Peer Review File

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Author's note: We have made some changes to improve the readability of our commentary. In addition to a few minor edits, we have organized the contents under the following headings: Abstract, The Approval of CoronaVac, Evidence of CoronaVac Efficacy, Issues of Transparency, Use of CoronaVac in Groups Not Included in Phase III Trials, Effectiveness of CoronaVac, and Conclusions and Recommendations. The last two headings mostly address weaknesses identified by the reviewer.

Reviewer comments

Below, I list a number of concerns that the authors should consider when revising their article.

1) **Comment:** Title.
The current title could be misleading since not all the COVID-19 vaccines are discussed in depth here. On the contrary this editorial is almost exclusively centered on the Sinovac vaccine. Perhaps the current title the need for transparency in COVID-19 vaccine trials and vaccination policies". Could be more informative and accurate: "The need for transparency in COVID-19 vaccine trials and vaccination policies". The case of the Sinovac vaccine in Latin America and the Caribbean.

Response: Following the reviewer's suggestion, we have changed the title to (added text highlighted in yellow): "The need for transparency in COVID-19 vaccine trials and vaccination policies. The case of CoronaVac in Latin America." We dropped "and the Caribbean", because Spanish speaking countries, like the Dominican Republic, are usually considered as part of Latin America.

2) **Comment:** Poorly strengthened governance

In lines 42-46, authors said "Even though CoronaVac has been administered to hundreds of millions of people, (Mallapaty 2021) Sinovac has shown no interest in data sharing or transparency, has made minimal efforts to evaluate its vaccine, and has distributed misleading information about its efficacy and safety, with the support of local governments".

I would not say here "with the support of local governments". Countries where Sinovac was authorized may have not strong national regulatory authorities with adequate tools to take action.

I miss specifically a comment on the lack of regulatory mechanisms to enhance transparency thought the access to clinical trials data, such as the policies by the EMA in Europe (https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication) or more recently in Canada (https://www.bmj.com/content/365/bmj.l1825?fbclid=IwAR1lCxJKGd2ZDA5uCYEIIAiHuEwfb59wh50dGM3d7DWHU_SeBslEU1WiWCs, as far I know, no country in Latin American and the Caribbean have developed such mechanism. I would recommend noting this aspect as potential deficiency rather than proposing that the lack of transparency is being supported from the governments.

Response: Following the reviewer's comment and appreciated advice, we have changed this paragraph to:

Even though CoronaVac has been administered to hundreds of millions of people,(2) Sinovac has shown no interest in data sharing or transparency, has made minimal efforts to evaluate its vaccine, and has distributed misleading information about its efficacy and safety. Unfortunately, some countries where Sinovac was approved for emergency use do not have strong regulatory agencies with adequate tools to evaluate the efficacy and safety of vaccines in the context of a global health emergency and to operate independently from political interference. Indeed, most Latin American countries have not developed mechanisms to enhance data sharing and transparency, such as those of the European Medicines Agency, (3-5) the Food and Drug Administration of the United States,(6) and Canada.(7) CoronaVac, and other vaccines like Gamaleya and Sinopharm, have not been approved by these agencies. This suggests that approval procedures in countries like Colombia and Dominican Republic are more lax and provide less assurance. In consequence, the strengthening of regulatory bodies should be a political priority in these countries.

3) **Comment:** Authorizations from "weak evidence"

In lines 48-56 "In contrast to companies like Pfizer, Moderna, and AstraZeneca, Sinovac started selling CoronaVac without adequate evidence of its efficacy and safety".

I miss a commentary on the context of authorization in exceptional conditions of the pandemic vaccines from less evidence than usual using accelerated procedures (emergency authorization, conditional authorizations) and therefore assuming a greater grade of uncertainty (please refer to this referential papers on the matter https://pubmed.ncbi.nlm.nih.gov/32199486/; https://pubmed.ncbi.nlm.nih.gov/32199487/; This was the case for most COVID-19 vaccines including Sinovac but also, Moderna, and AstraZeneca Pfizer vaccine with notable regulatory and ethical discussions (https://pubmed.ncbi.nlm.nih.gov/33216636/). In this context of weak evidence, Sinovac was on the same league than Gamaleya, or Sinopharm vaccines https://pubmed.ncbi.nlm.nih.gov/34373256/;

The fact that some of these latest vaccines (Simovac, Gamaleya, Sinopharm) have not been authorized in Europe or in the United States perhaps worth commenting on. Are these authorizations evidencing differences on the regulatory bodies strength? Are the less strengthened governments using lax procedures and hence providing less guarantees? Should it be a political priority to adequately strengthen these bodies?

