Editorial Commentary

The need for transparency in COVID-19 vaccine trials and vaccination policies: the case of CoronaVac in Latin America

Leonelo E. Bautista[1]^, Víctor M. Herrera[2]^

[1]Department of Population Health Sciences, School of Medicine and Public Health, University of Wisconsin, Madison, WI, USA; [2]Departamento de Salud Pública, Facultad de Salud, Universidad Industrial de Santander, Bucaramanga, Colombia

Correspondence to: Leonelo E. Bautista, MD, DrPH. Department of Population Health Sciences, School of Medicine and Public Health, University of Wisconsin, 689 Walnut Street, WARF 703, Madison, WI 53711, USA. Email: lebautista@wisc.edu.

Keywords: Vaccine development; transparency; public health policy; safety; efficacy

Received: 02 March 2023; Accepted: 10 August 2023; Published online: 24 August 2023.

doi: 10.21037/jphe-23-19

View this article at: https://dx.doi.org/10.21037/jphe-23-19

Calls for transparency and full and immediate availability of clinical trials and public health data for scrutiny by health care personnel, researchers, policy makers, and the general public have been limited to vaccine manufacturers in the United States and Europe (1). However, more extreme examples of the prevailing culture of denying access to data and neglecting scientific evidence in the formulation of public health policies are prevalent in low- and middle-income Latin American countries and involve vaccine manufacturers from other regions. The latter includes Sinovac, the Chinese company that developed and marketed CoronaVac to low- and middle-income countries around the world.

The approval of CoronaVac

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), the Food and Drug Administration of the United States, (4) and Canada (5). 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 the Dominican Republic (DR) are laxer and provide questionable assurance. In consequence, the strengthening of regulatory bodies should be a political priority in these countries.

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 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 (6). 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 (7), which was necessary for defining and implementing optimal

^ ORCID: Leonelo E. Bautista, 0000-0002-9151-6920; Víctor M. Herrera, 0000-0002-6295-1640.

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 (8). 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.

Evidence of CoronaVac efficacy

At the time of approval, the only evidence on clinical efficacy and safety of CoronaVac came from PROFISCOV (9), a randomized trial in 12,396 health care professionals (6,195 vaccinated and 6,201 placebo controls). The main outcome in PROFISCOV was symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection ≥14 days after administration of the second dose of the vaccine, confirmed by quantitative reverse transcription polymerase chain reaction (RT-qPCR) (9). Only 18–59 years old individuals were eligible at the start of PROFISCOV, but eligibility criteria were changed during the course of the study to include individuals ≥60 years old (n=632) and an unknown number of participants with previous SARS-CoV-2 infection (10). The main outcome was ascertained only in 79% of the participants (4,953 in the vaccine and 4,870 in the placebo group). Although a 21% lost to follow-up rate could have resulted in a lack of exchangeability between treatment groups, the distribution of prognostic factors by treatment received, among participants retained in the study, was not reported (9). Nevertheless, the investigators stated that the treatment group had a higher proportion of infected participants than the placebo group. Indeed, according to data from 109 participants selected at baseline for neutralizing antibody testing, the proportion of participants with previous infection was 2.27 times higher in the vaccine than in the placebo group. This imbalance could explain away the efficacy of CoronaVac observed in PROFISCOV (11), since previous infection with SARS-CoV-2 protects against future symptomatic infection.

On the other hand, a RT-qPCR test was conducted only if symptoms lasted ≥2 days (9). Participants with a previous infection may have had milder symptoms and may have been less likely to report symptoms than those who were unaware they had a previous infection, resulting in an overestimation of the efficacy of CoronaVac. Finally, there were no cases of severe coronavirus disease 2019 (COVID-19) in the vaccine group, and the authors reported an efficacy of 100% [95% confidence interval (CI): 16.9%, 100%] for this outcome. This estimate was obviously incorrect. When sparse data bias is accounted for in the calculation, the correct efficacy was 86.3% (95% CI: –0.11%, 98.3%) (12). Therefore, PROFISCOV's data were consistent with a null efficacy of CoronaVac to prevent severe COVID-19.

A second phase III trial of CoronaVac, conducted in Turkey, was published after the approval of this vaccine by the World Health Organization (WHO) on June 1st, 2021 (13). Investigators enrolled 10,214 volunteers aged 18–59 years with no history of COVID-19 and with negative RT-qPCR and antibody test results for SARS-CoV-2: 6,646 assigned to CoronaVac and 3,568 to placebo. The main outcome was symptomatic infection confirmed by RT-qPCR. The vaccine efficacy to prevent symptomatic infections was 83.5% (95% CI: 65.4%, 92.1%). Combined data from this trial and PROFISCOV indicate it was unlikely for the incidence of severe adverse effects to be higher than 2/10,000 vaccinees.

