The Rational Use of Ivermectin in COVID-19:
A Physician's Justification to the Medical Licensing Board

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To the Medical Licensing Board,

Greetings, members of the Board. Thank you for considering this issue.

I appreciate your devoting your time to serving the public on this Board, especially during the challenging era of this pandemic.

I'm a physician licensed by the Board for 32 years, and certified by both the American Board of Family Medicine and the American Board of Integrative Medicine. In my primary care outpatient practice, I'm applying all the evidence-based safe and effective means available to help my patients survive COVID-19. I'm vaccinating every willing patient and facilitating monoclonal antibody therapy when indicated. Until very recently, I was also offering ivermectin as early treatment to reduce the chance of dying from this disease.

I approach the Board now because the recent American Medical Association statement against ivermectin is impeding my use of it, wrongly so, based on reliable evidence for ivermectin's efficacy and safety. I need my licensing Board to recognize that offering this treatment for COVID-19 is reasonable medical practice, so I can use it to help my patients without risk of disciplinary action by the Board. My primary concern is that my patients receive the best evidence-based care available.

The crux of deciding to use any medicine involves weighing the probability of benefit against risk of harm. Let's focus first on the facts of evidence on ivermectin and clinical judgment in applying that evidence.

Evidence for Efficacy in Preventing Death

32 randomized controlled trials (RCTs) of ivermectin in COVID-19 have been reported. Of all the outcomes in these studies, the most clinically important is death from all causes. The best sources for this evidence are peer-reviewed published systematic reviews and meta-analyses of RCTs. Bryant (1) and Popp (2) reviewed all trials reported through May this year. Both applied Cochrane best-practice Risk-of-Bias Tool to assess trial reliability and GRADE approach to judging certainty of evidence.

First we consider Bryant. Initially Bryant included 10 RCTs, but then one was removed because its validity has been challenged. So Bryant meta-analyzed nine RCTs with 2038 participants observing the effect of ivermectin on COVID fatality. Meta-analysis demonstrates ivermectin reduces death overall by 49% with the 95% confidence interval (CI) being 27-95%. Meta-analysis of these RCTs also indicates 70% less death when ivermectin is started early in the infection and less effect when started later.

Some of these trials have weaknesses. There are small trials, thus the importance of meta-analysis. A majority were not blinded, thus the importance of death as an outcome resistant to observer bias. And some compared ivermectin to agents now understood as ineffective. But these weaknesses do not make the trials invalid. In fact, one of the trials having pristine design (double-blinded, placebo-controlled, randomized controlled trial) demonstrated that early treatment with ivermectin reduced death by 82% (CI 45 – 94%). (3) Taking the RCTs' strengths and weaknesses into account in applying the Cochrane process of analysis, Bryant concludes, **"moderate-certainty evidence finds that large reductions in COVID-19 deaths are possible using ivermectin."**

It's helpful to compare Bryant to Popp, because Popp chooses to exclude data from numerous trials in a way similar to other groups who conclude that the evidence for ivermectin is not sufficient. Popp chooses to exclude five trials comparing ivermectin to other drugs, despite those drugs now being understood as having trivial effect. And Popp chooses to exclude trials reporting mortality at any time other than their pre-defined 28 days, although death from COVID comes while the patient is under intense care and so is not likely to be missed. This leaves Popp only two trials to meta-analyze. They are weighted toward late treatment and have only 185 participants combined. They showed 40% less death, but with a wide confidence interval due to low numbers. Popp's concluding uncertainty about ivermectin's reducing death is the consequence of Popp choosing to exclude most of the RCT data *a priori*.

The difference between Bryant's and Popp's conclusions about whether the evidence for ivermectin is sufficient results from the difference in their judgment about whether certain trials provide reliable information. Specifically, judging whether trials with other agents as placebo and trials reporting death at various times are reliable enough to support use of ivermectin in COVID decides whether the evidence is sufficient.

Rational judgment on whether to include or exclude these trials in meta-analysis does not depend on infectious disease expertise. It depends on the clinical impact of ivermectin: on the value of its benefit and on its safety. High value benefit – like saving life - justifies a degree of uncertainty, especially if the drug is safe, because then the patient stands only to benefit.

