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FLCCC Alliance Response to All National and International Health Agency Recommendations Against Ivermectin in COVID-19

Drs. Paul Marik and Pierre Kory – founding members of the Front Line Covid-19 Critical Care Alliance (FLCCC), along with Dr. Andrew Hill, researcher, and consultant to UNITAID and the World Health Organization (WHO) – presented extensive ivermectin data to the National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel on January 6, 2021. Subsequently, on January 14, the NIH Panel upgraded their recommendation from "against the use of ivermectin outside clinical trials" to "there is insufficient evidence to recommend for or against use."

Curiously, since that decision, multiple other national and international health agencies, including but not limited to the European Medicines Agency and the regulatory health agencies of all of North America and Europe, have issued cursory reviews with negative recommendations against use of ivermectin. Notable exceptions instead supporting use of ivermectin are the European union members Slovakia, Bulgaria, Macedonia, and the Czech Republic.

As one of the leading expert research groups studying the ivermectin use in COVID-19, the FLCCC Alliance find ourselves responsible for providing the necessary corrections to the agency's multiple erroneous assessments of the existing data as follows;

Agency Concerns: "*Because most of these studies have significant limitations, we cannot draw definitive conclusions on the clinical efficacy of ivermectin for the treatment of COVID-19*."

FLCCC Response: Health care agencies should be aware that on February 20, 2021, the results of a comprehensive, protocolized assessment of the quality of the existing ivermectin trials were presented by the Technical Working Group of the British Ivermectin Recommendation Development (BIRD) group to their Recommendation Development Panel. The presentation consisted of the details and results of a systematic review and meta-analysis of 21 randomized controlled trials (RCT's), including over 2,500 patients. The audience consisted of over 65 general practitioners, specialists, researchers, and patient representatives representing over 15 countries from all world regions. *Following a guideline development process consistent with the WHO standard*, the BIRD Panel reviewed not only the RCT data, but also a summary of the observational controlled trials (OCT) and the numerous examples of epidemiologic analyses showing the effects of ivermectin distribution campaigns and/or widespread treatment adoption on population-wide rates of excess death.[1] The majority of Panel members (75%) found that this comprehensive evidence base's overall certainty was overall moderate-to-high. Importantly, they identified no apparent conflicts of interest amongst the trials. Finally, *the Panel consensus gave the strongest recommendation option for ivermectin adoption in both the prevention and treatment of COVID-19.*

We are severely troubled by the multiple examples of health care agencies failing to undertake as extensive an effort as the BIRD or Unitaid/WHO teams that have conducted "active" reviews. The best example of such an effort is the Unitaid team, which identified and established communication with the principal investigators of all 59 active registered, randomized, controlled treatment trials of ivermectin in COVID-19. In this fashion, they were able to receive trial results immediately upon completion of each trial and all the necessary details required to assess the quality of the trials adequately. The Unitaid/WHO team has repeatedly offered to share the data they have compiled in their "active" review with any regulatory agency. To our knowledge, no recent negative recommendation has been informed by the most recent trial results compiled by Unitaid.

Further, all such health agency recommendations conflict with the findings reported in multiple other recent expert systematic reviews and meta-analyses from across the world, including a recent report co-authored by the Nobel Prize-winning discoverer of ivermectin, Professor Satoshi Omura:

1. Unitaid/W.H.O Ivermectin team preliminary meta-analysis, Univ. of Liverpool[1]
2. Bryant et al., The Evidence Based Medicine Consultancy, Bath, UK[2]
3. British Ivermectin Recommendation Development Panel[3]
4. Kalfas et al., University of Melbourne[4]
5. Padhy et al., All India Institute of Medical Sciences[5]
6. Covid-19 Study Group at
7. Nardelli et al. San Raffaele Scientific Institute, Milan, Italy[7]
8. Kory P et al. Front Line COVID-19 Critical Care Alliance[8]
9. Yagisawa, M et al. Kitasato Institute, Japan[9]

It is essential to recognize that two of the above studies have passed peer review and are pre-publication.[8,9] In particular, the FLCCC comprehensive ivermectin review by Kory et al. recently passed a rigorous peer review performed by two career FDA scientists and a Senior Scientist/Subject Matter Expert for the Therapeutics Branch of Translational Medicine Division of the Defense Threat Reduction Agency (DTRA) of the Department of Defense. The manuscript concludes that the existing evidence base supports the immediate global adoption and deployment of ivermectin in the prevention and treatment of COVID-19.