Issues of transparency

PROFISCOV's investigators had no plan to make data available to doctors, researchers, or the public (10), and the availability of data and materials from PROFISCOV has been reported as undecided (14). Almost 26 months after being disseminated as a pre-print and used as the main support for the purchase and use of CoronaVac, findings from PROFISCOV have not been published in a peer-reviewed journal.

Made aware of the fatal flaws in the PROFISCOV trial, officials from the Dominican and Colombian governments contended that Sinovac had provided additional information on the efficacy and safety of CoronaVac. Up to this date, the purported additional information provided by Sinovac has not been made available to the public.

It is likely the Dominican government approved the emergency use of Sinovac without a technical evaluation. Indeed, in order to deny a request for the technical evaluation that justified the approval of CoronaVac for emergency use in the country, the Dominican government issued a post-facto resolution (15) alleging a need to protect the intellectual property of Sinovac, and has neglected to answer a lawful appeal of this decision, filled on October 4th, 2021. If any proprietary data were included in the evaluation for approval, it could have been blackened out before making the evaluation publicly available. The

authorization for emergency use of CoronaVac expired on February 9th, 2022, because full approval had not been granted by that time. For the approval of its vaccine for emergency use, Sinovac agreed to generate updated reports on CoronaVac efficacy and safety in the DR every 6 months, as recommended by the WHO (16). Up to today, no safety report has been put forward. Moreover, the Dominican government has ignored a request for the first report, which was due on August 9th, 2021 (17). Use of CoronaVac continued in adults and children, without due approval.

According to their statement at ClinicalTrials.Gov (https://clinicaltrials.gov/ct2/show/NCT04582344), investigators from the Turkish trial (13) did not plan to share individual participant data. However, in their paper they stated that anonymous participant data would be available upon request, after completion of the clinical trial and publication of the results. In response to a request on information about access to trial data, the Health Institute of Turkey asked how the data would be used, before considering approval.

Use of CoronaVac in groups not included in phase III trials

Even though Sinovac has not conducted phase III trials among adults ≥60 years old and children ≤18 years old, it actively promoted the use of CoronaVac in these groups (8). In addition, and in contrast to other vaccine manufacturers, Sinovac neglected its ethical responsibility to evaluate how the effectiveness of its vaccine changed with time since vaccination, with the number of doses administrated, and with the emergence of new SARS-CoV-2 variants.

On October 31st, 2021, Colombia started vaccinating children 3–11 years old with a full dose of CoronaVac. On February 14th, 2021, the DR followed suit and started vaccinating children 5–11 years old. In both cases, the decision was made without a technical report about the efficacy, safety, risk, and benefits of CoronaVac in children. Indeed, the efficacy and safety of CoronaVac in children is unknown (18). In an attempt to document the safety of CoronaVac in children 6–11 years old, paving the way for other countries, the Chilean government issued a report of vaccine-related adverse events in children who had been followed by an average of 10.5 days after a single dose of CoronaVac (18,503 person-years) (19). Fortunately, in a display of transparency, the authors of the report explicitly stated the data from the Chilean surveillance system were not adequate to evaluate the safety of CoronaVac or any other vaccine. In fact, the number of cases of a first episode of epilepsy detected by surveillance in Chile was 23 times lower than expected (18).

On the other hand, Sinovac submitted a report of vaccine-related adverse effects in children 3–17 years old vaccinated in China from May 28th to October 10th 2021 (20). However, according to independent reports, the vaccination of children in China was scheduled to start in the week of October 17th (21). Only one case of an epileptic attack was reported by Sinovac. Nevertheless, taking into account the prevalence and frequency of epileptic attacks in Chinese children (22), and the total person-time of follow-up in vaccinated children included in the report, 4,166 attacks should have been observed. Moreover, the number of vaccine doses administered to children 3–5 years old was the same as that in children 6–11 years old (exactly 100 million doses in each group), even though the population of 6–11 years old should be larger than that of 3–5 years old. These inaccuracies, and the lack of information on how its surveillance system works, shed doubts on the credibility of Sinovac's report (18).

Risk/benefit assessments in the DR and Colombia clearly showed the vaccination of low-risk children with CoronaVac was far from justified. In 2021 the COVID-19 mortality in Dominican children 5–11 years old was 0.87 per million. Were the incidence and lethality of COVID-19 to remain similar to that in 2021, one COVID-19 death would have occurred in children 5–11 years old in 2022, and there was a 74% chance that one or less deaths would have occurred. Moreover, the Omicron variant, which has a lower lethality than those that circulated in 2021, was then predominant in the country and no child had died from COVID-19 since February 2021. As expected, no Dominican child died from COVID-19 in 2022. Unfortunately, the government neglected to collect data on severe, non-lethal COVID-19 in Dominican children. Given its practically null benefit on preventing mortality and the uncertainty about its adverse effects, the use of CoronaVac in Dominican children was not ethically justifiable.