Evidence for Safety

The safety of ivermectin has been well established through billions of doses used globally over decades. (4, 5). COVID is treated with dosing at 0.2-0.4 mg/kg/day. Systematic review and meta-analysis of six trials with this dosing revealed no adverse effect. (6) Bryant's meta-analysis of 11 trials using ivermectin in COVID documents no significant difference in adverse events. (1) Thus **there is no expectation of harm from treating COVID-19 with prescribed ivermectin, and substantial evidence of its safety.**

Physician's Clinical Judgment

As a physician, I'm obligated to use my best informed judgment to act in my patient's best interest. Faced with a patient at risk of dying from COVID-19, I consider whether the likelihood of benefit from ivermectin outweighs risk of harm. As there's no risk of harm, the question becomes "what is the probability of benefit." Here judgment about the reliability of RCT evidence for ivermectin's efficacy becomes key. I agree with Bryant that it's reasonable to consider evidence from trials with ineffective comparators, and trials reporting death at times other than 28 days. I judge that these trials are providing evidence reliable enough to support using a potentially life-saving treatment given that it's also harmless. So I conclude that **our best evidence indicates with moderate certainty that early treatment with ivermectin safely reduces risk of death 49**

- 70%. Thus I serve my patient best by offering a prescription for ivermectin, in addition to every other evidence-based treatment available.

Additional Evidence for Efficacy

In addition to RCTs demonstrating large reduction in death, there's an abundance of other evidence supporting ivermectin's effectiveness in COVID-19. (7) Pre-clinical studies have elucidated mechanisms of action that impair viral replication and dampen the excess inflammation that leads to death. RCTs have demonstrated accelerated viral clearance. (5) RCTs show ivermectin prevents infection in exposed persons by 87%. (1) Population interventions in India, Honduras, Argentina, Mexico, Brazil, Peru, and Paraguay have shown ivermectin reducing mortality compared to neighboring regions not using it. All this evidence contributes to certainty that ivermectin is effective medicine for COVID.

Timeline of Official Statements on Ivermectin

With the strength of evidence for the efficacy and safety of ivermectin in COVID-19, how have we come to the point of physicians needing to justify its use to their licensing Boards? To understand, we must consider the financial and political dimension of ivermectin in this pandemic. Reviewing its timeline provides perspective.

Here context is important. Billions of dollars to be made globally for years to come on novel COVID therapies depend on the absence of an effective alternative. And the career work of some infectious disease specialists involves funding by drug companies focused on new drug development. This situation may foster even unintentional bias against inexpensive re-purposed drugs like ivermectin. Such bias may influence judgment about the reliability of trials and sufficiency of evidence.

In reviewing this timeline, I'm not making any assertions about any person nor any group; I'm only observing events and raising reasonable questions regarding the possibility that bias for novel treatment has influenced them.

In July 2020, a group of intensive care doctors in Florida reported an 83% reduction in COVID death associated with ivermectin. Reviewing this report in August 2020, the National Institutes of Health (NIH) said RCTs were needed, taking the position that the drug should not be used outside of trials, despite acknowledging ivermectin's "excellent safety profile." (8)

By January 2021, the NIH had funded 32 trials on novel treatments, but only four on old drugs, and none on ivermectin. (9) Meanwhile 22 RCTs of ivermectin had been conducted on every continent except North America, including six RCTs showing large mortality benefits. Despite that evidence, and an additional 40 ongoing trials, the Infectious Disease Society of America (IDSA) website on COVID-19 treatment had no mention of ivermectin, not even as a therapy under investigation. (10) This pattern of inattention to ivermectin as a potential treatment among US infectious disease leadership raises the question of bias for novel treatment and against ivermectin.

In January 2021, two meta-analyses using Cochrane process on six RCTs with 1255 patients demonstrated with moderate certainty that ivermectin reduces COVID death by 75% (CI 48-88%). (5, 11) These systematic reviews also found no harm from ivermectin in the 22 trials then reported.

In February 2021, the United States was in the midst of its worst COVID surge, with over 3,000 people dying daily and widespread hospital overwhelm. Upon its review of the trials, the NIH changed its position on ivermectin to being "not for nor against its use", due to significant but "insufficient" evidence of benefit. (12)

This was based on their analysis judging those RCTs as not reliable enough to support recommending its use. The IDSA made a similar analysis, but further recommended ivermectin not be used outside of trials, in consideration of "highly uncertain benefits and known putative harms." (13) The discordance between evidence then available and these positions raises the question whether novel treatment bias might have influenced their formation.

At the same time in February that the NIH acknowledged evidence for ivermectin, Merck, the original developer of the drug for humans, issued a statement denying the existence of any positive evidence from pre-clinical and clinical studies. (14) Actually, there was substantial evidence for both. (5,7) That same week Merck announced to their investors that they'd contracted with the United States government to receive $356 million in advance of Food and Drug Administration (FDA) emergency use authorization (EUA) for their novel COVID drug CD24Fc, costing approximately $4,562 per patient. (15) FDA EUA approval requires the absence of another effective treatment. The question arises whether Merck's interest in its new drug influenced its denial of evidence for ivermectin.

