all
- [x] Stromectol (active ingredients: ivermectin)
- [x] Trade name not specified (active ingredients: ivermectin)

Search summary counter

Reports (cases)	Single suspected medicine	Reported deaths
9	5	1

Medicine summary - (35 rows)

Hover over the table to view exporting data and other options. Click on the dots to see more options.

MedDRA system organ class	MedDRA reaction term	Number of cases	Cases with a single suspected medicine	Cases where death was a reported outcome
Hepatobiliary disorders	Hepatic failure	2	0	0
Respiratory, thoracic and mediastinal disorders	Dyspnoea	2	2	0
Cardiac disorders	Arrhythmia	1	0	1
Cardiac disorders	Cardiac arrest	1	0	1
Congenital, familial and genetic disorders	Genetic polymorphism	1	1	0
Eye disorders	Blindness	1	0	0

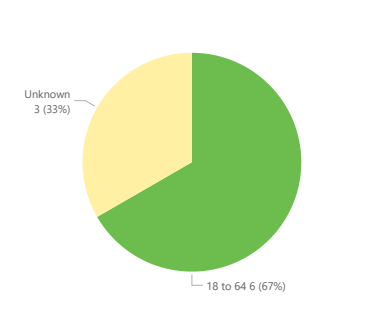
List of reports - (9 rows)

Hover over the table to view exporting data and other options. Click on the dots to see more options.

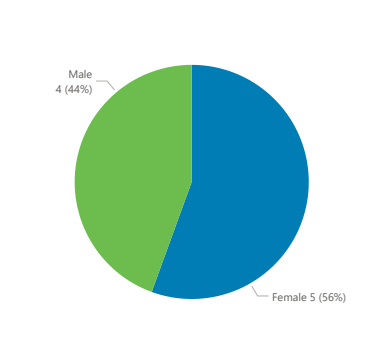
Case number	Report entry date	Age (years)	Gender	Medicines reported as being taken	MedDRA reaction terms
					• Fibromyalgia • Hepatic failure • Muscle spasms • Strongyloides test positive • Vision blurred
467833	11/06/2019	51	Female	• Stromectol (ivermectin) - Suspected • Trade name not specified (albendazole) - Suspected	• Blood zinc decreased • Fall • Fatigue • Hepatic failure • Immobile • Myalgia • Pain • Paralysis • Visual impairment

Data visual representation

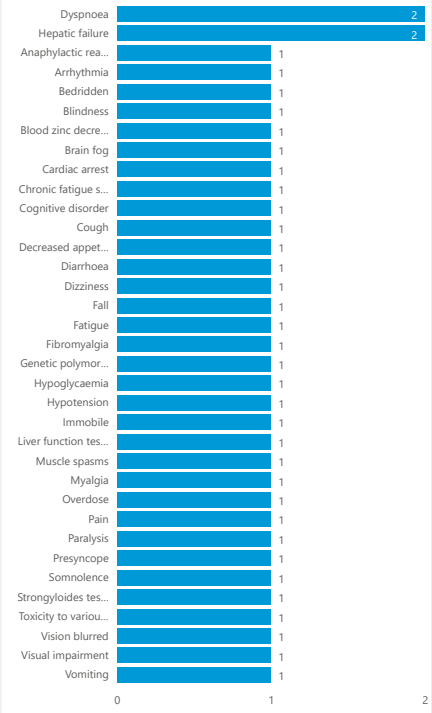
Age



Gender



MedDRA reaction terms (top 25 view only)



Data visual representation

Tables and graphs | Graphs

Advanced search options

MedDRA system organ class

(All selected)

Search
- [ ] Select all
- [ ] Cardiac disorders
- [ ] Congenital, familial and genetic disorders
- [ ] Eye disorders
- [ ] Gastrointestinal disorders
- [ ] General disorders and administration site

MedDRA reactions

(All selected)

Search
- [ ] Select all
- [ ] Anaphylactic reaction
- [ ] Arrhythmia
- [ ] Bedridden
- [ ] Blindness
- [ ] Blood zinc decreased

Age (years)