In the absence of strong evidence before the authorization, the evidence should be generated after the authorization (https://pubmed.ncbi.nlm.nih.gov/32199487/),

Response: We concur with the reviewer's opinion. We have changed this paragraph to:

In contrast to companies like Pfizer, Moderna, and AstraZeneca, Sinovac started selling CoronaVac without adequate evidence of its efficacy and safety. In early 2021, countries like Colombia and the Dominican Republic (DR), among others, committed to the purchase of tens of millions of vaccine doses. Given the extraordinary circumstances of the pandemic, it is understandable that vaccines were granted expedited emergency use approval, with less evidence than usual regarding their efficacy and safety than in normal circumstances. (8, 9) Nevertheless, the regulatory approval process in both countries lacked incentives for Sinovac to generate credible

evidence regarding the performance of CoronaVac. Both countries, as well as Sinovac, had an ethical obligation to generate this evidence, (10) which was necessary for defining and implementing optimal public health policies. Indeed, both countries could have improved their capacity to negotiate prices by leveraging on assessments of efficacy and safety and by conditioning the purchase of additional doses of CoronaVac to the successful completion of efficacy trials. (11) Regrettably, the absence of accountability among local governments encouraged the endorsement of vaccines with uncertain efficacy and safety and hindered the evaluation of their effectiveness after approval.

4) Comment:

I miss comments on post-approval studies evaluating effectiveness of CoronaVac (https://pubmed.ncbi.nlm.nih.gov/35366959/; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9375192/; https://pubmed.ncbi.nlm.nih.gov/35791428/) and safety (https://pubmed.ncbi.nlm.nih.gov/35770253/)

Accessibility of information on the studies, summary of the evidence from reliable sources for decision-making.

Response: To address this gap we have added the following findings regarding post-approval studies on the effectiveness of CoronaVac.

In view of the scarcity of clinical trial data on the efficacy of CoronaVac, studies of effectiveness of this vaccine are of greater importance. As part of an ongoing evaluation, we have identified 39 studies of CoronaVac effectiveness conducted in 11 countries, 34 in adults adults(34-67) and 6 in children ≤18 years old.(68-73) We obtained random-effect averages of CoronaVac effectiveness against COVID-19. Vaccine effectiveness to prevent moderate COVID-19 was 61.8% (51.7, 69.7) in adults and 47.7% (3.8, 71.6) in children. Effectiveness to prevent severe infection was was 64.3% (60.5, 67.8) in adults, and unidentifiable in children, due to a lack of data.

Although well-designed observational studies provide trusthworthy findings,(74) studies of CoronaVac effectiveness should be interpreted with great caution.(75) These studies incorrectly assummed that the effect of CoronaVac did not spillover from vaccinate to non-vaccinated individuals. In fact, vaccinating individual *A* may prevent infection in individual *B*, even if they socially interact, because *A* does not becomes infected (susceptibility effect) or because the vaccine makes the infeccion less contagious (infectiousness effect). This could lead to under or overerestimation of vaccine effectiveness and compromise extrapolability to other populations.(76-78) Non-comparability between vaccinated and non-vaccinated individuals could have resulted from the prioritization of those at higher risk of exposure to SARS-CoV-2 and severe COVID-19, which may have also been more willing to get vaccinated. Unfortunately, most studies relied on surveillance systems that lack data on risk factors for vaccination, infection, and COVID-19 severity. Nevertheless, it is unlikely for confounding bias alone to fully account for the observed effectiveness of CoronaVac.(79-80) Most studies used a test-negative design,(81) and it is uncertain if COVID-19 test-negative individuals were representative of the population from which test-positive cases came from. Indeed, as a consequence of a limited availability of PCR tests, testing was more likely in individuals at higher risk of infection or severe disease, and in recent contacts of a COVID-19 case.