In June 2021, with an additional four RCT's on ivermectin's impact on death reported, Bryant's meta-analysis was published (1), updating the state of evidence: nine RCTs with 2038 participants demonstrating with moderate certainty ivermectin reduces death overall by 49% (CI 27-95%), with earlier treatment trials indicating 70% less death. Also in June, the very well designed (double-blinded placebo-controlled randomized) trial by Niaee et.al. had passed peer review and was published (3), showing 82% (CI 45-94%) reduction in COVID death with early ivermectin. However, there was no update to the positions of the NIH and IDSA on the use of ivermectin in COVID.

In August 2021, results from the Together Trial were announced in the LA Times as if they showed ivermectin had "no effect whatsoever" in COVID-19. (16) In fact, the trial demonstrated ivermectin reducing death (17), even though the way it was conducted would be expected to minimize that observation. Specifically, it did not exclude patients who may have self-treated with ivermectin (18), which would blunt the magnitude of benefit observed. And it did exclude patients at higher risk of severe disease (17), which would lower the number of deaths and so reduce certainty about this effect. The trial was stopped as it was showing an 18% reduction in deaths, but before that effect achieved statistical significance. (In contrast, for perspective, when the RECOVERY trial showed dexamethasone lowered COVID death by 17%, this therapy was celebrated and immediately adopted.) A month after the press announcement, the trial's full details were still not available for public scrutiny (18), though the NIH presented it as a negative study. (17) This pattern of RCT irregularities raises the question whether bias against ivermectin influenced its design and conduct. (It also begs careful scrutiny for irregularity in other trials of ivermectin.)

In September 2021, the American Medical Association (AMA) with the American Pharmacist's Association called for the end of use of ivermectin in COVID (19), because of people experiencing toxicity from taking large animal doses of it. The FDA and Centers for Disease Control made similar statements. Certainly large animal doses are toxic in humans resorting to it for lack of a prescription, and no person should take animal ivermectin. But instances of poisoning in people self-treating with veterinary preparations do not imply any harm with human dosing. To the contrary, prescribing ivermectin appropriately for people desiring its COVID benefits would reduce accidental self-poisoning.

The AMA statement cites Merck as an authority on ivermectin's role in COVID-19, endorsing its denial of evidence for ivermectin in this disease. One month following the AMA's call to halt the use of ivermectin, Merck announced its upcoming release of molpuniravir, pending FDA EUA approval, as the "first drug…for early outpatient treatment of COVID-19", at a cost of $700 per patient. (20) Again, Merck's denial of evidence

for ivermectin's efficacy and safety is temporally associated with its interest in a novel treatment. This raises the question of whether bias for novel therapy and against ivermectin influenced the AMA position.

Obligation to Serve the Patient's and Public's Best Interest

It may be that many physicians and pharmacists are unaware of ivermectin's safety and efficacy due to the absence of information about it in their usual channels for staying up to date with current evidence. And it may be that media statements like those of the Together Trial and AMA have resulted in similar misperception among members of the public. But **widespread denial does not change the reality that evidence for ivermectin indicates with "moderate-certainty that large reductions in COVID-19 deaths are possible."** (1) Nor does it change my physician's obligation to apply this evidence in my patient's best interest and offer a prescription.

Misperception about ivermectin is now resulting in formal complaints to licensing boards against physicians prescribing it. Also because of misperception, pharmacists are refusing to fill prescriptions of ivermectin for COVID and some insurers are denying coverage for this use. In its mission to serve public safety, Board actions under the pandemic threat of COVID-19 need to prevent harmful treatments while allowing beneficial ones. Thus it has become essential for the Board to consider now the evidence presented above supporting the use of ivermectin in COVID-19 as reasonable medical practice, as well as appreciate that complaints against it may unwittingly represent novel treatment bias.

Rational Use of Ivermectin to Prevent COVID

Considering the rational use of ivermectin to prevent COVID-19 is also important, because it may also be met by formal complaint. Vaccination is the most reliably known protection against severe COVID, reducing it by up to 96%. (21) But for several reasons, there are fully vaccinated people who can benefit from ivermectin prophylaxis in addition to vaccination.

Firstly, vaccine has limited efficacy in preventing infection by the dominant delta variant of SARS-CoV-2 and in reducing its transmission by infected persons. Five months after mRNA vaccination, reduction of infection has waned to 47% (22), with infected persons having the same amount of virus in the upper respiratory tract as unvaccinated persons. (23) Secondly, immunocompromised persons often are unable to mount an effective immune response to vaccine. Thirdly, some people are ineligible for vaccine, including some with higher risk of severe COVID, like young children with asthma. Thus both the immunocompromised and the young with chronic disease are vulnerable to severe delta COVID-19 transmitted to them by fully vaccinated adults whose work involves conditions of higher exposure. These include, for example, first responders, health care workers, teachers, bus drivers, indoor dining workers, and people in airplanes. All these people can benefit from ivermectin to protect their vulnerable loved ones until the pandemic abates.