- [ ] Select all
- [ ] 18 to 64
- [ ] Unknown

Gender

- [ ] Select all
- [ ] Female
- [ ] Male

The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

MedDRA system organ class	MedDRA reaction term	Number of cases	Cases with a single suspected medicine	Cases where death was a reported outcome
Hepatobiliary disorders	Hepatic failure	2	0	0
Respiratory, thoracic and mediastinal disorders	Dyspnoea	2	2	0
Cardiac disorders	Arrhythmia	1	0	1
Cardiac disorders	Cardiac arrest	1	0	1
Congenital, familial and genetic disorders	Genetic polymorphism	1	1	0
Eye disorders	Blindness	1	0	0
Eye disorders	Vision blurred	1	0	0
Eye disorders	Visual impairment	1	0	0
Gastrointestinal disorders	Diarrhoea	1	1	0
Gastrointestinal disorders	Vomiting	1	1	0
General disorders and administration site conditions	Chronic fatigue syndrome	1	0	0
General disorders and administration site conditions	Fatigue	1	0	0
General disorders and administration site conditions	Pain	1	0	0
Immune system disorders	Anaphylactic reaction	1	0	0
Injury, poisoning and procedural complications	Fall	1	0	0
Injury, poisoning and procedural complications	Overdose	1	1	0
Injury, poisoning and procedural complications	Toxicity to various agents	1	1	0
Investigations	Blood zinc decreased	1	0	0
Investigations	Liver function test abnormal	1	1	0
Investigations	Strongyloides test positive	1	0	0
Metabolism and nutrition disorders	Decreased appetite	1	1	0
Metabolism and nutrition disorders	Hypoglycaemia	1	1	0
Musculoskeletal and connective tissue disorders	Fibromyalgia	1	0	0
Musculoskeletal and connective tissue disorders	Muscle spasms	1	0	0
Musculoskeletal and connective tissue disorders	Myalgia	1	0	0
Nervous system disorders	Brain fog	1	0	0
Nervous system disorders	Cognitive disorder	1	0	0
Nervous system disorders	Dizziness	1	1	0
Nervous system disorders	Paralysis	1	0	0
Nervous system disorders	Presyncope	1	1	0
Nervous system disorders	Somnolence	1	1	0
Respiratory, thoracic and mediastinal disorders	Cough	1	1	0
Social circumstances	Bedridden	1	0	0
Social circumstances	Immobile	1	0	0
Vascular disorders	Hypotension	1	1	0

Applied filters:Tradename and Active Ingredient contains 'ivermectin'Date is on or after 2/06/2019 and is before 1/04/2023

Ivermectin

Drug Info

Last Updated: February 11, 2021

Ivermectin is a Food and Drug Administration (FDA)-approved antiparasitic drug that is used to treat several neglected tropical diseases, including onchocerciasis, helminthiases, and scabies.[1] It is also being evaluated for its potential to reduce the rate of malaria transmission by killing mosquitoes that feed on treated humans and livestock.[2] For these indications, ivermectin has been widely used and is generally well tolerated.[1,3] Ivermectin is not approved by the FDA for the treatment of any viral infection.

Proposed Mechanism of Action and Rationale for Use in Patients With COVID-19

Reports from in vitro studies suggest that ivermectin acts by inhibiting the host importin alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process that viruses hijack to enhance infection by suppressing the host's antiviral response.[4,5] In addition, ivermectin docking may interfere with the attachment of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein to the human cell membrane.[6] Ivermectin is thought to be a host-directed agent, which may be the basis for its broad-spectrum activity in vitro against the viruses that cause dengue, Zika, HIV, and yellow fever.[4,7-9] Despite this in vitro activity, no clinical trials have reported a clinical benefit for ivermectin in patients with these viruses. Some studies of ivermectin have also reported potential anti-inflammatory properties, which have been postulated to be beneficial in people with COVID-19.[10-12]

Some observational cohorts and clinical trials have evaluated the use of ivermectin for the prevention and treatment of COVID-19. Data from some of these studies can be found in Table 2d.

Recommendation

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19.