By itself, this would not result in bias. Nevertheless, testing was also influenced by access to healthcare and by vaccination status, which are predictors of severe COVID-19. Consequently, selection bias was likely in test-negative studies, because participation depended on both the individuals' exposure (vaccination) and the outcome (SARS-CoV-2 infection).(82,83) The direction and magnitude of this bias are uncertain, as they are contingent on the strengths of the vaccination-testing and the infection-testing associations, and on the prevalence of these factors.(83,84) Finally, evidence from our ongoing analysis strongly suggest confirmation bias.(85) Indeed, in studies with a government employee as the first author vaccine effectiveness to prevent mild, moderate, and severe disease was 2.23 (95% CI: 1.70, 2.94), 1.89 (95% CI: 1.16, 3.09), and 1.81 (95% CI: 1.31, 2.50) times higher than in studies with a non-government employee as the first author, respectively.

The WHO used a minimum efficacy threshold of 50% to grant approval for COVID-19 vaccines. However, when approving CoronaVac, the WHO based its decision on the average rather than the minimum efficacy of the vaccine. (https://www.who.int/news-room/feature-stories/detail/vaccine-efficacy-effectiveness-and-protection) Considering the potential for biases, findings from effectiveness studies give only weak support to the WHO decision. Indeed, a variable that doubled the risk of vaccination and the risk of severe COVID-19 would drive the effectiveness of CoronaVac below the 50% approval target.(14, 86)

5) Comment:

I miss a possible comment on the availability and utility of reliable information for decision making. In this sense, it seems worth mentioning some interesting initiatives that have been developed with access in the Latin American and Caribbean area (https://iloveevidence.com; https://covid-19pharmacovigilance.paho.org). From a constructive point of view, should they be used and promoted by the governments for decision-making considering all the available scientific evidence? Do the authors have any proposals to reinforce a change of mentality in decision-making?

Response: Following the reviewer's advice, we now proposed possible strategies to improve the quality and the transparency of the process of vaccine approval in both countries (see Conclusions).

Sinovac must be held accountable for its refusal to abide by current scientific and public health policy standards, to generate evidence of minimum quality to justify the use of CoronaVac in tens of millions of people, to monitor the safety of its product, and to caution against its use in untested populations.(11, 87, 88) Politicians should also be held accountable for jeopardizing the welfare of their constituents by prioritizing political consensus over available scientific evidence in public health policy making, as well as for their lack of transparency and reluctance to generate and disseminate crucial public health data.

Although regulatory agencies should consider diverse interests and perspectives, it is essential to ensure that participants in the vaccine approval process have the relevant expertise, knowledge, and experience related to the subject matter under consideration. Governments should ensure that subject matter experts participate in the process of vaccine approval. That they are selected based on their professional expertise rather than their political views and that they are free to express their opinions

without fear of reprisals. Moreover, governments and professional organizations should promote an open and constructive dialogue between scientists and policymakers. This could be achieved by establishing platforms or forums where scientists can directly engage with policymakers, share their expertise, and actively contribute to evidence-based decision-making processes.

To enhance transparency and accountability, governments and vaccine manufacturers most ensure not only that policy decisions are based on scientific evidence, but also that the rationale and evidence behind those decisions are communicated clearly to the public. Vaccine manufactures must be required to make their research findings openly accessible and to give clear statements regarding the availability of underlying data. On the other hand, governments must guarantee that guidelines for vaccine approval, updates on the progress of applications and the status of approvals, and summaries of the scientific evaluations conducted during the approval process are easily and timely accessible to the public. This could also be achieved through the use of new or existing internet platforms, such as those from the Panamerican Health Organization (https://covid-19pharmacovigilance.paho.org/) and Epistemonikus (https://iloveevidence.com), for instance. Moreover, government regulatory agencies should ensure that the approval process provides opportunities for public consultation, foster collaboration with international regulatory agencies, make efforts to comply with international standards, and establish an independent oversight body or mechanism to monitor its activities and ensure compliance with transparency and ethical standards.

6) Comment: Conclusions

Authors conclude "In view of the misconduct of some vaccine manufacturers and national Governments, we should give further consideration to whether public health malpractice in the handling of COVID-19 should be considered "social murder", a crime against humanity that should be addressed by public inquiry, by voting out elected officials, and by constitutional 218 means, such as the International Criminal Court. (Abbasi 2021; Godlee 2021)

I suggest to tone down the conclusion. Rather than a "J´accuse" I recommend a more constructive commentary pointing the aspects of improvement identified, and any proposals to improve transparency and decision-making.

Response: We thank the reviewer for his/her thoughtful, useful, and impartial comments. We have deleted the original statement and have adopted a more constructive tone in our conclusions (see our response to the previous comment).