From: Pierre Kory
Subject: Manuscript Concerns..
Date: 21 January 2021 at 04:50:27 GMT
To:

Dear Andrew,

Thanks so much for sharing your pre-print and also we both really enjoyed your talk with S. Africa yesterday, it was excellent, especially the Q and A. Further, we are so encouraged by your identification of a number of active prophylaxis trials, some quite large and we eagerly anticipate these trial results when available.

However, we developed some significant concerns over the current pre-print version of your manuscript, as its conclusions and interpretations were severely discordant, not only with the available data therein, but also with the tone and content of your subsequent presentation to S. Africa and numerous private comments you have shared with us during discussions of these data.

We thought it would be helpful if we performed a peer review of the manuscript as we quickly identified a number of troubling statements within the manuscript that we feel should be immediately revised lest it cause more harm than it is already causing. We hope you find the below suggested revisions helpful to you prior to your embarking further on a peer-review process with a journal.

Please see below and we kindly ask that you undertake these revisions quickly. We implore you to do this because we are highly disturbed at the evidence of what appears to be scientific misconduct.
We understand that you appear to be caught between two forces and wish you the strength in exerting your moral conscience in this situation. Many thousands of lives depend on your exercise of this courage. We are happy to chat with you about this today if you

would like. Although some of the revision comments below may appear harsh, it because we were severely troubled – but remain committed to helping you in what appears to be a terribly difficult situation. – Paul and Pierre

Abstract:
"In-vitro, ivermectin showed some antiviral activity but at higher concentrations than achieved in human plasma after normal oral dosing."

Comment #1– this statement is erroneous and should be removed or re-worded as it has been refuted by several sources; 1) the known poor relevance between cell culture models, in particular monkey kidney cells and human models 2) the data shared by Kylie Wagstaff with both of us after she repeated the experiment with alveolar cells 3) the numerous other mechanisms suggested by recent studies and 4) the numerous outcomes measured in the numerous clinical trials in the meta-analysis using standard or a slightly increased dosing, thus making such a limitation impossible to exist

"*... and meta-analyses are prone to confounding issues*."

Comment #2 - This statement is false. Meta-analyses are performed to determine the treatment effect of multiple studies, although admittedly the underlying studies might individually be prone to confounding issues of varying degrees. No assessment of the degree of bias was performed and thus this statement is vague and ill-defined. We suggest you more formerly grade/assess the quality of the underlying trials and state that quantitative grading instead. Further, meta-analysis allows the assessment of the degree of heterogeneity among studies. The I^2 among studies was not significant in this study and any statement should reflect that.

"*..and ivermectin dose and duration of treatment was heterogeneous:*

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Comment #3 This is a profound strength rather than limitation. It allows the assessment of the optimal dose and duration of therapy and your analysis and summary of these different dosing strategies was and is a major contribution to our understanding of optimal treatment approaches. This should be removed from the limitations section and placed in the listing of strengths.

Ivermectin should be validated in larger, appropriately controlled randomized trials before the results are sufficient for review by regulatory authorities."

Comment #4 The most important function of a peer-reviewer is to determine whether the conclusion of a study are supported by the data presented. It is common for authors to overstate the conclusions of a study based on their data and it is often the responsibility of the peer-reviewer to soften or limit such over-interpretation of their data. This manuscript is nearly unique in our careers given that, for the first time we can recall, the author dismisses the strength of the evidence and profoundly understates the findings of the meta-analysis. We are disturbed by the implications of this occurrence as it could only be explained by the author's allowing the inclusion of a non-scientifically supported opinion by an external influence with a clear interest in mitigating the import of the data presented. This must be corrected to avoid what will clearly invite deserved, deeper scrutiny as well as a questioning of the scientific integrity of the author.

Introduction:

"Three re-purposed anti-inflammatory drugs have shown significant survival benefits to date: the corticosteroiddexamethasone in the UK RECOVERY trial [3], and theInterleukin-6 (IL-6) receptor antagonist drugs, tocilizumab andsarilumab, in the REMAP-CAP trial [4].

Comment #5 This statement is biased and ignores the 5 previous RCTs which showed NO benefit from anti- IL-6 therapy. Thus,

this statement suggesting a "proven" benefit must include the above qualifier.

"... has proven survival benefits for oxygen-dependent patientswith COVID-19, while tocilizumab and sarilumab improvessurvival for patients in intensive care [3, 4].

Comment #6 Again this statement is factually incorrect, several prior studies included critically ill patients and this should again be qualified.