Agency Concerns: Agencies continue to state the need for "adequately powered, well-designed, and well-conducted clinical trials."

FLCCC Response: Agencies dismissal of *data from observational* controlled trials (OCT's) due to concerns over possible misinterpretation from the presence of unmeasured confounders or imbalanced comparison groups is well known. What is both worrying and unprecedented is the agencies' application of similar concerns to a large body of *prospective, randomized, controlled trials,* as they have long been considered the "gold" standard of scientific investigation. What is more concerning is that among these over two dozen RCT's, the results from double-blind, single-blind, open-label, placebo-controlled or standard-of-care comparison designs ***all*** report similar benefits in clinical outcomes. The known bias against OCT data is exactly why Unitaid/WHO restricted its

ivermectin research team to studying results of RCT trials only. Dismissing the value of over two dozen RCT's, including thousands of patients, raises the bar for proof of efficacy so high that almost no therapeutic could ever be considered to have proven efficacy. A possible exception would be a single, massive trial performed by a pharmaceutical company or major academic medical center within North America or Europe, which neither has elected yet to do. However, even if such a trial were done, the strength of its findings would not outweigh the current evidence base, as the existing evidence is derived from a meta-analysis of RCT's, considered the highest form of medical evidence in support of an intervention, more so than any single--even large--RCT. The meta-analyses of the over 20 RCT's by the Unitaid/W.H.O consultant team and the international collaboration British Ivermectin Recommendation Development Panel find;

- Statistically significant reductions in the **time to viral clearance**
- Statistically significant reductions in the **duration of hospitalization or time to clinical recovery**
- Statistically significant reductions in **mortality** (75% absolute reduction in risk of dying)

Agency Concerns: The NIH Panel on February 12 claimed that the 17 available RCTs at that time were "underpowered" or "small" based on their impression of the absolute number of included patients. We must remind all such Panels that although the sample size of a RCT is an important contributor to statistical "power", the most significant variable determinant is the *treatment effect size*. Ivermectin's treatment effects on time to viral clearance, time to clinical recovery, and mortality are of such magnitude that "large" sample sizes are not necessary to ensure the required low risk of Type I error. The large treatment effect size can be evidenced by the majority of these supposedly "small" trials *repeatedly* finding differences in outcomes that reach a high level of statistical significance. The probability of such findings *repeatedly* occurring among trials from various centers and countries in the absence of a "true" large treatment effect is near nil. In fact, as per Dr. Andrew Hill, the lead researcher of Unitaid's ivermectin team, **"the *current calculated probability that ivermectin's measured effects on survival are due to chance* is *1 in 5,000".***

FLCCC Response: The references supporting multiple agency recommendations consistently provide evidence of reviews containing only a subset of available studies. One example is the NIH Panel recommendation update of February 12, which curiously excluded 9 of the 17 RCT results presented to the Panel on January 6, 2021, with data on almost 1,100 patients.

- 3 *excluded* RCTs reported statistically significant reductions in mortality
- 4 additional *excluded* RCTs reported statistically significant reductions in viral clearance
- One included RCT was mischaracterized as unblinded when it employed a single-blind design

FLCCC Response: Further, several agencies also *selectively* include only a minority of observational controlled trials (OCT's). Using the NIH recommendation from February 12 again as an example;

- 3 *excluded* OCT's reported statistically significant reductions in mortality or viral clearance
- 1 "negative" OCT was included despite numerous and widely criticized design, conduct, and interpretation flaws and the firing of multiple authors and supervisors of the study [1,2]
- 1 cited OCT (the large ICON study from Florida published in the high impact journal *Chest* of the American College of Chest Physicians) did not give recognition to the investigators' use of multivariate analysis and sophisticated propensity matching, techniques considered to match prospective RCTs in accuracy. This was the only trial performed in the United States, and it reported a large reduction in mortality in hospitalized patients treated with ivermectin.