Rationale

Ivermectin has been shown to inhibit the replication of SARS-CoV-2 in cell cultures.[13] However, pharmacokinetic and pharmacodynamic studies suggest that achieving the plasma concentrations necessary for the antiviral efficacy detected in vitro would require administration of doses up to 100-fold higher than those approved for use in humans.[14,15] Even though ivermectin appears to accumulate in the lung tissue, predicted systemic plasma and lung tissue concentrations are much lower than 2 μM, the half-maximal inhibitory concentration (IC_{50}) against SARS-CoV-2 in vitro.[16-19] Subcutaneous

administration of ivermectin 400 µg/kg had no effect on SARS-CoV-2 viral loads in hamsters. However, there was a reduction in olfactory deficit (measured using a food-finding test) and a reduction in the interleukin (IL)-6:IL-10 ratio in lung tissues.[20]

Since the last revision of this section of the Guidelines, the results of several randomized trials and retrospective cohort studies of ivermectin use in patients with COVID-19 have been published in peer-reviewed journals or have been made available as manuscripts ahead of peer review. Some clinical studies showed no benefits or worsening of disease after ivermectin use,[21-24] whereas others reported shorter time to resolution of disease manifestations that were attributed to COVID-19,[25-27] greater reduction in inflammatory marker levels,[26] shorter time to viral clearance,[21] or lower mortality rates in patients who received ivermectin than in patients who received comparator drugs or placebo.[21,27]

However, most of these studies had incomplete information and significant methodological limitations, which make it difficult to exclude common causes of bias. These limitations include:

- The sample size of most of the trials was small.
- Various doses and schedules of ivermectin were used.
- Some of the randomized controlled trials were open-label studies in which neither the participants nor the investigators were blinded to the treatment arms.
- Patients received various concomitant medications (e.g., doxycycline, hydroxychloroquine, azithromycin, zinc, corticosteroids) in addition to ivermectin or the comparator drug. This confounded the assessment of the efficacy or safety of ivermectin.
- The severity of COVID-19 in the study participants was not always well described.
- The study outcome measures were not always clearly defined.

Table 2d includes summaries of key studies. Because most of these studies have significant limitations, the Panel cannot draw definitive conclusions on the clinical efficacy of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide further guidance on the role of ivermectin in the treatment of COVID-19.

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Ivermectin is generally well tolerated. Adverse effects may include dizziness, pruritis, nausea, or diarrhea.
- Neurological adverse effects have been reported with the use of ivermectin for the treatment of onchocerciasis and other parasitic diseases, but it is not clear whether these adverse effects were caused by ivermectin or the underlying conditions.[28]
- Ivermectin is a minor cytochrome P 3A4 substrate and a p-glycoprotein substrate.
- Ivermectin is generally given on an empty stomach with water; however, administering ivermectin with food increases its bioavailability.
- The FDA issued a warning in April 2020 that ivermectin intended for use in animals **should not be used** to treat COVID-19 in humans.
- Please see Table 2d for additional information.

Considerations in Pregnancy

In animal studies, ivermectin was shown to be teratogenic when given in doses that were maternotoxic. These results raise concerns about administering ivermectin to people who are in the early stages of pregnancy (prior to 10 weeks gestation).[29] A 2020 systematic review and meta-analysis reviewed the incidence of poor maternal and fetal outcomes after ivermectin was used for its antiparasitic properties during pregnancy. However, the study was unable to establish a causal relationship between ivermectin use and poor maternal or fetal outcomes due to the quality of evidence. There are numerous reports of

inadvertent ivermectin use in early pregnancy without apparent adverse effects.[30-32] Therefore, there is insufficient evidence to establish the safety of using ivermectin in pregnant people, especially those in the later stages of pregnancy.

One study reported that the ivermectin concentrations secreted in breastmilk after a single oral dose were relatively low. No studies have evaluated the ivermectin concentrations in breastmilk in patients who received multiple doses.

Considerations in Children

Ivermectin is used in children weighing >15 kg for the treatment of helminthic infections, pediculosis, and scabies. The safety of using ivermectin in children weighing <15 kg has not been well established. Ivermectin is generally well tolerated in children, with a side effect profile similar to the one seen in adults. Currently, there are no available pediatric data from clinical trials to inform the use of ivermectin for the treatment or prevention of COVID-19 in children.

Clinical Trials

Several clinical trials that are evaluating the use of ivermectin for the treatment of COVID-19 are currently underway or in development. Please see ClinicalTrials.gov for the latest information.

References +

https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ivermectin/ accessed 9 Jan 22