"Antiviral activity of ivermectin has been demonstrated for SARS-CoV-2 in Vero/hSLAM cells [IB6]. However, concentrations required to inhibit viral replication in vitro (EC50=2.8?M; EC90=4.4?M) are not achieved systemically after oral administration of the drug to humans [6, 7]. The drug is estimated to accumulate in lung tissues (2.67 times that of plasma) [8], but this is also unlikely to be sufficient to maintain target concentrations for pulmonary antiviral activity [7, 9]. Current data suggest that the dosages of ivermectin used in human trials are unlikely to provide systemic or pulmonary concentrations necessary to exert meaningful direct antiviral activity."
Comment #7 As above, this has been now proven factually incorrect. The repetition and persistence of this inaccurate summary of the EC50 issue again suggests a non-listed author influencing the contents of a scientific manuscript. We know this based on the multiple email records exchanged between yourself, FLCCC members and Dr. Wagstaff and her team, where it was clearly demonstrated to you that the above old theory has been proved erroneous based on more recent data. Further, in collaboration with you, we presented the opposite conclusion to the NIH Panel on January 6, 2021. We cannot overstate how troubling it is that the above mis-truth was included despite our efforts at clarifying this issue, something which our records indicate we had done.

"Current data are insufficient to determine whether the minor

form or a circulating metabolite has higher direct potency against SARS-CoV-2, but it seems likely that it would need to be profoundly more potent than the reported values."

Comment #8- We have never heard of such a concern and cannot determine its relevance in the face of the massive amounts of clinical data showing large clinical impacts of the trials using normal to slightly increased dose ranges. This statement should be removed as it will unnecessarily introduce doubt in the face of such consistent and large findings. We also have never heard this concern in any of your presentations or our discussions and again suspect an external influence attempting to mitigate the import of the data you are presenting. It is not subtle.

Irrespective of gender, no impact of ivermectin on viral titers in lung or nasal turbinate was observed in this model, supporting a mechanism of action not relating to direct antiviral activity.

Comment #9 - This again appears an attempt to distort the truth. Our manuscript, which we have shared with you, and we assume serve as background to the writing up of your manuscript, contains numerous references beyond Wagstaff's model above showing a number of studies showing anti-viral mechanisms – this statement above should be re-worded to say "suggesting a mechanism of action in addition to the anti-viral properties shown in other studies"

In pharmacokinetic studies, the Area Under the Curve (AUC) andmaximum concentration (Cmax) of ivermectin are generally dose proportional, and bioavailability of ivermectin increases 2.57-foldin the fed state [8]. Increasing the frequency or dose of ivermectin does increase the Cmax and AUC of total drug, butnot sufficientlyto reach the published EC50 against SARS-CoV-2 in monkeyVero/hSLAM cells [8].

Comment #10 - 'This is the third time (so far) in the manuscript where inaccurate statements suggesting that therapeutic

concentrations are unachievable with ivermectin. This is a clear attempt to undermine the clinical utility of ivermectin. The vero kidney cell model is irrelevant. We know that you understand that the IC50 in alveolar cells is significantly lower than in monkey kidney cells and achievable by standard doses. This must be corrected immediately, and all such inferences removed from your paper.

Limitations of current analysis is important as it is being performed with secondary data from a wide variety of different trials in many different parts of the world with designs that were not originally meant to be compatible. Further refined analysis, including direct data examination, are warranted.

Comment #11 - Here is yet another paragraph that we find nearly unique in our careers of peer-reviewing manuscripts. The long-adhered to scientific manuscript format whereby discussion of study limitations occurs after the study results, in the conclusion/ discussion section, has been violated here. We are again troubled as to why the author(s) felt the need to include two limitation sections, one in introduction, one in discussion with yet a third in the conclusions. Furthermore, these limitations are actually a strength. These studies are real world studies which have enormous clinical utility and clinical relevance in a real world situation.

The primary outcome was all-cause mortality from randomization to the end of follow-up. Changes in inflammatory markers, viral suppression, clinical recovery and hospitalization were measured in different ways between trials and were summarized for individual clinical trials where endpoints could not be combined.

Comment #12 The primary outcome is listed as mortality. Therefore when the results are presented the mortality data <u>should be presented first</u> and it should be stated that this is the primary outcome and profoundly significant. When the primary outcome of a study or meta-analysis is positive (statistically significant).. the study is considered positive. This manuscript instead violates this

interpretation and inexplicably concludes the opposite.. this is again very troubling. Please state the primary outcome first and emphasize the results statistical significance.

RESULTS

Effects on Inflammatory Markers

Five trials provided results of the effect of ivermectin on inflammatory markers including C-reactive protein (CRP), ferritin and d-dimer (Table 2). Four of these trials demonstrated significant reductions in CRP compared to control. Furthermore, in the Elgazzar trial [22], ivermectin significantly reduced ferritin levels compared to control in the severe patient population while no significant difference was demonstrated ……..

Comment #13 We do not understand the emphasis on inflammatory markers. This is a secondary end-point. The primary end-point should be presented first.

Discussion:

However, the data should be interpreted carefully in the contextthat meta-analyses are highly prone to confounding bias,

Comment #14 As discussed above, please correct similarly.

and current viral PCR assays have several important limitations.