Agency Concerns: All agency recommendations provide a summary of RCT trial design limitations with a marked underemphasis of the numerous beneficial outcomes reported by the RCT's. Again using the recent NIH panel as an example, among the randomized trials data available to the NIH at the time of their last recommendation and review;

- 3 RCT's, (one double-blind, one open-label), with over 600 total patients, reported a statistically significant **reduction in mortality**, while the third, smaller one found a near statistically significant reduction (p=.052)
- 2 RCT's (one double-blind) found **statistically significant reductions in time to viral clearance**
- 1 RCT found a **statistically significant decrease in viral load, days of anosmia, and days of cough**
- 1 RCT (double-blind) found a **near statistically significant, large reduction in recovery time**, p=.071
- Only 1 small RCT. reported a clinical benefit that did not approach statistical significance.

Agency Concerns: Multiple agencies' recommendations highlight concerns regarding the safety of ivermectin in COVID-19.

- In a recent review of over 350 articles on ivermectin by the prominent French toxicologist Jacques Descotes, "serious adverse events are unequivocally and exceedingly rare."[10]

[1] https://wayka.pe/essalud-retira-a-investigadores-tras-estudio-que-advierte-riesgos-en-3-medicamentos-para-covid/

[2] https://saludconlupa.com/noticias/replica-y-despido-este-es-el-segundo-informe-que-genero-la-salida-de-la-gerenta-de-investigacion-de-essalud/

Based on the BIRD meta-analysis, the "number needed to treat" to save one life with ivermectin in COVID-19 is 1.5, indicating that of every *nine* patients treated with ivermectin that would otherwise have died from covid-19, *six* would be saved. Even more potent is the data showing that the number needed to treat to prevent transmission of the disease is 1.16, indicating that for every seven people treated preventively, only one would risk falling ill with COVID.

Given the above unparalleled safety profile, along with the large magnitude efficacy being reported, many agencies have adopted the use of ivermectin, based on a pragmatic approach utilizing a risk/benefit analysis in the midst of a global public health emergency. The rapidly growing list of the national and regional health ministries and institutions across the world that have, in contrast, *recently* decided to incorporate or recommend ivermectin in treatment guidelines includes:

- Slovakia – National Treatment Guideline (1/26/21)
- Bulgaria- Approved for Over the Counter Use (2/21)
- Czech Republic – Legalized use (3/12/21)
- Peru – National Treatment Guideline (1/8/21)
- Japan - Tokyo Medical Association (2/9/21)
- Mexico – Institute of Social Security (2/3/21)
- Belize - National Treatment Guideline (12/18/20)
- South Africa – Health Products Regulatory Association (1/27/21)
- Zimbabwe – National Ministry of Health (1/28/21)
- North Macedonia – National Health Minister (1/15/21)
- Uttar Pradesh, India – Treatment Guideline (pop. 234 million -9/3/21)
- State of Bihar, India – Treatment Guideline (pop. 122 million - 8/21)
- Egypt- National Treatment Guideline (11/30/20)
- Guatemala - National Treatment Guideline (1/23/21)
- Nicaragua– National Treatment Guideline (1/25/21)
- State of Chiapas, Mexico (8/1/20)
- Jamaican Medical Association (2/26/20)
- Argentina, 1/3 of territory – States of Pampa, Jujuy, Salta, Tucuman, Misiones, Corrientes (2/26/20)

Agency Concern: Multiple agency reviews negatively assess the fact that various doses and schedules of ivermectin were used amongst the available trials.