Evidence that ivermectin prevents COVID-19 comes from 14 studies, including four RCTs, all showing benefit. Meta-analysis of RCTs reported by May 2020 indicates that in healthcare workers and people with known exposure, ivermectin prevents COVID illness by 87% (confidence interval 79 – 92%), though with low certainty because they observed symptomatic illness rather than objective viral testing. (1) However, a recent RCT using objective viral testing demonstrated ivermectin (with carrageenan) reduced COVID infection by the same 87% (CI 60-97%). (24).

These studies reliably demonstrate that a single dose of ivermectin upon known exposure, or a weekly dose in those with ongoing risk of exposure, result in 87% reduction in COVID.

In addition to protecting the vulnerable persons described above, ivermectin as prophylaxis can reasonably be used to interrupt SARS-CoV-2 virus transmission to help end the pandemic. Given that exposed vaccinated persons can contract and transmit it, and ivermectin greatly reduces the frequency of that event, it's reasonable to interrupt the spread of COVID-19 by treating those with known exposure.

Ivermectin can benefit people who are not vaccinated and those around them. An unvaccinated person who takes ivermectin is less likely to suffer from COVID and less likely to spread the virus to others.

Unique Benefits of Ivermectin in COVID-19

Ivermectin's mechanisms of action make it unique among COVID-19 therapies. Early in the infection, ivermectin blocks the entry of SARS-CoV-2 proteins into the host cell nucleus, impairing viral replication. Later in the disease, ivermectin blocks the entry of NFKb into the nucleus, thereby dampening the excess inflammatory response to viral debris that leads to death. (7) As such, ivermectin combines prophylactic with therapeutic, and anti-viral with anti-inflammatory benefits, making it useful throughout the course of COVID, from exposure through hospitalization. (The use of ivermectin in hospitalized patients is outside the scope of this rationale.)

Ivermectin's actions complement the immune-based mechanisms of vaccine and monoclonal antibodies, as well as that of direct antiviral drugs. **With the patient's and public's interest foremost, ivermectin and these other agents should be considered allies rather than competitors in preventing infection and helping a patient survive it.**

Ivermectin's safety profile makes it reasonable empirical therapy prior to results of the viral testing required for monoclonal antibodies and direct anti-viral drugs. Further, ivermectin can be used in people not meeting the other criteria limiting use of these therapies, including older age, co-morbidities, degree of oxygen use, and location of care. Ivermectin's limitations are loiasis among people of West and central Africa, pregnancy and breastfeeding, and weight less than 15 kg (though COVID-19 studies to date have not included children and adolescents). It's only drug interaction is with warfarin. Thus ivermectin can be immediately employed to benefit most people with or exposed to COVID, independent of their testing status, medical condition, and location.

Ivermectin is also unique among COVID-19 therapies because its low cost and simplicity make it very accessible, except for the forces presently opposing its use. Costing only $35 and available at many pharmacies, treatment is once daily oral dosing for a few days. Thus ivermectin is a practical treatment option for those with barriers to accessing, or hesitancy to undergo, monoclonal antibody infusion, as well as those who may not be able to afford the cost of novel drugs now or in the future. Novel COVID therapies tend to favor the privileged, whereas ivermectin is accessible to the underprivileged. Thus ivermectin can enhance equity of outcomes in a pandemic disproportionately harming them.

Need for Licensing Board Action

As a licensed physician, I'm obligated to act in my patient's best interest using my best clinical judgment based on the best available evidence. To support my fulfilling this obligation, given present opposition, I need my licensing Board to acknowledge using ivermectin in COVID-19 as reasonable medical practice. Similarly, pharmacists and the Board of Pharmacy need to be aware that the medical licensing Board recognizes ivermectin as safe, effective COVID medicine. Without Board action, the AMA position will continue to impede use of ivermectin. Potential public health interventions with ivermectin, which are succeeding in many communities around the globe, also depend on clinicians and pharmacists being supported in its use.

The potential benefit of ivermectin to the public also begs the Board to act in the interest of their safety under the threat of COVID-19.

There is no good reason people have been denied the option of ivermectin nor that this uniquely beneficial medicine for COVID should be banned. It is not ethical for the medical profession, obligated to serve the public's well-being, to create a society in which the only oral treatment for COVID is a $700 novel drug, when $35 ivermectin is more effective. We should be using all safe and effective means to help our people survive this disease and bring the pandemic to a close.

A Board statement to achieve these goals need not endorse ivermectin for any specific indication. It would suffice for the Board to state a position supporting licensees in applying their clinical judgment based on evolving evidence in the treatment of COVID-19, including the use of ivermectin if medically appropriate.

Thank you again, members of the Board, for thoughtfully considering this issue. The people of our state have suffered so much avoidable disease, death, and trauma from COVID. There is more yet to be averted.

Sincerely,

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