Shortly after its start, we evaluated the potential benefits of vaccinating 3–11 years old Colombian children. According to data from the Colombian National Institute of Health (https://www.ins.gov.co/Noticias/Paginas/Coronavirus.aspx), up to November 15th, 2021, two weeks after the country started vaccinating children, 65 children 3–11 years old had died from COVID-19. The cumulative lethality, 36.5 per 100,000 diagnosed cases, was likely overestimated, since 60–74% of COVID-19 cases in children are asymptomatic and are rarely tested and

reported (23). COVID-19 lethality had decreased from 70.2 to 51.6 per 100,000 diagnosed cases from the first to the second semester of 2020. It further decreased and remained stable around 28.0 per 100,000 cases in 2021, even during the third and highest peak of COVID-19 cases in the country. On the other hand, the COVID-19 mortality rate during the whole epidemic had been 4.6 per million children-years and had a small, non-significant increase of 24% from 2020 to 2021. Taking into account the number of Colombian orphan children attributable to COVID-19 (24), the COVID-19 mortality in 20–49 years old, and that 16.3 million 20–49 years old have not been vaccinated, we estimated 11,640 additional COVID-19 deaths would occur in this age group in 2022, had conditions remained similar to those in 2021. This would have resulted in an excess of 33,418 orphan children. Had CoronaVac had an unlikely but optimal 90% effectiveness and had all 7.1 million children 3–11 years old been vaccinated, 29 COVID-19 deaths would have been avoided. In contrast, had 16.3 million 20–49 years old individuals remained unvaccinated, there would have been 1,152 new orphans per child death avoided. Considering its low potential for benefit, that vaccinating 20–49 years old would have had greater benefits for children than vaccinating them, and the lack of evidence on the efficacy and safety of CoronaVac in children, the vaccination of healthy 3–11 years old Colombian children with CoronaVac was hardly justifiable.

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. In a meta-analysis of the effectiveness of CoronaVac to prevent infection was 46.6% (95% CI: 38.6%, 53.5%) (25), but ranged from 36.8% to 65.0% in individual studies. Although well-designed observational studies provide trustworthy findings, studies of CoronaVac effectiveness should be interpreted with great caution (26). Investigators in these studies incorrectly assumed that the effect of CoronaVac did not spillover from vaccinated to non-vaccinated individuals. In fact, vaccinating individual A may prevent infection in individual B, even if they socially interact, because A does not become infected (susceptibility effect) or because the vaccine makes the infection less contagious (infectiousness effect). This could lead to under or overestimation of vaccine effectiveness and compromise extrapolability to other populations (27). 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, who may have also been more willing to get vaccinated. Unfortunately, most effectiveness 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 (28). Most studies used a test-negative design (29), 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 RT-qPCR 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) (30). 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 (31). Finally, many effectiveness studies have been conducted by employees of governments committed to the use of CoronaVac as the main strategy against COVID-19 and this may have led to confirmation bias (32).

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 (11).

Conclusions and recommendations

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 (8,33). 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 truthful 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 Pan American 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, complies with international standards, and includes an independent oversight body or mechanism to monitor its activities and ensure compliance with transparency and ethical standards.

Strengthening the regulatory agencies and process for vaccine approvals should be an integral part of a global strategy for pandemic preparation.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Public Health and Emergency*. The article has undergone external peer review.

Peer Review File: Available at https://jphe.amegroups.com/article/view/10.21037/jphe-23-19/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jphe.amegroups.com/article/view/10.21037/jphe-23-19/coif). LEB serves as an unpaid editorial board member of *Journal of Public Health and Emergency* from February 2022 to January 2024. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Doshi P, Godlee F, Abbasi K. Covid-19 vaccines and treatments: we must have raw data, now. BMJ 2022;376:o102.
2. Mallapaty S. China's COVID vaccines have been crucial - now immunity is waning. Nature 2021;598:398-9.