FLCCC Response: We strongly reject this as a "limitation" of the evidence base because precisely the opposite is true: the variety of doses and schedules is a *strength*. An evidence base consisting of varying treatment regimens allows for the identification of an optimal treatment strategy. Dr. Hill's data, compiled for Unitaid and the WHO, compared trials with a single day vs. multi-day treatment strategies using various dose amounts. These data actually revealed a dose-response relationship in

terms of time to viral clearance and time to clinical recovery, providing another pillar of scientific support for the efficacy of ivermectin against COVID-19.

Agency Concern: On January 6, the FLCCC was asked by the NIH Panel to submit all newly available ivermectin data going forward. On January 26, the FLCCC emailed the Panel a recently completed manuscript by the analysts Chamie et al. Their study analyzed vast amounts of publicly available (and verifiable) epidemiologic data which reported conclusive evidence (via the ruling out of multiple possible confounders) that widespread ivermectin distribution campaigns repeatedly and closely preceded large reductions in both COVID-19 case-fatality rates and "excess deaths" measured in many regions of Peru and other countries.[11] The FLCCC considers this manuscript to be a historic, landmark paper and a must-read for all public health officials, given that it demonstrates the population-wide role that ivermectin can play in bringing about control of the pandemic. Although no mention of this paper was included by the NIH, the EMA, or any other European or North American Agency review, we were strongly encouraged to learn that the WHO Treatment Guidelines committee asked for and received a presentation of these data by the senior author.

Since the completion and submission of their Peru analysis manuscript, Chamie et al have continued to produce numerous other epidemiological analyses finding profound reductions in hospitalizations and case fatality rates after national or regional adoption. One of the most notable examples was the Social Security Institute of Mexico's decision on December 29, 2020 to adopt a "test and treat" strategy at all 250 testing locations in the metropolitan area of Mexico City. All patients underwent a rapid COVID test, and if positive, were immediately provided ivermectin. What followed was an immediate drop in both hospitalizations and death throughout Mexico City over the next 6 weeks, now approaching near pre-pandemic levels.

We encourage all health agencies to review these compelling data supporting ivermectin as part of a global solution to COVID-19.

Agency Concern: The agencies continue to post the now disproven theory "*that ivermectin doses up to 100-fold higher than those approved for use in humans would be required.*"

FLCCC Response: Data proving this statement to be false was presented by Dr. Paul Marik during The FLCCC presentation to the NIH Panel on January 6. Multiple agencies around the world continue to repeat this erroneous theoretical concern, despite being fully refuted based on the following;

1) the known poor relevance of inhibitory concentration estimates between cell culture models (in particular monkey kidney cells) and human models
2) the unpublished data shared by the scientist Dr. Kylie Wagstaff after the experiment above was repeated using alveolar lung cells, which found inhibitory concentrations easily achieved with standard dosing (personal communication).

3) studies showing standard doses can achieve tissue concentrations between 3 -10 times higher than serum, particularly in adipose and lung tissue that highly express ACE-2 receptors
4) studies that have identified numerous other mechanisms of action than those theorized in the above experiment using high concentrations (detailed in our now accepted review manuscript)
5) studies and meta-analyses finding repeated large clinical outcome benefits after standard doses were used, thus disproving the above theoretical limitation

Conclusion

In almost all of the now-over-two-dozen randomized clinical trials of ivermectin in the treatment of COVID-19, repeated, large, statistically significant benefits at every stage are noted, chief among them being a reduction in mortality. These benefits make ivermectin unique amongst COVID-19 therapeutics because no other medication has simultaneously shown impacts on prevention of transmission, viral clearance, time to clinical recovery *and* survival. Further, Unitaid/WHO findings of dose-dependent impacts on time to viral clearance (an objective outcome), provide an additional, unassailable pillar of evidence that ivermectin has highly potent anti-viral properties. It is impossible to argue of a task more important than agencies conducting a more detailed, in-depth review of the entire body of now over two dozen RCT's reporting repeated reductions in morbidity and mortality.

The FLCCC thus recommends that such expert and well-resourced agencies, some capable of participating in projects with the scope and success of Operation Warp Speed, should assign further resources and manpower to gather the critical "incomplete" details from the large Unitaid/W.H.O research team or the recently formed BIRD panel, given that both expert groups have amassed and closely analyzed these critical trial details. Again, both groups have stated they are willing to share trials data with and/or present to any public health regulatory agency upon request.

