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FLCCC Alliance Response to the N.I.H. Guideline Committee Recommendation on Ivermectin use in COVID-19 dated February 11, 2021

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 (N.I.H.) COVID-19 Treatment Guidelines Panel on January 6, 2021.[1] Subsequently, on January 14, the Panel upgraded their recommendation from "against use of ivermectin outside clinical trials" to "there is insufficient evidence to recommend for or against use." After reviewing further selected evidence, more recently, on February 12, the Panel again concluded the following;

"*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*."

FLCCC Response: The N.I.H. Panel should be aware that on February 20, 2021, the results of a comprehensive, protocolized assessment of the quality of the existing ivermectin trials was presented by the Technical Working Group of the British Ivermectin Recommendation Development (BIRD) group to their Recommendation Development Panel. A systematic review and meta-analysis of 21 randomized controlled trials with over 2,500 patients was presented at that meeting to over 65 general practitioners, specialists, researchers and patient representatives representing over 15 countries from all regions of the world. Following a guideline development process consistent with the W.H.O. standard, the Panel arrived at "strong" recommendations that ivermectin be adopted in both the prevention and treatment of COVID-19.

Based on our and the BIRD Panel's review, we have identified a series of oversights that the N.I.H. update of February 12 continues to demonstrate as outlined below.

Guideline Panel Oversight 1: The N.I.H. Panel continues to state the need for "adequately powered, well-designed, and well-conducted clinical trials" while not applying the conclusions from the entirety of the existing evidence base due to "incomplete information and significant methodological limitations.".

Using Cochrane Methodology in the assessment of quality, the BIRD technical group found the majority (15 of the 21 reviewed) of trials were at low or moderate risk of bias and that the certainty of the evidence for effects on survival was overall low to moderate with large effects on this outcome. After reviewing the R.C.T. data, a summary of the observational controlled trials data, and the numerous examples of epidemiologic analyses showing the effects of ivermectin distribution campaigns on population-wide rates of excess death, the majority of Panel members (75%) found that the overall certainty of the evidence was moderate-to high, with the most common view being that it was "high certainty" of evidence. No apparent conflicts of interest were identified amongst the trials.

[1] See our Press Release from January 7, 2021. https://covid19criticalcare.com/flccc-pressrelease-nih-c19-panel-followup-jan7-2021/

In addition, the persistent claim that even more trials need to be conducted is concerning given that, as of February 5, five more R.C.T. results were made available to the UNITAID team, with another 500 patient trial scheduled to report on February 23. This will bring the total number of patients included among the soon-to-be 23 completed R.C.T.'s to approach nearly 4,000 in February alone. We have been told that the W.H.O/UNITIAD team is willing to share these trials data with other regulatory agencies such as the N.I.H. if they so desire. With these rapidly accumulating trials data, we trust the N.I.H. will be able to support, at minimum, a cautious recommendation for use in the upcoming weeks.

Guideline Panel Oversight 2: The N.I.H. Panel excluded 9 of the 17 randomized controlled trial (R.C.T.) results presented by the FLCCC/UNITIAD presenters on January 6, 2021, with data on almost 1,100 patients

- 3 *excluded* R.C.T.'s reported statistically significant reductions in mortality
- 4 separate *excluded* R.C.T.'s reported statistically significant reductions in viral clearance
- One included R.C.T. was mischaracterized as unblinded when it employed a single-blind design

Guideline Panel Oversight 3: The N.I.H. panel *selectively* included only a minority of observational controlled trials (OCT's);

- 3 *excluded* OCT's reported statistically significant reductions in mortality (2) or viral clearance (1)
- 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 [2,3]
- 1 cited OCT did not note the use of sophisticated propensity-matching, a technique considered to match prospective R.C.T.'s accuracy. This was the only trial performed in the United States and reported a large reduction in mortality in hospitalized patients treated with ivermectin.

Guideline Panel Oversight 4: Whereas a summary of trial limitations was listed, the Panel did not provide a summary of the 8 trial benefits;

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

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

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

Guideline Panel Oversight 5: The N.I.H. Panel did not perform a "meta-analysis" of the R.C.T.'s, considered to be the highest and most robust form of medical evidence, more so than any single R.C.T. can provide.

- Fortunately, the UNITAID/W.H.O consultant team and the BIRD group have done so. Both expert teams have found that meta-analyses of R.C.T.'s studying the use of ivermectin in COVID-19 leads to;
    - Statistically significant reduction in the time to viral clearance
    - Statistically significant reduction in the duration of hospitalization or time to clinical recovery
    - Statistically significant reduction in mortality rates (75% absolute reduction in risk of dying)

Guideline Panel Oversight 6: On January 6, the FLCCC was asked by the N.I.H. 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 cae-fatality rates and "excess deaths" measured in many regions of Peru and other countries. 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. The FLCCC Alliance asks that the Panel review and include comment on this study's methods and conclusions.