Comment #15 The author(s), both named and unnamed (it is now 100% clear there are non-named authors "assisting" you in the write-up of this study and "they" appear to continually attempt to inject as many limitations into the soundness of the study findings as "they" can). You must put a stop to this - this sentence should be removed as PCR is regarded as the standard of care to diagnose COVID-19 infection.

Limitations

Key limitations to this meta-analysis include the comparability of the data, with studies differing in dosage, treatment duration, and inclusion criteria. Furthermore, the SOC used in the background

treatment differed between different trials.
Comment #16 The limitations of these data are overstated and again are clearly an indication of a profound bias and a readily apparent, "hidden agenda". These limitations are strengths as they reflect real world experience with his drug and should be stated as such.

Across three studies, in a cumulative 683 patients, we found a slight increase in lymphocyte counts [22, 34, 35] following ivermectin administration. CRP, a marker of infection and inflammation, were reduced following ivermectin administration across four trials [22, 23, 25, 34]. D-dimer is a fibrin degradation product, often raised in severe COVID-19 due to thrombus formation. Ferritin can also be raised in severe COVID-19 due to the cytokine storm and hyperinflammation. Levels of both d-dimer and ferritin following one week of ivermectin treatment in severe COVID-19 cases were reduced to levels less than half of those receiving SOC [22]. These reductions in D-dimer and ferritin were more significant in patients with severe disease compared to those with mild/moderate disease at baseline. Furthermore, erythrocyte sedimentation rate and lactate dehydrogenase, non-specific markers of inflammation and tissue damage, respectively, were both reduced slightly following ivermectin administration in two separate studies of patients with COVID-19 [34, 36].
Comment #17 The overplay of biomarkers is inappropriate. This was a minor secondary endpoint. In contrast, the discission/ implications and relevance regarding the PRIMARY end-point is understated. You must change the emphasis and order when presenting these results.

At the time of writing, knowledge gaps prevent a robust conclusion about the mechanism of action, but current in vitro data do not support a direct antiviral activity of the drug.
Comment #18 This statement is COMPLETELY false and a misrepresentation of the truth. Multiple mechanism of action have been demonstrated by in vitro studies. These studies cannot be ignored. It is likely that Ivermectin has multiple modes of action,

e.g. Effect on importin, spike protein binding, binding to RdRp etc . This sentence cannot stand, especially in light of the prophylactic data, which we have shared with you and you are starting to further compile, and have tweeted publicly about. It clearly has massively potent anti-viral "blocking" properties and we know you are aware of this.

Despite the encouraging trend this existing data base demonstrates, it is not yet a sufficiently robust evidence base to justify the use or regulatory approval of ivermectin. However, the current paucity of high-quality evidence only highlights the clear need for additional, higher-quality and larger-scale clinical trials, warranted to investigate the use of ivermectin further.
The maximum effective dose of ivermectin needs to be clarified and new clinical trials should use a consistent multi-day dosing regime, with at least 0.4mg/kg/day. The appropriate dose and schedule of ivermectin still requires evaluation and the current randomized clinical trials of ivermectin need to be continued until ready for rigorous review by regulatory agencies
Comment #19 See above comments pertaining to multiple similar concluding sentences. This concluding statement is false given it does not follow from an interpretation of the data. Per your words recently, "the probability that ivermectin's impacts on survival are due to chance in COVID-19 is 1 in 5,000". Again, 1 in 5,000. This is a more appropriate conclusion than the above. We strongly suggest you change more in line with your own analysis of the data and either reject the opinion of who-ever has authored this section, or you must include them either as an author and/or you must state that your study sponsors had a role in the writing and interpretation of the data in a new section called "conflicts of Interest" (which we noticed you did not include, also a standard part or any scientific manuscript which is uniquely missing here). It appears to us that that there is a sinister underlying motivation to understate the importance of the lifesaving effects of this drug. We ask that you stand up to this influence and maintain your scientific integrity, which we know you possess. We cannot begin to imagine the pressures upon you here and so we wish you similar amounts of

courage, clarity, and strength.

Lastly, Andrew, for your sake and science's sake, we are concerned that if your scientific integrity is formally brought into question or investigation by finding that outside influences shaped your supposedly independent interpretation and conclusions (and we are already seeing questions popping up on social media), then we worry about both your past work being brought into question (i.e. many will wonder whether this the first time you have allowed external forces to influence your scientific conclusions) and thus will begin to question prior conclusions/recommendations on various medications you have studied.. as well as future ones, which would likely affect future employment opportunities. We are so sorry about this position you are in and trust we are helping give perspective and support here. Finally, we hope we are wrong about all the above but we just cannot find any other explanation for the erroneous and misleading statements in your manuscript in light of your prior presentations and shared opinions of the available data on ivermectin in COVID-19.