Similarly, the NIH could and should assemble a team of epidemiologists to independently validate the analyses by Chamie et al which unequivocally demonstrate the near-immediate population-wide effects of ivermectin distribution campaigns in reducing case fatality rates and excess deaths to near pre-pandemic levels in the many regions where these events took place.

Similar to the international BIRD consortium, it is our recommendation that further efforts in planning for or conducting placebo-controlled clinical trials may not only pose serious ethical concerns, but will likely produce redundant data and further delays in the mass deployment of ivermectin that could instead simply and rapidly decrease both case counts and deaths. The urgency of recommending ivermectin is particularly acute amongst low and middle income countries (LIMC) given that the mass vaccination strategy embarked upon by all the same agencies referred to in this letter will take years to reach LMIC's. These delays combined with an absence of other countermeasures will give the wildtype virus more opportunities to transmit and form escape

variants that may compromise the global immunization effort. Therefore, if a highly safe and inexpensive intervention like ivermectin has a reasonable chance of cutting down transmission, it must be deployed without delay.

The FLCCC also asks that a level of recommendation be provided that is commensurate with the most updated data compiled and analyzed by the BIRD and UNITAID teams. The BIRD Panel experts were surveyed and found that the evidence for ivermectin's overall certainty was "moderate to high." This conflicts with the NIH Panel's current recommendation that "there is insufficient evidence to recommend for or against," which is further undermined by its failure to follow its own recommendation rating scheme, which allows for "optional", "moderate", or "strong" levels of recommendation dependant on the size and type of evidence base supporting the therapy. The most recent evidence base presented to the NIH consisted of over 17 RCTs and a half dozen OCT's, with nearly all showing statistically significant benefits in at least one important clinical outcome. This suggests that, even given the misplaced concerns over study quality or size, the evidence would support at minimum "B-IIa" designation, which would equate to a "moderate strength" recommendation based on "other randomized trials or subgroups analyses of randomized trials." In the Panel's own words, on the evidence for ivermectin on February 12 "…we cannot draw *definitive* conclusions." We are unaware that a definitive (e.g., an I-A) evidence base is required to formulate a recommendation. We thus remind all agencies that "a full" or "definitive" recommendation during a pandemic is not required nor is it ideal to wait for. We are perplexed why many agencies continue to avoid a recommendation by demanding data which takes years and large resources to acquire. Even a weak or cautious recommendation would suffice in guiding practitioners throughout the world in the use of one of the safest medicines known in history.

Finally, we ask that agencies place a greater effort in further defining the overall quality of the increasing amounts of evidence supporting the efficacy of ivermectin. Again, a recent systematic review and meta-analysis by Lawrie et al submitted their trials data to an independent expert reviewer who found the quality of evidence to be of "moderate" certainty, similar to that supporting the use of corticosteroids in COVID-19, which are the standard of care worldwide. To say that the existing evidence is *low quality* and/or *insufficient to recommend for or against* is incorrect given the recent conclusions of the BIRD conference Panel's findings and the near totality of existing trials finding statistically significant benefits in at least one important patient-centered outcome. Again, we struggle to identify an explanation for the reluctance to issue even a weak recommendation for one of history's safest medicines in the setting of repeated escalations of case counts, hospitalizations, and deaths from COVID-19. Again, in the words of the world expert toxicologist Jacques Descotes, "serious adverse events are unequivocally and exceedingly rare".

Those agencies failing to offer even a weak recommendation is becoming an increasingly isolated position as it departs from a number of expert reviews along with an increasing number of countries and regional and institutional health ministries that are instead fully adopting ivermectin based on the available evidence. We must remind the agencies that, absent even a weak recommendation, the vast majority of many nations' health care providers will be unwilling to

prescribe ivermectin. Given the evidence presented, we ask the worlds health agencies to rapidly issue a recommendation commensurate with the clear, strong documented evidence above.

Sincerely,

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