Guideline Panel Oversight 7: The N.I.H. Panel does not recognize the rapidly growing list of national and regional health ministries and institutions across the world that, based on the totality of the available evidence, have, in contrast to the Panel, *recently* (list below) decided to incorporate ivermectin into treatment guidelines to decrease deaths and case counts.

International

Slovakia – National Treatment Guideline (1/26/21)
Bulgaria- National Treatment Guideline
Peru – National Treatment Guideline (1/8/21)
Japan - Tokyo Medical Association (2/9/21)
Mexico – Social Security Institute Respiratory Disease (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)
Pampa State, Argentina (2/26/20

United States

Urgent Care Chain, South FL
Numerous Tele-Health Providers
Brockton Hospital, MA
Broward Health System, FL
United Memorial, TX
Dayton VA Hospital, OH
Univ. Tennessee, Knoxville, TN
Lincoln Hospital, WA
7 SNFs, Buffalo, NY
7 SNFs, Virginia
Lexington Med. Ctr., S.C.
DeTar Hospital, TX
Citizens Med Ctr., TX
Mission Hospitalists, Trenton, NJ
23 ALFs, Southern US

Guideline Panel Oversight 8: The N.I.H. Panel continues to publish the now disproven theory "*suggesting that ivermectin doses up to 100-fold higher than those approved for use in humans would be required.*" This concern was addressed by Dr. Paul Marik during the FLCCC presentation to the Panel on January 6. He presented more recent data from Caly and Wagstaff's recent experiment which used lung alveolar cells instead of monkey kidney cells. Their lab is now reporting an estimated "IC_{50}" that standard doses of ivermectin easily exceed. We suggest the Panel communice with these researchers if verification is needed.

Guideline Panel Oversight 9: The N.I.H. Panel continues to suggest that the 17 available R.C.T.'s are "underpowered" or "small" based on their impression of the absolute number of included patients. We must remind the Expert Panel that although sample size is an important contributor to statistical "power", the most determinant variable 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 necessary low risk of Type I error. This 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 occurring *repeatedly* among trials from various centers and countries in the absence of a "true" large treatment effect is near nil. The N.I.H. Panel should be aware that the UNITAID team's "*current calculated probability that ivermectin's measured effects on survival are due to chance* is *1 in 5,000".*

Conclusion

In almost all of the over two dozen clinical trials of ivermectin in the treatment of COVID-19, repeated, large benefits in at least one important outcome is being reported. These benefits make ivermectin unique amongst COVID-19 therapeutics, given no other medication has simultaneously shown impacts on prevention of transmission, viral clearance, time to clinical recovery *and* survival. Further, the dose-dependent impacts on time to viral clearance (an objective outcome), provides 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 verifying that the repeated reductions in morbidity and mortality among the now almost two dozen randomized controlled trials are scientifically valid given the N.I.H. Panels repeated concerns of study quality.

The FLCCC thus recommends that an institution as expert and well-resourced as the N.I.H., capable of participating in a project with the scope and success of Operation Warp Speed, should assign further resources and manpower to gather the critical "incomplete" details that other teams have amassed. This can be easily accomplished by forging a closer collaboration with either 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. 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 N.I.H. 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 in which these events took place. It is our opinion 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 would rapidly decrease both case counts and deaths.

The FLCCC also asks for a level of recommendation that is most commensurate with the most updated data compiled and analyzed by the BIRD and UNITIAD teams. The BIRD Panel experts have since found that the overall certainty of the evidence for ivermectin is “moderate to high.” This conflicts with the N.I.H. Panels current recommendation that “there is insufficient evidence to recommend for or against”. Given that in the NIH COVID-19 treatment guidelines, the recommendation rating scheme allows for either “optional”, “moderate”, or “strong” levels of recommendation to be assigned along with multiple types of evidence bases to cite in support of the recommendation option. The most recent evidence base presented to them consisted of over 17 R.C.T.'s and half a dozen OCT's, with nearly all showing statistically significant benefits in at least one important clinical outcome. This suggests that, even given the outsized concerns over study quality or size, the evidence would support a “B-IIa” 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 (i.e. a I-A) evidence base is required to formulate a recommendation. We thus ask for a “less definitive” recommendation option such as even a "B-IIb" which requires only non-randomized trials or observational cohort trials.

In conclusion, we ask that more effort be placed in further defining the overall quality of the increasing amounts of evidence in support of the efficacy of ivermectin. To say that the existing evidence is *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. We struggle to identify an explanation for the reluctance to issue even a weak recommendation of one of history’s safest medicines in the setting of repeated escalations ub case counts, hospitalizations, and deaths from COVID-19. In addition, this refusal departs from the increasing numbers of countries and regional and institutional health panels that are instead fully adopting ivermectin based on the available evidence. We must remind the Panel that in the absence of even a weak recommendation, the vast majority of the nation's health care providers will be unwilling to prescribe ivermectin despite it being far safer than medicines such as aspirin or acetaminophen. Given the evidence presented, we ask the Panel to rapidly issue a recommendation commensurate with the existing evidence base's now known strengths.

Sincerely,

The Front Line Covid-19 Critical Care Alliance

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