3. European Medicines Agency. European Medicines Agency Policy on Publication of Clinical Data for Medical Products for Human Use. London: EMA; 2014.
4. Zarin DA, Tse T, Williams RJ, et al. Trial Reporting in ClinicalTrials.gov - The Final Rule. N Engl J Med 2016;375:1998-2004.
5. Lexchin J, Herder M, Doshi P. Canada finally opens up data on new drugs and devices. BMJ 2019;365:l1825.
6. Cipriani A, Ioannidis JPA, Rothwell PM, et al. Generating comparative evidence on new drugs and devices after approval. Lancet 2020;395:998-1010.
7. Dal-Ré R, Caplan AL, Gluud C, et al. Ethical and Scientific Considerations Regarding the Early Approval and Deployment of a COVID-19 Vaccine. Ann Intern Med 2021;174:258-60.
8. Sojo A. Approval of CoronaVac in Brazil and Chile: some lessons on vaccine regulatory challenges. Rev Panam Salud Publica 2022;46:e104.
9. Palacios R, Batista AP, Albuquerque CSN, et al. Efficacy and safety of a COVID-19 inactivated vaccine in healthcare professionals in Brazil: the PROFISCOV study. SSRN Electronic Journal 2021.
10. Palacios R. COV-02-IB. PROFISCOV Study Protocol. Sao Paulo: Instituto Butantan; 2020:135.
11. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-Value to Assess the Potential Effect of Unmeasured Confounding in Observational Studies. JAMA 2019;321:602-3.
12. Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. BMJ 2016;352:i1981.
13. Tanriover MD, Doğanay HL, Akova M, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet 2021;398:213-22.
14. Palacios R, Patiño EG, de Oliveira Piorelli R, et al. Double-Blind, Randomized, Placebo-Controlled Phase III Clinical Trial to Evaluate the Efficacy and Safety of treating Healthcare Professionals with the Adsorbed COVID-19 (Inactivated) Vaccine Manufactured by Sinovac - PROFISCOV: A structured summary of a study protocol for a randomised controlled trial. Trials 2020;21:853.
15. Ministerio de Salud República Dominicana. Resolución num. 000043. 21 de Septiembre, 2021:6.
16. World Health Organization. Interim recommendations for use of the inactivated COVID-19 vaccine, CoronaVac, developed by Sinovac: interim guidance, 24 May 2021. Geneva: World Health Organization; 2021.
17. Ministerio de Salud de la República Dominicana. Exención temporal de aplicación de los reglamentos de control sanitario y permiso especial transitorio para la importación y uso de emergencia de la vacuna absorvida COVID-19 (INACTIVA), fabricada por Sinovac Life Sciences Co. Ltd. (China). 2021.
18. Bautista LE, Rodríguez-Villamizar LA, Herrera-Galindo VM, et al. ¿Es prioritario vacunar a niños de 3-11 años contra COVID-19 en Colombia? Salud UIS 2021;53:e21038.
19. Ministerio de Salud Chile. Informe Estadístico: ESAVI de Vacuna de SARS-CoV-2 (CoronaVac) notificados en niños entre 6 y 11 años de edad, (Periodo13 septiembre - 7 octubre 2021). 2021.
20. Sinovac. COVID-19 Vaccine (Vero cell), Inactivated AEFI Analysis Report among the Population Aged 3-17 Years. 2021.
21. Dyer O. Covid-19: US and China prepare for mass vaccination of children under 12. BMJ 2021;375:n2631.
22. Wong V. Study of seizure and epilepsy in Chinese children in Hong Kong: period prevalence and patterns. J Child Neurol 2004;19:19-25.
23. Hurst JH, Heston SM, Chambers HN, et al. Severe Acute Respiratory Syndrome Coronavirus 2 Infections Among Children in the Biospecimens from Respiratory Virus-Exposed Kids (BRAVE Kids) Study. Clin Infect Dis 2021;73:e2875-82.
24. Hillis SD, Unwin HJT, Chen Y, et al. Global minimum estimates of children affected by COVID-19-associated orphanhood and deaths of caregivers: a modelling study. Lancet 2021;398:391-402.
25. Zeng B, Gao L, Zhou Q, et al. Effectiveness of COVID-19 vaccines against SARS-CoV-2 variants of concern: a systematic review and meta-analysis. BMC Med 2022;20:200.
26. Vandenbroucke JP. When are observational studies as credible as randomised trials? Lancet 2004;363:1728-31.
27. Tchetgen Tchetgen EJ, VanderWeele TJ. On causal inference in the presence of interference. Stat Methods Med Res 2012;21:55-75.
28. Bross ID. Pertinency of an extraneous variable. J Chronic Dis 1967;20:487-95.
29. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. Vaccine 2013;31:2165-8.
30. Jackson ML, Phillips CH, Benoit J, et al. The impact of

selection bias on vaccine effectiveness estimates from test-negative studies. Vaccine 2018;36:751-7.
31. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. Epidemiology 2004;15:615-25.
32. Nickerson RS. Confirmation bias: A ubiquitous phenomenon in many guises. Rev Gen Psychol 1998;2:175.
33. Abbasi K. Covid-19: Social murder, they wrote-elected, unaccountable, and unrepentant. BMJ 2021;372:n314.

doi: 10.21037/jphe-23-19
Cite this article as: Bautista LE, Herrera VM. The need for transparency in COVID-19 vaccine trials and vaccination policies: the case of CoronaVac in Latin America. J Public Health Emerg 2023;7:22.